



The mutagenesis-selection-cascade theory of sexual reproduction

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Abstract

Sexual reproduction is common in eukaryotic organisms from yeasts to humans. However, the question as to why sexual reproduction is so ubiquitous is a conundrum in evolutionary biology. In theory, sexual populations suffer a twofold cost compared to asexual populations. A multitude of theories attempts to explain this conundrum, but none gained wider acceptance. In this comprehensive work with more than 8,500 references I present compelling evidence that it takes a joint holist and reductionist approach to solve this “queen of problems in evolutionary biology”.

In a world of limited resources, the twofold cost of sexual reproduction may only be relevant in organisms that live far below the carrying capacity of their habitat. Near the habitat's carrying capacity, however, quality (fitness) of offspring is much more important than quantity and the theoretical twofold cost of sexual reproduction has no evolutionary meaning.

Environments never remain static. They continuously undergo changes that alter the fitness landscapes, displacing populations towards suboptimal fitness regions. Sexual reproduction has its evolutionary roots in a microbial stress response. Environmentally challenged microorganisms take up foreign DNA to either use it as template for DNA repair or increase their genetic repertoire. Thus organisms that are poorly adapted to their current environmental conditions “bet-hedge” (as part of a variety of stress-related responses) hoping to boost their fitness. What evolved as reactive process to environmental challenge was genetically accommodated in higher taxa as cybernetic and proactive evolutionary engine. A multitude of both direct and circumstantial evidences reveals the metabolic/oxidative stress, particularly of males, under which higher taxa generate the genetic variation of gametes (e.g. explaining mammalian testicular extra-abdominal descent or lower-temperature comfort zone of male fishes).

Stochastic mutagenesis and epimutagenesis are fraught by the substantially higher risk that mutations are rather deleterious than beneficial. Therefore, the evolutionary fate of mutators is inextricably linked to their effective population size: only with a large

population size chances are substantial that some individuals may create beneficial mutations that provide a fitness advantage. Under environmental stress, microorganisms take advantage of their large population sizes, create increased numbers of mutations and let natural selection select the mutants with the best fit to the actual environment. The evolutionary success of sexual reproduction in multicellular organisms was dependent on solving the “mutator-population size dilemma”. In multicellular organisms, the large investment of scarce resources into mature organisms limits population sizes. Exposing small populations of mutated organisms to natural selection would mean a large investment into possibly poorly viable organisms. Evolution selected for an alternative approach: to invest as little as possible into small, mutated units and to bet-hedge with large gamete populations. The huge energetic investment into this “waste” production leads to gonadal functional hypoxia in higher taxa and is associated with increased oxidative stress and genetic instability. During gametogenesis, oxidative stress, mutagenesis and epimutagenesis increase along the phylogenetic axis, particularly in the smaller gametes, the sperm, resulting in male-driven mutagenesis. In addition to the legendary twofold cost of sex this manifold “costs of gamete overproduction” (e.g. the human testicular output is approx. 2,000 spermatozoa per second), if it were non-adaptive, should definitely deter any organism from investing into sexual reproduction.

Gamete overproduction requires a gamete bottleneck: a stochastic bottleneck inevitably would drive Muller's ratchet and result in strong mutational meltdown and, together with their low number of offspring, this would have detrimental effects on population fitness in higher taxa. Only a selection-associated gamete bottleneck ensures long-term viability of populations. Conversely, the selection-associated gamete bottleneck allows to infer the (epi)mutagenic generation of gamete variation. Thus sexual reproduction selects the “pearls among the pebbles” before natural selection may possibly frustrate a larger investment into more mature organisms. Using a variety of stressors and competitive regimes as selection principle, e.g. oxidative stress and competition for limited trophic factors, a cascade of selective steps at the level of (primordial) germ cells, differentiated gametes,

fertilization, embryos, offspring and nonrandom mating select from this extreme abundance the most viable, competitive and stress resistant gametes and offspring. These selection principles are increasing mutational and environmental robustness and evolvability/adaptation to life in general, rather than to any particular mode of life and environment. The pervasive germ-soma conflict is the Red Queen that drives the coevolutionary dynamics underlying the maintenance of sexual reproduction. Along the phylogenetic axis, the mutagenic spectrum and the population size of gametes that is exposed to sexual selection cascades were increased and the population size of offspring that is exposed to natural selection was reduced. As a result of this evolutionary process, particularly male gametes represent quasi-species whose quasi-species structure, however, remains cryptic due to their gamete bottleneck. Oxidative stress as final common pathways of stress responses is the joint mediator of mutagenesis, epimutagenesis, canalization and gamete quality control by gamete competition. Thus both evolvability and robustness are phenotypes of the same fundamental processes, mediating “educated guess”-based innovation, plasticity and phenotype conservation in the face of environmental and genetic variation.

Ecological resource availability and stress intensity define the distribution of sexual and asexual reproduction. In resource-limited, moderately stressful habitats, the pre-selected genetic variation provided by sexual mutagenesis-selection cascades determines the short- and long-term benefit of sexual reproduction. The flip side of oxidative stress-driven mutagenesis-selection-cascades is that sexual reproduction, particularly male reproduction, became sensitive to additional environmental stressors and, particularly when exposed to extreme environmental challenges, operates near or above a threshold of “error catastrophe”. Thus, in larger animals geographic parthenogenesis is the phenotype of impaired male gametogenesis under intense environmental stress. On the other hand, a favorable ratio of habitat resource availability and minute individual biomass allows asexually reproducing bdelloid rotifers, Darwinulid ostracods, and oribatid mites a microorganism-like lifestyle with large population sizes and species-specific solutions with regard to their balance between evolvability and robustness in response to environmental challenges. In cyclical parthenogenesis, ecological factors that modulate the resource-stress balance determine the switch between asexual and sexual reproduction. Modular organisms (e.g. plants, benthic aquatic invertebrates) do not fall under Weismann’s doctrine

(the separation of germline and soma), and in addition to creating genetic variation by shuffling their genes during sexual reproduction are able to transmit heritable somatic mutations that are acquired and selected during the organism’s lifetime. In addition, polyploidy, long-term seed/egg banks, and phenotypic plasticity help these organisms to face the manifold challenges of variable environments. This capacity makes them flexible to switch habitat- and disturbance-dependently between asexual and sexual reproduction.

I can show that the predictions of the genetic theories of sexual reproduction (Fisher-Muller model, Muller’s ratchet, Kondrashov’s hatchet) are simplistic, incompatible with evolutionary dynamics, and based on fallacious post hoc, ergo propter hoc argumentation. In addition, it is argued that the DNA repair theory and parasite-host conflict theory (aka Red Queen theory), focussing on partial aspects of the resource-stress ecological network are insufficient to explain the evolutionary success of sexual reproduction.

That stochasticity is a property of evolutionary mechanisms like mutation, recombination and drift has been recognized earlier but I argue that stochasticity is, in addition to selection, the second pillar and organizing principle on which evolution is resting. Bet-hedging is the evolutionary risk-spreading response to stochasticity. Sexual reproduction is the ultimate bet-hedging enterprise and its evolutionary success the selective signature of stochastic environments. The identification of stochasticity/uncertainty as input variable into the cybernetic machine of evolution has far-reaching implications for a multitude of evolutionary enigmas such as the levels of selection enigma, the selection-genetic variation enigma, the adaptationism controversy, the mystery of low heritability and the Darwinian-Lamarckian type evolution controversy. Since sexual reproduction is so pervasive in nature and involved in the vast majority of genetic transmissions, deciphering its underlying mechanisms provides, as a corollary, insights into a variety of evolutionary conundrums such as the viability paradox, the molecular evolution–population size conundrum, and latitudinal biodiversity gradients. Moreover, sexual reproduction and the germ-soma conflict are identified as the processes causing punctuated evolution (e.g. the Cambrian explosion), and a mixed genetic/non-genetic type heritability. Finally, Francis Crick’s central dogma of molecular biology is extended taking into account the feedback of the environment to the genome via the phenotype using the noncoded signals energy (ATP), Ca^{2+} , and redox homeostasis

(reactive oxygen and nitrogen species). This feedback cycle reveals that environmental modulation of the epi/genome is subject to the dualism of stochasticity (resulting in variation) and selection vindicating the Darwinian evolutionary principles.

Table of contents

1. Introduction
2. An ecological definition of stress
3. Reproduction in a world of limited resources
 - 3.1 Germline-derived signals limit the soma's reproductive potential
4. The phylogenetic roots of sexual reproduction
 - 4.1 Oxidative and nitrosative stress, DNA repair and mutagenesis
 - 4.2 Stress and microbial transformation
 - 4.3 Stress and multicellular reproductive behavior
5. Mutagenesis and fitness
 - 5.1 Are mutations genetic "accidents"?
 - 5.2 May mutagenesis be adaptive?
6. Developmental and reproductive biology hold the clue
 - 6.1 A primer on the evolutionary roots of multicellular development
 - 6.2 A primer on reproductive biology
7. Sex: Proactive mutagenesis....
 - 7.1 Sexual reproduction: domesticating the fire
 - 7.2 The oxidative stress of gametogenesis
 - 7.2.1 Functional hypoxia
 - 7.2.2 Metabolic and replicative stress
 - 7.2.3 Oxidative stress
 - 7.2.4 Hypoxia-inducible factors
 - 7.2.5 Cytokines and nuclear factor-kappaB
 - 7.2.6 Heat shock response
 - 7.2.7 Stress and germ granules
 - 7.2.8 DNA damage and repair
 - 7.2.9 Mitochondrial ROS, uncoupling and aquaporin-8
 - 7.2.10 Membrane lipid unsaturation
 - 7.3 Male-driven mutagenesis
 - 7.3.1 Chromatin remodeling in elongating spermatids
 - 7.3.2 The gametogenesis-cancerogenesis connection
8. Sex:and selection of the "pearls among the pebbles"
 - 8.1 Selection: the pervasive phenomenon in evolution
 - 8.1.1 Cell competition and Myc
 - 8.1.2 Germ cell competition
 - 8.2 Germ cell selection
 - 8.2.1 Case study: paternal age effect disorders
 - 8.3 Selective mitochondrial bottleneck
 - 8.3.1 Mitochondrial homoplasmy
 - 8.3.2 Follicle atresia
- 8.4 Gametic selection
- 8.5 Fertilization selection
- 8.6 Embryo and offspring selection
- 8.7 Sexual selection
9. Coevolutionary dynamics of the germ-soma conflict
10. The redox regulation of gametogenesis and development: mutagenesis, epigenesis, canalization and gamete quality control
 - 10.1 Mutagenesis
 - 10.2 Recombination
 - 10.3 Epimutagenesis
 - 10.3.1 DNA methylation
 - 10.3.2 Histone modifications
 - 10.3.3 Noncoding RNA
 - 10.3.4 Epi/genetic reprogramming
 - 10.4 Canalization
 - 10.5 Apoptosis
 - 10.6 Transposable elements and epigenetics
 - 10.6.1 Role of microRNAs in gametogenetic DNA instability
11. Sexual mutagenesis-selection cascades (SMSC): there is more than meets the eye
 - 11.1 Excursion: RNA virus quasispecies
 - 11.2 SMSC, bottlenecks and natural selection
12. Random trial or educated guess?
 - 12.1 Stress-induced mutagenesis
 - 12.2 Non-random recombination
 - 12.3 Mutability of simple sequence repeats
 - 12.4 Activity of transposable elements
 - 12.5 Phenotypic plasticity, genetic assimilation and accommodation
 - 12.5.1 Assimilation and accommodation
 - 12.6 Sexual reproduction
13. Sexual reproduction: evolvability and robustness
 - 13.1 Evolvability
 - 13.1.1 The ecological pattern of evolvability
 - 13.1.2 The tempo of evolution
 - 13.2 Robustness
14. Stress and sex: a double-edged relationship
 - 14.1 Male reproduction is more susceptible to a variety of stressors
 - 14.2 Hormonal modulation of oxidative stress as evolutionary tuning knobs of reproductive activity and genetic variation
 - 14.2.1 Glucocorticoids
 - 14.2.2 Thyroid hormones
 - 14.2.3 Melatonin
15. Asexual reproduction
 - 15.1 Non-sexual ways to increase evolvability
 - 15.1.1 Large population size
 - 15.1.2 Polyploidy
 - 15.1.3 Automixis and mitotic recombination

- 15.1.4 Phenotypic plasticity
- 15.1.5 Seed/egg banks and dormancy as bet-hedging strategies
- 15.2 Asexual reproduction in sessile organisms
- 15.3 Asexual reproduction in mobile animals
 - 15.3.1 The “evolutionary scandals”: microscopic organisms in r-selected habitats
 - 15.3.2 Cyclical parthenogenesis
 - 15.3.3 Geographical parthenogenesis: when males are too stressed to reproduce
- 16. Germ granules and transgenerational epigenetic information transfer
 - 16.1 Germ granules are germ cell markers
 - 16.2 Transgenerational epigenetic information transfer
 - 16.3 Are germ granules the vehicles of transgenerational epigenetic information?
- 17. Stochasticity and selection, the organizing principles of evolution
 - 17.1 The cybernetics of evolution
 - 17.2 Bet-hedging as response to stochasticity
 - 17.3 Stochasticity and selection: dualism in evolution
- 18. Earlier theories that attempted to explain why most organisms reproduce sexually
 - 18.1 Fisher-Muller-model, Muller’s ratchet and Kondrashov’s hatchet
 - 18.1.1 Flawed static concepts
 - 18.1.2 Flawed teleological concepts
 - 18.2 DNA repair
 - 18.3 Host-parasite coevolution: the Queen is dead, long live the Queen
- 19. Evolutionary enigmas and controversies
 - 19.1 The selection-genetic variation enigma
 - 19.2 Levels of selection controversy
 - 19.3 The selectionist-neutralist controversy
 - 19.4 The adaptationism controversy
 - 19.5 Paradox of viability
 - 19.6 Mystery of low heritability
 - 19.7 The Cambrian explosion
 - 19.8 The Darwinian-Lamarckian evolution controversy
- 20. The resource-stress dimensions and ecological window of sexual/asexual reproduction
 - 20.1 The resource-stress dimensions
 - 20.2 The ecological window of asexual and sexual reproduction
- 21. Extension of Crick’s central dogma of molecular biology
- 22. Conclusions
- 23. Abbreviations
- 24. References

Introduction

Sex is the queen of problems in evolutionary biology. Perhaps no other natural phenomenon has aroused so much interest; certainly none has sowed so much confusion.

Graham Bell, 1982

It is [...] surprising that finding a convincing explanation for the evolutionary success of sex has proven to be one of the most difficult challenges for modern evolutionary biologists.

Nick Colegrave, 2012

Summary

Sexual reproduction is common in eukaryote organisms from yeasts to humans. But the near ubiquitous presence of sex has proven to be notoriously hard to rationalize in terms of an evolutionary cost–benefit perspective. Traditionally it has been argued that the evolutionary cost of sex is at least twofold given that sexual females would need a twofold amount of offspring (with a 1:1 sex ratio) to keep up with reproduction of asexual females. On the other hand, there is as of now no simple explanation for the benefit(s) of sex. Hypotheses for the maintenance of sex have been grouped into two main categories: (i) ecological and (ii) genetic theories. No single theory has obtained unanimous support and the rationale for the origin and maintenance of sex remains unresolved.

At its heart, evolutionary theory has an economic algorithm, a cost–benefit calculation: if a trait is beneficial for fitness, it will be selected for, when it is costly, it will be selected against. Reproduction is arguably the most fundamental activity of an organism. Reproduction is the sine qua non for the propagation of species and continuation of life. The vast majority of eukaryotic organisms reproduce sexually — at least occasionally. Among named animal species, only 0.1% are considered to be exclusively asexual (White, 1978; Vrijenhoek, 1998) and less than 0.1% of vertebrate species (some 90 species) (Dawley, 1989; Vrijenhoek et al., 1989; Vrijenhoek, 1989). Eighty vertebrate taxa from 14 families of fish, amphibians and reptiles have been found to reproduce asexually and are usually closely related to sexually reproducing species (Alves et al., 2001; Janko et al., 2007) with many examples demonstrating coexistence of unisexual and bisexual populations (Moore and McKay, 1971; Schlupp, 2005; 2010). As of 2003, over 900 species of insects were known to be asexual or have

asexual forms (Normark, 2003). Asexual reproduction is mainly confined to small twigs in the phylogenetic tree suggesting that asexual lineages have a higher extinction rate than sexual lineages, possibly due to mutational meltdown (Lynch et al., 1993; Vrijenhoek, 1998; Schwander and Crespi, 2009). While the ability to reproduce asexually is more widespread in plants, less than 1% of the approximately 250,000 angiosperm species are thought to be substantially asexual (Asker and Jerling, 1992; Whitton et al., 2008). Sex is argued to be advantageous because it generates variability by allowing independent assortment of genetic material through recombination (Weismann, 1889; Muller, 1932). But the near ubiquitous presence of sex has proven to be notoriously hard to rationalize in terms of evolutionary cost-benefit calculations (Maderspacher, 2011). There is as of now no simple, single-cause explanation for the benefit(s) of sex (Birky, 2009; Otto, 2009). On the other side of the equation, the costs of sex are easily spelled out. According to classical theory, reiterated in almost every publication on the evolutionary role of sexual reproduction, the evolutionary cost of sex is at least twofold (Maynard Smith, 1978a). Sexual populations consist of two genders, one (female) which can produce offspring and the other (male) which cannot. However, in an asexual population, any individual can produce its own offspring. Sexual females would need a twofold amount of offspring (given a 1:1 sex ratio) to keep up with reproduction of asexual females. Thus, asexuals should rapidly outgrow sexuals, which they usually don't. The second most obvious benefit is the twofold fitness advantage of an asexual female (Williams, 1975; Schwander and Crespi, 2009). For the same number of offspring produced, each asexual female transmits twice as many genes to each offspring as compared to a female producing offspring sexually, the "costs of meiosis" (Williams, 1975).

A more comprehensive inventory over all groups of organisms showed five potential costs of sex (Lewis, 1987; Joshi and Moody 1998; Hörandl, 2009): (1) cellular-mechanical costs of meiosis and syngamy (the time needed for meiosis, syngamy and karyogamy, which confers an inactive stage and a delay of synthetic processes); (2) recombination (breakup of favorable combinations of alleles); (3) fertilization (risk exposure and density dependence of locating a mating partner); (4) cost of males and 'genome dilution' *sensu* Lewis, 1987 (a sexual parent transmits only 50% of its genes to the offspring); and (5) costs of sexual selection. In fact, sexual selection has generally been viewed as reducing population mean fitness (Haldane, 1932; Lande, 1980; Kirkpatrick,

1982; Grafen, 1990; Kirkpatrick and Ryan, 1991; Price et al., 1993; Tanaka, 1996; McLain et al., 1999; Gavrillets et al., 2001; Houle and Kondrashov, 2001). Whereas (1) and (2) are costs of meiosis, (3) – (5) are costs of outcrossing.

Agrawal (2002) pointed to a key difference in the equilibrium genetic load (the reduction in fitness of a population of interest relative to a population composed solely of the most-fit genotype) in sexual and asexual populations under constant and fitness-dependent mutation rates. If the mutation rate is constant, then sexual and asexual populations are expected to have the same genetic load at mutation-selection equilibrium. In contrast, if the mutation rate is fitness-dependent, the expected fitness in an asexual population at equilibrium will be that of the most-fit genotype, while in a sexual population, the equilibrium fitness will be less than that of the most-fit genotype, perhaps much less. Thus surprisingly, the "cost of sex" may in fact be much greater than 2-fold (Baer, 2008). In chapter 8.1, I will introduce another cost of sexual reproduction, the overproduction of a huge "waste" of gametes. In the face of such legendary costs, we might expect sexual reproduction to be rare. Given the costs of sex and the widespread potential for asexual reproduction, why do so many species reproduce sexually? The question as to why sexual reproduction is so pervasive is a conundrum that has been described as "the outstanding puzzle in evolutionary biology" (Williams, 1975; Maynard Smith, 1978a; Bell, 1982; Stearns, 1987a; Otto, 2009).

Like Birdsell and Wills (2003), I follow the example of Margulis and Sagan (1986) that defined sex in the broadest sense to include any natural process that combines genes from more than a single source in an individual cell. This definition of sex thus includes any horizontal transmission of genetic materials in natural environments and includes conventional sex in eukaryotes that involves cell fusion and meiosis; genetic exchange among viral particles; and prokaryotic sex such as transformation, transduction, and conjugation. To avoid confusion, recombination is defined as breakage and reunion of genetic materials in genomes (DNA or RNA) and includes both crossing-over and independent assortment. Reproduction refers to processes that replace or increase the number of cells or organisms in populations (Xu, 2004a).

The main difficulty with the evolution of recombination is that parents who survive to reproduce have a genotype that works under local environmental conditions. Tinkering with their offsprings' genotypes

by recombination risks making the situation worse, with little hope of making it better (Otto and Michalakis, 1998). This idea underlies the Reduction Principle: in a constant environment without mutation, only modifier alleles that reduce recombination can invade a randomly mating population at equilibrium (Feldman, 1972; Charlesworth, 1976; Barton, 1995; Feldman et al., 1997; Otto and Michalakis, 1998). Lower recombination rates evolve whenever there are genetic associations among loci (linkage disequilibria), whether these are positive or negative (Feldman, 1972; Charlesworth, 1976; Barton, 1995; Feldman et al., 1997). Hypotheses for the maintenance of sex can be grouped into three main categories (Kondrashov, 1993; West et al., 1999; Birdsall and Wills, 2003; Hörandl, 2009; Otto, 2009): (1) The ecological theories posit sex as an effective way to create genetic variation in the offspring, which allows for a faster adaptation to environmental variability (for example, Burt, 2000). (2) The genetic theories consider sex as a restoration mechanism for damage of DNA strands, or mutational or epimutational change of the genome; here the main arguments are that meiosis would provide a tool for repair of double-strand breaks (e.g., Bernstein et al., 1988; 1989; Michod, 1995) or would restore DNA methylation patterns (for example, Holliday, 1984). Moreover, sex, allowing for recombination and segregation, is thought to be advantageous because beneficial mutations that arise in different individuals can be united in the same genome and therefore offspring with above average fitness can be produced (Fisher, 1930; Muller, 1932). Recombination would also avoid a long-term accumulation of disadvantageous mutations; an asexual lineage cannot produce offspring with a lower mutational load than any previous generation (Muller's ratchet) (Felsenstein, 1974). In addition, recombination can break up negative epistasis and thus allows for a more efficient purging of deleterious mutations (Kondrashov, 1988; 1993). The latter two advantages are predicted to strongly outweigh the reproductive disadvantage of sexual reproduction. On the other hand, Muller's ratchet and Kondrashov's hatchet are predicted to drive unisexual lineages into extinction within 10^4 to 10^5 generations (Lynch and Gabriel, 1990). (3) A third group of hypotheses regards sex as a consequence of phylogenetic fixation, that is, a feature inherited from ancestors that organisms cannot get rid of. This model does not seek an advantage of sexual reproduction per se, but regards it as an 'imperative relic' inherited from eukaryotic ancestry (Margulis and Sagan, 1986). The latter theory implies that sex is maladaptive but for some evolutionary constraints cannot be lost. A variety of taxa that can reproduce both sexually and asexually

(see chapter 15.3.2) clearly refute this theory. Since I will show that sex is adaptive I will not delve into this theory that, moreover, has not found much support. Many modern authors argue for pluralistic approaches and combinations of ecological- and genetic-based models (Howard and Lively, 1994; 2002; West et al., 1999; Pound et al., 2004; Ben-Ami and Heller, 2005; Cooper et al., 2005; Bruvo et al., 2007; Hörandl et al., 2008; Hörandl, 2009; Neiman and Koskella, 2009; Park AW et al., 2010). However, no single theory has obtained unanimous support and the evolution and maintenance of sex remain unresolved (Birky, 2009; Otto, 2009; Colegrave, 2012; Hartfield and Keightley, 2012). Hypotheses concerning the phylogenetic history and age of asexual taxa have been especially controversial (Judson and Normark, 1996; Little and Hebert, 1996), due to the paucity of reliable phylogenetic data for clades with sexual and asexual species and the difficulty of inferring dates of speciation events. Ancient asexual taxa may yield critical clues to understanding the causes of the evolution of sex, as aspects of their genetics and ecology presumably differ from shorter-lived asexuals in ways that indicate the selective advantages of asexual and sexual systems (Judson and Normark 1996).

Recently, I published a paper explaining the ecological-evolutionary causation of aging (Heininger, 2012). I could show that aging/death and reproduction are co-selected. I urgently advise the reader of this paper to make himself familiar with some of the concepts in this paper, e.g. the limited resources paradigm, the germ-soma conflict and its Red Queen coevolutionary dynamics.

Referring to "The heritability hang-up" Feldman and Lewontin (1975) wrote: "There is a vast loss of information in going from a complex machine to a few descriptive parameters. Therefore, there is immense indeterminacy in trying to infer the structure of the machine from those few descriptive variables, themselves subject to error. It is rather like trying to infer the structure of a clock by listening to it tick and watching the hands". The hypothetico-deductive theories start from assumed laws or premises taken from population genetics and make inferences concerning the operation of sexual reproduction.

According to Bell (1982), robust evaluation of alternative hypotheses for the evolution of sex and asexuality requires integration of phylogenetic, biogeographic, ecological and genetic data. Thus, my approach is to open the clock to observe the gearwheels in the clockwork and infer general principles or rules from these specific facts. I look at

the triggering event(s) and the processes that evolution “devised” to reach a goal. With this approach I try to reconstruct the evolutionary rationale behind the phenomenon starting from unicellular organisms and tracing the phylogenetic path along which patterns unfold. Most importantly, this approach is based solely on empirical and experimental observations (documented by more than 8,500 references) instead of assumed laws or premises as is inherent to approaches based on population genetics (see chapter 18.1). My approach has provided compelling evidence for the co-selection of reproduction and death and the programming of aging (Heininger, 2012).

In the following, I will elaborate a comprehensive theory explaining the evolutionary roots and mechanisms underlying the evolutionary success of sexual reproduction. The complexity of the causation and regulation of sexual reproduction is reflected by the argumentation and hence the paper is no easy reading. I have tried to assist the reader by providing short summaries at the beginning of the main chapters. This assistance may abet a rather saltatory style of reading with intermittent full text reading depending on the reader's focus of interest. Taking the potentially saltatory style of reading and the complexity of the topic into account there is some inbuilt redundancy of argumentation both to keep track and stress the consistency and consilience of data.

2. An ecological definition of stress

Knowledge is the object of our inquiry, and men do not think they know a thing till they have grasped the 'why' of it (which is to grasp its primary cause).

Aristotle

Summary

An ecological definition of stress should make a distinction between a stressor (external factor), stress (an internal state brought about by a stressor), and stress response (a cascade of internal and external changes triggered by stress). Stress is here defined as an environmental condition to which organisms are poorly adapted and that reduces Darwinian fitness. What is perceived as stressor depends on the evolutionary and ecological history of an organism, a change in the usual environmental conditions for any given life form.

The daily routines of animals and humans alike

include nutritional inputs to maintain normal activities and to anticipate additional requirements (e.g., breeding, migrating, acclimating to cold and heat, etc.) during the day–night cycle and the seasons. These homeostatic mechanisms, including functional and structural changes in brain and body, allow the individual to maintain physiological and behavioral stability despite fluctuating environmental conditions. (Throughout this work, when not specified otherwise, environmental conditions will refer both to abiotic and biotic conditions.) It is more than an empty tradition when dealing with stress to engage the problem of definition (Greenberg and Wingfield, 1987). The stress concept means too many things to too many workers to do otherwise, and clearly definition can set the research agenda. In common usage, stress usually refers to an event or succession of events that cause a response, often in the form of “distress” but also, in some cases, referring to a challenge that leads to a feeling of exhilaration, as in “good” stress. But, the term “stress” is full of ambiguities. It is often used to mean the event (stressor) or, sometimes, the response (stress response). Furthermore, it is frequently used in the negative sense of “distress”, and sometimes it is used to describe a chronic state of imbalance in the response to stress (McEwen and Wingfield, 2003; Romero et al., 2009; Koolhaas et al., 2011). The definition of Hoffmann and Parsons (1991) is widely used that defined stress as an ‘environmental factor causing a change in a biological system, which is potentially injurious’. An ecological definition of stress should make a distinction between a stressor (external factor), stress (an internal state brought about by a stressor), and stress response (a cascade of internal and external changes triggered by stress) (Parker et al., 1999; van Straalen, 2003). Stress is here defined as an environmental condition to which organisms are poorly adapted and that reduces Darwinian fitness (Sibly and Calow, 1989; Zhivotovsky, 1997). Optimal stress responses are those that maximize Darwinian fitness (Sibly and Calow, 1989). Stressful local ecological processes to which organisms are by definition poorly adapted, possibly associated with colonizations and introductions, include exposure to: (1) a novel host, infectious agent, or limited food resource; (2) new, variable or unpredictable biophysical environments; (3) a new predator community; and (4) a new coexisting competitor (Reznick and Ghalambor, 2001). Stress, in any form, exerts strong (co)evolutionary pressures on all organisms. To survive, any organism must develop tolerance, resistance or avoidance mechanisms. Tolerance allows the organism to withstand the challenge unharmed. Resistance involves active

countermeasures, while avoidance prevents exposure to the stressors. In addition to ecological stressors, internal stresses, such as spontaneous gene mutations or aberrant cell division might cause adverse effects on metabolic or genetic regulation.

Selye (1936) was the first to recognize the relative uniformity of the general stress response (GSR) (that he dubbed "general adaptation syndrome") to diverse stressors. The evolutionarily highly conserved GSR has been studied extensively in yeast, animals and plants (Kültz, 2003; 2005; Fujita et al., 2006). At the cellular level, the GSR results in oxidative and nitrosative stress as the final common pathway and a response pattern including heat shock protein expression (Lindquist, 1986; Sanchez et al., 1992; Finkel and Holbrook, 2000; Mikkelsen and Wardman, 2003; Sørensen et al., 2003). Most importantly, stress is not only an attribute of the stressor (the environmental component), but also an attribute of the stressed (the biological component). What is perceived as stressor depends on the evolutionary and ecological history of an organism, a change in the usual environmental conditions for any given life form. A certain environment may be claimed as stressful only if considered with respect to both a given population and the environment in which the population has evolved (Zhivotovsky, 1997; Bijlsma and Loeschcke, 2005). It follows that while a specific condition (e.g., a temperature of 65°C) may be stressful (or even lethal) to a certain species that normally lives at 37°C, it will be optimal for growth to a thermophilic organism (Conway de Macario and Macario, 2000). As an extreme example, the deep-sea barophilic hyperthermophile *Thermococcus barophilus* obviously experiences stress when grown under atmospheric pressure (Marteinsson et al., 1999). Similarly, abundant resources are stressful for human populations that have been selected for their thrifty genotype (Neel, 1962; Editorial (1989); Hales and Barker, 1992; Allen and Cheer, 1996; Fernández-Sánchez et al., 2011).

3. Reproduction in a world of limited resources

Of the ecological forces that shape evolution of life histories, competition seems particularly important. When competition is absent, those genotypes which reproduce more rapidly and prolifically are favored; when resources are limiting the advantage goes instead to those best able to compete.

Taylor and Condra (1980)

Summary

Traditional concepts with their "all else being equal" scenarios emphasize the twofold costs of sex. The implicit assumption of these scenarios is the unlimited availability of resources. A resource-rich, noncompetitive, r-environment selects for traits that enhance population growth rate, including early maturity, small body size, high reproductive effort, and high fecundity. However, most habitats are resource-limited. Resource-limited, competitive, K-environments select for traits that enhance persistence of individuals, including delayed maturity, large body size, high investment in individual maintenance at the cost of low reproductive effort, low fecundity with a large investment in each offspring, and longer lifespan. In resource-limited habitats quality of offspring is more important than quantity and individuals that invest into more competitive individuals are selectively favored. Thus, in resource-limited habitats, offspring quantity-quality trade-offs are observed in sexually reproducing plants and animals. Underscoring the self-containment of reproduction, reproductive activity is self-limited by negative feedback loops in sexually reproductive organisms.

Dobzhansky notoriously said in 1964: "Nothing in biology makes sense except in the light of evolution." This was supplanted half a century later by Grant and Grant's (2008): "Nothing in evolutionary biology makes sense except in the light of ecology." Pelletier et al. (2009) followed with "Nothing in evolution or ecology makes sense except in the light of the other," and this sentiment is pretty much where we are today (Schoener, 2011). Kokko and Lopez-Sepulcre (2007) call this "ecogenetic feedback": "If density influences everyone's reproductive prospects to the same extent, one has merely restated the ecological concept of density dependence. But if density variation has a differential effect on individual fitness depending on...phenotype, we have a feedback loop. In this loop, individual behavior or life history, influenced by genes, has an effect on population dynamics...and the resulting change in population dynamics in turn...[may] differentially favour...[certain] genotypes...in the population....".

According to Mallet (2010), the earliest ecologists to investigate competition were motivated by an interest in Darwin's 'struggle for existence,' or natural selection (Gause 1934; Scudo and Ziegler 1978), but later ecologists focused mainly on population densities of competing species. In contrast, the originators of

population genetic theory, Ronald A. Fisher, J.B.S. Haldane and Sewall Wright, based their theories on population ecology, but generalized selection almost exclusively in terms of gene frequencies within species. As a result, textbooks today treat population ecology and evolution by natural selection as almost entirely separate topics. This separation is reasonable if gene frequencies and population density do not interact. However, interaction is likely: selection is caused by differences in fertility and survival, the same parameters that affect population density (Mallet, 2010).

Competition among species closely resembles natural selection among genotypes, so it ought to be possible to build theories of population genetics equivalent to ecological competition. However, efforts to unify ecology and evolution have been frustrated because theories of population growth and competition conflict with common sense about evolution. In particular, ecological theory seems to demand that genotypes with the highest carrying capacities K will be fitter, while intrinsic growth rate r does not affect the outcome (MacArthur, 1962; Roughgarden, 1971); meanwhile classical evolutionary theory employs r as the basis of fitness (Fisher, 1930).

Traditionally, hypotheses for the evolution and maintenance of sex have been grouped into ecological and genetic theories (West et al., 1999; Birdsell and Wills, 2003; Hörandl, 2009; Otto, 2009; Hartfield and Keightley, 2012), reflecting the scientific divide between ecology and population genetic theory. Many previous theories and studies of the evolution of sex have implicitly assumed infinite populations that have access to limitless resources (Ackerman et al., 2010). Limited resources, however, are a pervasive selective force (Heininger, 2012). Classical concepts with their "all else being equal" scenarios emphasize the twofold costs of sex (Maynard Smith, 1971a; 1989; Jokela et al., 1997; Peck et al., 1999), but, ignoring the selective force of limited resources, are flawed from their basic assumptions. It is assumed that asexuals would produce twice as many offspring capable of reproducing than the sexual individuals, and would soon dominate the population. Tacit implication of this assumption (only realized by man-made culture conditions) is the inexhaustibility of resources. Indeed, this may happen when scientists introduce asexual mutants into cultures of sexual organisms such as yeast, algae or some rotifers (Hayden, 2008). But even with unlimited resources this assumption is not always correct. Sexual and asexual *Potamopyrgus* snails had an almost identical reproductive output (Jokela et al., 1997). Lamb and Willey (1979) reported

lower hatching rates in parthenogenetic *Drosophila*. In reptiles, a study comparing sexual and parthenogenetic *Aspidocelis* lizards found no difference in fecundity between the two reproductive forms (Congdon et al., 1978), while asexual geckos (*Heteronotia*) have a 30% smaller size-corrected fecundity as compared to several sexual congeners (Kearney and Shine, 2005).

In this chapter, I will gauge how realistic this assumption is in the wild. Intriguingly, this resource allocation argument (Uyenoyama, 1984) has been rarely discussed in the context of ecological resource availability.

Since Darwin, it has been one of the central tenets of evolutionary theory that organisms maximize their fitness including their reproductive output (Darwin 1859; Dawkins 1976; Dennett 1995; Grafen, 1999). However, organismal fitness as measured by reproductive success is not relatively constant from generation to generation but is density- and time-scale-dependent (Goodnight et al., 2008). The short-term reproductive success of a genotype does not necessarily correspond to its long-term success (Rauch et al., 2002). There are evolutionary scenarios that may favor some kind of reproductive self-restraint. Self-limitation of reproduction attenuates the oscillations predicted by the Lotka-Volterra equation, stabilizes populations and prevents their extinction (Mitteldorf et al., 2002; Rauch et al., 2002; 2003; Killingback et al., 2006; Mitteldorf, 2006; 2010; Goodnight et al., 2008). The feedback between exploitation and extinction is seen to have the effect originally proposed as the "prudent predator" concept (Slobodkin, 1961). Modern concepts advocate optimization of reproduction instead of maximization as "sound" evolutionary strategy (de Magalhães and Church, 2005; Grafen, 2006). In fact, a multitude of genes operate to limit the reproductive potential of organisms (Heininger, 2012). Gonadal hormones both advance and limit reproductive activity (see chapter 3.1).

The concept of density-dependent natural selection was proposed in the original r/K -selection model (MacArthur and Wilson, 1967; Pianka, 1970; Boyce, 1984). The terms refer to the suggestion that r -selection will increase r (the instantaneous growth rate), whereas K -selection will increase K (the equilibrium size, usually called the carrying capacity) (Armstrong and Gilpin, 1977). This classification has been of enormous heuristic value in ecology, although it is of only limited value in describing nature (Begon and Mortimer, 1986; Rogers, 1992). (Dawkins [1982] observed that "ecologists enjoy a curious love/hate

relationship with the r/K concept, often pretending to disapprove of it while finding it indispensable"). The central idea of r - and K -selection is that populations living in environments imposing high density-independent mortality (r -strategists) will be selectively favored to invest into population growth while populations living in environments imposing high density-dependent regulation (K -strategists) will be selectively favored to invest into more competitive individuals (Gadgil and Solbrig, 1972). Even under nearly ideal conditions in the laboratory, the maximum value of r which can be attained is greatest for small organisms and declines with increasing size (Blueweiss et al., 1978; Bell and Koufopanou, 1991). Lotka-Volterra competition seems to demand that species or genotypes with the highest carrying capacities K will be fitter. The intrinsic growth rate r does not affect the outcome of competition. At the same time, classical evolutionary theory uses r as a measure of fitness (Fisher, 1930; Mallet, 2010). MacArthur (1962) provided genetic models of how density-dependent selection should act and concluded that in equilibrium populations, "the carrying capacity, K , replaces fitness (r) as the agent controlling the action of natural selection". A resource-rich, noncompetitive, r -environment selects for traits that enhance population growth rate, including early maturity, small body size, high reproductive effort, and high fecundity. Conversely, resource-limited, competitive, K -environments select for traits that enhance persistence of individuals, including delayed maturity, large body size, high investment in individual maintenance at the cost of low reproductive effort, low fecundity with a large investment in each offspring, and longer lifespan. These alternative constellations of life-history traits became known as life-history strategies (Pianka 1970; 1974a; Reznick et al., 2002).

The basic premise of density-dependent selection theory is that genotypic fitness is a function of population density (Joshi et al., 2001). Thus, for populations at low densities well below carrying capacity, natural selection favors genotypes with the highest value of r . In populations at carrying capacity, genotypes with the highest value of K are favored. Recent theoretical studies have shown that the presence of males can incur a considerably less than twofold cost on population growth for sexual populations at density-dependent carrying capacity (Doncaster et al., 2000; Kerszberg, 2000; Pound et al., 2002; 2004; Tagg et al., 2005a; b). Small advantages in competition for the sexual population are sufficient to halt the invasion of asexual mutants. The asexual competitors then exert a weaker inhibitory effect on the carrying capacity of the sexual population than

they exert on their own carrying capacity through intraspecific competition. The stable outcome is coexistence on a depleted resource base, both locally and regionally (Doncaster et al., 2000; 2003). Under these ecological conditions the sexual population eventually may drive out the asexual competitor by virtue of the longer-term benefits to its inherent genetic variation (Pound et al., 2004). This is a general treatment of ideas present in earlier models of 'sib-competition' (the 'Tangled Bank' of Bell, 1982; Koella, 1988) and niche differentiation (the 'Frozen Niche Variation Hypothesis' of Vrijenhoek, 1979). The recent theory differs from those models by calibrating the competition between sexual and asexual types against competition within each type, using the conceptual framework of classical Lotka-Volterra dynamics (Pound et al., 2002; Tagg et al., 2005a; b). Adler and Levins (1994) predicted that viability selection (= offspring fitness) would become more important than fecundity selection as the level of intraspecific competition increased (e.g. in K -selected populations), and a number of subsequent studies (Mappes et al., 2008) have provided empirical evidence in support of this prediction. Obligate parthenogens may have a higher mortality than their sexual counterparts (Roth, 1974; Corley and Moore, 1999; Kramer and Templeton, 2001). Reduced fitness in terms of fertility and/or offspring survival of asexual populations in comparison to sexual populations (Lamb and Willey 1979; Lynch, 1984; Corley and Moore, 1999; Weinzierl et al., 1999) has been observed.

The concept of density-dependent selection affecting the evolution of demographic traits was apparent to Salisbury (1942), Dobzhansky (1950), and Fisher (1958). According to Bolnick (2004), density and frequency dependence of fitness results in a dynamic landscape: a fitness "sphagnum bog" (Rosenzweig, 1978). A key driver of frequency-dependent fitness is intraspecific competition (Milinski and Parker, 1991; Doebeli and Dieckmann, 2000). The fitness landscape shifts between stabilizing and directional selection at low density to disruptive selection at high density (Svanbäck and Persson, 2009). If the fitness of each phenotype depends on its frequency in the population — that is, if fitness is frequency dependent — then the fitness landscape will be dynamic and the mean phenotype will be kept in a fitness valley, allowing for persistent disruptive selection. Strong competition between similar phenotypes (e.g. parents and offspring or individuals in a clonal population) can disproportionately affect the most abundant (mean) phenotype even though it may be adapted to the most abundant resource. Rarer consumer phenotypes may

have fewer resources available, but also have fewer competitors with which to share those resources, so their overall fitness is relatively high. In K-selected environments (MacArthur, 1962), frequency- and density-dependent selection regimes may be highly dynamic thereby favoring sexual reproduction mode. In competitive coevolution, evolution proceeds towards a so-called evolutionary branching point, where selection becomes disruptive and splits the population into two strategies. Coevolution of these strategies eventually leads to the extinction of one of them (Kisdi et al., 2001). Disruptive selection due to frequency-dependent fitness may not only be the causal agent in the evolution of ecological variation and speciation but may equally have been operative in the selection of postreproductive aging and death (Heininger, 2012).

Accordingly, in a broad range of animal and plant taxa differences in yearly survival affect fitness disproportionately more than differences in yearly fecundity, even in many exponentially growing populations, reinforcing the notion that it may be more important to measure survival than fecundity as a single surrogate of population growth (Pfister 1998; Crone, 2001; Burns et al., 2010). Taken together, the twofold costs of reproduction may have to be paid in r-selected habitats, but in K-selected organisms fitness of the progeny plays a larger role than reproductive output. Many mammals, birds, fishes and insects are found living at densities at the carrying capacity of their environments (Sibly et al., 2005; Brook and Bradshaw, 2006). Populations of vertebrate and invertebrate taxa are in general regulated by the production of adult individuals being a decreasing function of population density (Klomp, 1964; Tanner, 1966; Harrison, 1995; Myers et al., 1995; Kuang et al., 2003; Sibly et al., 2005; Bassar et al., 2010) which explains the relative stability of animal populations that do not increase at rates their fertility would allow.

Reviewing parthenogenetic reproduction in the animal kingdom and in the protists, Bell (1982, 1988a) concluded that the best predictor of the initiation of sexual reproduction in species with intermittent mixes is scarcity of resources. For instance, when supplied with sufficient nutrients, yeast cells reproduce vegetatively (asexually), but if starved they undergo the process of meiosis, producing four spores that are functionally equivalent to the gametes involved in sexual reproduction. These spores then fuse in pairs to produce the next generation of vegetative cells (Berry, 1982; Hoekstra, 2005). Under various food levels, the cyclical parthenogenetic rotifer *Brachionus plicatilis* flexibly changes its reproductive patterns and

lifespans. In a food-rich environment, *B. plicatilis* produces approximately 30 offspring during its lifespan of approximately 10 days. In contrast, with limited resources it suppresses active reproduction and produces less than 10 offspring, while surviving for nearly a month (Yoshinaga et al., 2000; 2003). Offspring quality (starvation resistance) also increases when *B. plicatilis* reproduces in a food poor environment (Yoshinaga et al., 2001). There are several documented cases of *Brachionus* strains that have permanently lost the ability to reproduce sexually (Boraas, 1983; Buchner, 1987; Bennett and Boraas, 1988; Fussmann et al., 2003; Stelzer, 2008; 2011; Stelzer et al., 2010). Boraas (1983) found that newly established cultures of *Brachionus calycifloru* collected from the field produced 40% mictic (sexual) females when induced. After 2–3 months in a chemostat, i.e. with unlimited resources, that percentage was reduced to 0 in similarly inducing environments. This work has been confirmed (Bennet and Boraas, 1989; Fussmann et al., 2003), establishing the costs of sex under unlimited resources (Stelzer, 2011). Similar resource-dependent mechanisms appear to operate within sexually reproducing populations. Population density and fecundity are inversely correlated in a multitude of populations (Clarke, 1955; Christian, 1961; French et al., 1965; Tanner, 1966; Dahlgren, 1979; Clark and Feldman, 1981; Reznick and Endler, 1982; Albon et al., 1983; Andersen and Linnell, 2000; Bonenfant et al., 2009). MacArthur and Wilson (1967) predicted that increased intraspecific competition will select for increased investment of resources in somatic growth, a decreased rate of investment in reproductive tissues, and a tendency to produce fewer, larger and hence more competitive offspring. Supporting this concept, in populations in resource-limited habitats, offspring quantity-quality trade-offs are observed in sexually reproducing plants and animals (Salisbury, 1942; Lack, 1947a; MacArthur and Wilson, 1967; Harper et al., 1970; Smith and Fretwell, 1974; Perrins and Moss, 1975; Gustafsson and Sutherland, 1988; Dijkstra et al., 1990; Hardy et al., 1992; Koskela, 1998; Badyaev and Ghalambor, 2001; Blanckenhorn and Heyland, 2004; Mappes and Koskela, 2004; Charnov and Ernest, 2006; Hagen et al., 2006; Gillespie et al., 2008; Walker et al., 2008; Meij et al., 2009) and also in asexually reproducing organisms (Marshall et al., 2006). Similarly, evolution favors r-selected reproductive strategies at lower population densities and K-selected strategies at the carrying capacity (Sinervo et al., 2000). A test of concept is available within the field conditions experienced by *Daphnia pulex*. Sexuials might suffer the cost of males in the r-selected environment at the

beginning of the season, when resource competition is low; accordingly, reproduction is asexual. But when conditions deteriorate as the population approaches carrying capacity, sexuals seem to be better competitors in spite of male production (Wolinska and Lively, 2008). Ecological studies in aquatic meiobenthic communities including ostracods and copepods revealed that dominance is dependent on tolerance to environmental conditions in the broadest sense, including competitive abilities, and not on the rate of increase, hence not with fertility or generation time (Heip, 1977). In 21 species of woody plants and 45 herbaceous perennials progression to later stage classes, e.g. recruitment and growth, was more important than fecundity in almost all species (Silvertown et al., 1993). In laboratory microcosms where resources declined with time, density of parthenogenetic oribatid mite taxa suffered more from resource limitation than sexual species (Domes et al., 2007). Conversely, sexual processes such as outcrossing are abandoned in favor of inbreeding and parthenogenesis if resources are in ample supply (Hamilton, 1967; 1993; Bell 1982; Knowlton and Jackson, 1993; Scheu and Drossel, 2007; Song et al., 2012). In uniform, resource-rich, agricultural environments parthenogenetic reproduction might be favored over sexual reproduction in pest invertebrates (Corrie et al. 2002, Hoffmann et al., 2008).

Taken together, resources are the limiting factor to population growth. It should not come as a surprise that limited resources also can annihilate the theoretical twofold cost of sex and shape the ecological balance of sexual/asexual reproduction. In populations at or near their habitat carrying capacity, quality rather than quantity, offspring fitness rather than parent fertility is evolutionarily favored. That sexually reproducing organisms that allegedly already pay a twofold cost, further reduce their reproductive output (increasing their putative competitive disadvantage) to produce fitter progeny in more competitive environments argues in favor of the quantity-quality trade-off in reproductive strategies. The twofold cost of sexual reproduction, if at all, may only be realized under r-selected, resource-rich ecological conditions (see chapter 15).

3.1 Germline-derived signals limit the soma's reproductive potential

The legendary "twofold cost of sex" (Maynard Smith, 1978a) is a logical consequence of classical evolutionary thinking that evolution selects for organisms that maximize their fitness and reproductive output (Darwin 1859; Dawkins 1976; Giesel, 1976; Dennett 1995; Grafen, 1999). As Finch and Holmes

(2010) put it: "...under most circumstances selection is expected to eliminate germline mutations that decrease reproductive success or are otherwise detrimental to genetic fitness". Within this conceptual framework it is counter-intuitive that reproductive activity should be self-limited in sexually reproductive organisms. In fact, the female reproductive aging process is dominated by a gradual decrease in both the quantity and the quality of the oocytes residing within the follicles present in the ovarian cortex (te Velde and Pearson, 2002; Broekmans et al., 2009). Oxidative stress, at least in part mediated by gonadal hormones, is a hallmark of gametogenesis and a variety of other sexual reproduction-related events (Riley and Behrman, 1991; Heininger, 2001; Agarwal et al., 2005; Felty et al., 2005; Fujii et al., 2005; Nedelcu, 2005; Metcalfe and Alonso-Alvarez, 2010; Shkolnik et al., 2011; Rizzo et al., 2012). Oxidative stress is involved in granulosa cell estrogen and progesterone production (LaPolt and Hong, 1995; Yacobi et al., 2007) and estrogen-mediated oocyte maturation (Tarin et al., 1998; Behrman et al., 2001) but, on the other hand, appears to contribute to ovarian senescence (Tarin et al., 1998; Behrman et al., 2001; Miyamoto et al., 2010). Ovulation induces ROS generation in the ovaries that is an essential preovulatory signaling event for proper ovulation (Miyazaki et al., 1991; Shkolnik et al., 2011). Repeated exposure of stored oocytes to ROS at each ovulation results in oxidative damages, measured by 8-hydroxydeoxyguanosine levels in oocytes of the follicle pool (Chao et al., 2005; Miyamoto et al., 2010; Lim and Luderer, 2011), declining antioxidant defenses (Lim and Luderer, 2011), oocyte quality, and size of the ovarian follicle pool (Imai et al., 2012). Proapoptotic Bax is a key component of mitochondrial oxidative stress-mediated apoptotic pathways (Le Bras et al., 2005; Orrenius et al., 2007; Circu and Aw, 2010). Ovarian lifespan can be extended by selectively disrupting Bax function (Perez et al., 1999) suggesting a causal role of oxidative stress in ovarian aging (Miyamoto et al., 2010). The decrease in follicle numbers because of aging reinforces aberrant hormonal regulation as a result of impaired negative feedback mechanisms of the hypothalamic-pituitary-ovarian axis. Decreasing numbers of follicles in the ovaries result in decreasing concentrations of circulating estrogens and inhibins during aging (Broekmans et al., 2009).

In testicular Leydig cells, steroidogenesis is associated with aging of the steroidogenic capacity. In male reproductive senescence, Leydig cells, the testicular cells responsible for testosterone production, become steroidogenically hypofunctional (Zirkin et al., 1997).

Oxidative stress, although indispensable for spermatogenesis (Chainy et al., 1997), may play a causal role (Myers and Abney, 1988; Peltola et al., 1996; Zirkin et al., 1997; Chen et al., 2001; Desai et al., 2009) as evidenced by the prevention of Leydig cell aging following the suppression of Leydig cell steroidogenesis (Chen and Zirkin, 1999; Zirkin and Chen, 2000) and culturing Leydig cells with vitamin E, or administering vitamin E to rats (Chen et al., 2005). Cyclooxygenase-2, whose gene expression is up-regulated by many pathological and stress-related factors, including reactive oxygen (Turini and DuBois, 2002) is a putative mediator of the age-related decline in testosterone biosynthesis (Wang et al., 2005). Thus, testosterone-induced oxidative stress in the testes appears to advance the aging of the male reproductive organ (Luo L et al., 2006; Desai et al., 2009).

Reproductive activity not only has progeroid effects at the gonadal level but also degenerates the hypothalamic-pituitary axes. Both pro-oxidant and anti-oxidant effects of estrogens might involve different estrogen receptors that can have either genomic or non-genomic action to manifest further hormonal response (Kumar et al., 2010). The progeroid actions of estrogens appear to depend on neuronal cell types, ratio of different types of estrogen receptors present in a particular cell and context specificity of the estrogen hormone responses (Nilsen, 2008; Kumar et al., 2010). Specifically, estrogens, although neuroprotective at short term (Heininger, 1999), induce degenerative changes in cholinergic basal forebrain neurons upon chronic replacement (Gibbs, 1997). The neurotrophic/neuroinhibitory dualism of estrogens has also been described in hypothalamic slices and cell cultures (Bueno and Pfaff, 1976; Rasmussen et al., 1990); the neurotrophic actions presumably operate in cells regulating reproductive behavior while aging-pacemaker neurons may be targets of the toxic actions. Aging is associated with a disruption of hypothalamic catecholaminergic networks which engender the aging of the somatotrophic, thyrotrophic and gonadotrophic axes (Meites, 1990; Wise et al., 1997). Evidence indicates that estrogens contribute to the derangement of hypothalamic catecholaminergic rhythmicity and function (Wise et al., 1997; Legan and Callahan, 1999). Moreover, gonadal steroids are degenerative and cytotoxic in a variety of hypothalamic nuclei (Schipper et al., 1981; Brawer et al., 1983; 1993; Yang et al., 1993), incite loss of arcuate nucleus synapses (Leedom et al., 1994), actuate the oxidative stress-mediated degeneration of beta-endorphin neurons in the arcuate nucleus (Brawer et al., 1993; Desjardins et al., 1995) and elicit neuronal and glial stress reactions (Day et

al., 1993; Seifer et al., 1994; Mydlarski et al., 1995; Krebs et al., 1999). As a result, estrogens exert a self-limiting feedback control of reproductive activity by degenerating the HPG axis. The degeneration of the HPG axis by gonadal hormones not only promotes reproductive aging but has also systemic progeroid effects. Prepubertally ovariectomized mice that received young transplanted ovaries at 11 months showed a 40% increase in life expectancy, relative to intact controls. The 11-month-old recipient females resumed estrus and continued to cycle for several months past the normal point of reproductive senescence (Cargill et al., 2003). Estrogens and other ovarian factor(s) may also play a role in aging-related pituitary changes (Pasqualini et al., 1986; Telford et al., 1987). In a negative feedback loop, the aging-related activation of hypothalamic proinflammatory pathways inhibits the hypothalamic release of gonadotropin-releasing hormone and accelerates systemic aging (Zhang G et al., 2013). With the loss of negative ovarian feedback at the hypothalamic-pituitary level (MacNaughton et al., 1992; Burger et al., 1995; Landgren et al., 2004), follicle-stimulating hormone levels are elevated (Burger et al., 1995; Klein et al., 1996) which, in turn, accelerates the loss of follicles (McTavish et al., 2007). On the other hand, the increased length of male reproductive phase may, at least in part, depend on the protective action of testosterone against the neurotoxic action of estrogen on distinct hypothalamic neuron populations (Bloch and Gorski, 1988; Yang et al., 1993). As result of these actions, the reproductive phase is self-limited due to the multiple detrimental effects of gonadal steroids and reproductive activity-related oxidative stress on gonadal functioning and the HPG axis

4. The phylogenetic roots of sexual reproduction

In short, it seems certain — and here we must simply grit our teeth and swallow — that it is impossible to understand the function of sex without both a firm grasp of the rival hypotheses, their assumptions, logical development and consequences, and also a reasonably comprehensive knowledge of the nature, occurrence and correlates of sexual systems in nature.

Graham Bell, 1982

Summary

Cellular oxidative metabolism generates reactive oxygen species (ROS). ROS have both beneficial

and deleterious effects. Living organisms are heavily dependent on the signaling properties of ROS but, on the other hand, have developed specific mechanisms to contain the production and destructive effects of ROS. Oxidative stress is a state in which the production of ROS exceeds the capacity of the antioxidant defense systems in cells and tissues. Oxidative DNA lesions, if not repaired, possibly lead to mutagenesis and cell death. Environmental stress can alter the balance between stability/repair and mutagenesis. During microbial stress, mutation rates can be increased. Many bacterial species are capable of exchanging genetic material by three parasexual mechanisms: conjugation, transduction, and transformation as a means both to template-guide recombinational DNA repair or increase the genetic repertoire. The heritable incorporation of genetic information is a powerful mechanism of horizontal gene transfer. Microorganisms that are poorly adapted to the current environmental conditions gamble with their genome hoping to boost their fitness. Environmental stress is known to initiate sexual reproduction in a broad range of multicellular eukaryotic species that normally undergo asexual reproduction.

4.1 Oxidative and nitrosative stress, DNA repair and mutagenesis

The appearance of aerobic forms of life was an important step in evolutionary history, since oxygen consumption leads to the production of ten-fold more energy from glucose than does anaerobic metabolism. However, this process imposes constraints on cell viability, because of the generation of highly reactive intermediates, collectively referred to as reactive oxygen species (ROS) during respiration. For the complete reduction of an O_2 molecule, a transfer of four electrons is required to produce e.g. two molecules of water or equivalent compounds. The reduction of oxygen by less than four electrons generates unstable ROS. Intracellular ROS originate from multiple sites (Dikalov et al., 2007; Zinkevich and Gutterman, 2011), including the mitochondrial respiratory chain (Skulachev, 1996a; Ježek and Hlavatá, 2005), cytochrome P450 oxygenases (Fleming et al., 2001), nicotinamide adenine dinucleotide (NADPH) oxidase complexes, which include the Nox family (Altenhöfer et al., 2012), xanthine oxidase (McNally et al., 2003), lipid peroxidases (Zhang R et al., 2002), cyclooxygenases (Rowe et al., 1983; Boldyrev et al., 1999), and uncoupled nitric oxide (NO) synthase (NOS) (Vasquez-Vivar et al., 1998). Most of these enzymes

act in the mitochondria, which is the main source of oxidative stress. There is a functional connectivity between intracellular sites of ROS production. This cross talk has been termed ROS-induced ROS release and is supported by a variety of observations showing that ROS-induced ROS release is a common mechanism for ROS amplification and regional ROS generation (Zinkevich and Gutterman, 2011). For instance, a reciprocal activation of ROS-induced ROS release between mitochondria and NADPH oxidase can produce a feed-forward acceleration of ROS generation (Kimura et al., 2005; Lee SB et al., 2006; Hawkins BJ et al., 2007; Wenzel et al., 2008). NADPH oxidases are the only known enzyme family with the sole function to produce ROS (Altenhöfer et al., 2012) and induce the release of ROS produced by other enzymatic systems (Brandes and Kreuzer, 2005; Griendling, 2004) like xanthine oxidase (McNally et al., 2003). Approx. 90% of ROS arise in the mitochondria as byproducts of aerobic metabolism. Complex I (NADH dehydrogenase) and particularly complex III (cytochrome bc_1) are major sources of ROS (Boveris, 1977; Finkel and Holbrook, 2000; Ježek and Hlavatá, 2005). During mitochondrial respiration, 0.12 to 2% (in some reports even up to 5%) of the oxygen undergoes single electron transfer in vitro generating the superoxide anion radical ($O_2^{\cdot-}$) (Boveris and Chance, 1973; Boveris, 1977; Chance et al., 1979; Turrens, 2003; Harper et al., 2004; Orrenius et al., 2007; Murphy, 2009). However, these values cannot be extrapolated to the in vivo situation where mitochondrial $O_2^{\cdot-}$ production will be much lower (Murphy, 2009). This molecule shows limited reactivity but is converted to hydrogen peroxide (H_2O_2) by superoxide dismutase. H_2O_2 is not a free radical but in the presence of transition metals, such as iron and copper, is reduced to highly reactive hydroxyl radicals (OH^{\cdot}) (Loft and Poulsen, 1996). These ROS are potent oxidants of lipids, proteins, and nucleic acids (Halliwell and Gutteridge, 1984; Meneghini, 1988; Buettner, 1993). Living organisms have developed specific mechanisms to prevent the production and effects of ROS (Halliwell and Gutteridge, 1999). Oxidative stress is a state in which the production of ROS exceeds the capacity of the antioxidant defense system in cells and tissues (Sies, 1985; 1986; 1991; Davies, 1995; Finkel and Holbrook, 2000; Mittler, 2002; Slupphaug et al., 2003; Monaghan et al., 2009; Lushchak, 2011). The ROS-dependent inactivation of antioxidant enzymes can be expected to aggravate the dysregulation (Kono and Fridovich, 1982; Tabatabaie and Floyd, 1994; Kwon et al., 1998; Lee SM et al., 2001; Macmillan-Crow and Cruthirds, 2001; Alvarez et al., 2004). Nitric oxide (NO) is chemically rather unreactive

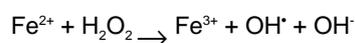
toward most bio-organic compounds but unstable in the presence of O₂ and ROS and will rapidly autoxidize to yield a variety of nitrogen oxide intermediates, some of which are potent nitrosating agents (Marletta, 1988; Williams, 1988; Bartsh et al., 1989; Huie and Padmaja, 1993; Packer et al., 1996; Szabo et al., 2007) that will produce mutagenic and carcinogenic nitrosamines (Wink et al., 1991; Laval and Wink, 1994; Wink and Laval, 1994; Tamir et al., 1996; Burney et al., 1999; Grisham et al., 2000). Moreover, mitochondria can act as a "redox signaling box," converting an NO signal into an ROS signal (Brookes and Darley-Usmar, 2002).

Initially, scientific interest was almost exclusively focused on investigating the destructive potential of oxidative stress. Increasingly, however, protein modification by oxidation/reduction is emerging as a critical mechanism for the modulation of protein activities, and the protective and creative actions of ROS signal transduction and their key role in cellular homeostasis have been recognized (Remacle et al., 1995; Lander, 1997; Finkel, 1998; Gamaley and Klyubin, 1999; Rhee, 1999; Thannickal and Fanburg, 2000; Heiningner, 2001; Dröge, 2002; Apel and Hirt, 2004; Forman et al., 2004; 2010; Pitzschke et al., 2006; Rhee, 2006; Veal et al., 2007; Janssen-Heiningner et al., 2008; Lane, 2011; Shapiguzov et al., 2012; Wong, 2012; Xie and Roy, 2012; Zarse et al., 2012). Because of these opposing and dose-dependent functions, the cellular level of ROS is likely to be subjected to tight regulation via processes involved in production, distribution and removal (Bienert et al., 2006). Compared with other ROS, H₂O₂ is a relatively long-lived molecule (1 ms) that is able to diffuse freely across cell membranes (Chance et al., 1979; Gutteridge, 1994; Bienert et al., 2006; but see Miller et al., 2010), making it the most prevalent ROS form (Mathai and Sitaramam, 1994). Due to their relatively low reactivity and long-range effects, H₂O₂ and superoxide qualify as messengers via (i) reversible modification of target protein molecules and (ii) changes of intracellular redox state (Finkel and Holbrook, 2000; Thannickal and Fanburg, 2000; Sauer et al., 2001; Neill et al., 2002; Van Breusegem and Dat, 2006; Bartosz, 2009). However, due to high concentrations of mitochondrial SOD, the intramitochondrial concentrations of O₂^{•-} are maintained at very low steady-state levels (Tyler, 1975) and mitochondria-generated O₂^{•-} is unlikely to escape into the cytoplasm. Serving various functions, cellular organelles maintain redox control unique to each compartment and may also influence membrane permeability to H₂O₂ (Makino et al., 2004; Hansen et al., 2006; Malinouski et al., 2011). Plasma membrane

was also shown to change H₂O₂ permeability under certain conditions (Antunes and Cadenas, 2000; Seaver and Imlay, 2001; Sousa-Lopes et al., 2004; Jang et al., 2012). Redox-sensitive cysteine residues are present in the interaction domains of many proteins. Enzymes that possess a highly reactive cysteine in either the catalytic centre or a regulatory site play a key role in the transmission of ROS signals (Barford, 2004; Forman et al., 2004). There are examples in all of the major categories of transcription factors, including basic region, leucine zipper, helix-loop-helix, and zinc finger (Webster et al., 2001). Proteins vulnerable to oxidation that can be reversed by thiol donors such as glutathione, glutaredoxin and thioredoxin, include transcription factors (such as the nuclear factor κ-B, activator-protein 1, hypoxia inducible factor, p53 and the p21 Ras family of protooncogenes), protein tyrosine kinase (PTKs), such as Src family kinases and some receptor tyrosine kinases (RTKs) and finally protein tyrosine phosphatases (PTPs), such as PTP1B, Low Molecular Weight-PTP, Src-homology-2 domain-PTP and PTEN (Lee et al., 1998; Chiarugi et al., 2001; Mahadev et al., 2001; Meng et al., 2002; 2004; Kwon et al., 2004; Chiarugi and Fiaschi, 2007). The activation of redox-regulated transcription factors such as NFκ-B and HSF1 may be selective for the type of oxidant, H₂O₂ being effective while superoxide is not (Schreck et al., 1992; Jacquier-Sarlin et al., 1995). Tyrosine phosphorylation/dephosphorylation in response to extracellular stimuli has been characterized most thoroughly (Cho et al., 2004; Fujii and Tsunoda, 2011). However, whereas both superoxide and hydrogen peroxide have low oxidative toxicity themselves and do not interact at all with DNA bases (Halliwell and Aruoma, 1991; Dizdaroglu, 1993), they are believed to elicit their toxicity to DNA by conversion to hydroxyl radicals mediated by transition metal ions (e.g. iron and copper) through Haber-Weiss and Fenton reactions (von Sonntag, 1987; Steenken, 1989). Superoxide and hydrogen peroxide are both components of the net Haber-Weiss reaction by oxidation of superoxide anion radical that readily produces hydroxyl radicals.

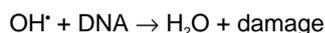


The main source of biological hydroxyl radicals is the metal-catalyzed breakdown of hydrogen peroxide by the Fenton reaction, one-half of the net Haber-Weiss reaction:



Both Cu⁺ and Fe²⁺ are capable of reacting with H₂O₂ to form OH[•] in vitro. However, Fe²⁺ is evidently the

coreactant *in vivo*, since cell-permeable iron chelators protect DNA from exogenous H₂O₂ (Imlay and Linn, 1988). The hydroxyl radical is highly reactive and is responsible for most of the damage incurred to biological macromolecules by ROS. Because of their short half life (less than 1 ns), hydroxyl radicals attack molecules very close to their site of formation (von Sonntag, 1987a; Halliwell and Gutteridge, 1999; Valko et al., 2004) and their very high reactivity makes them virtually impossible to scavenge (Halliwell and Gutteridge, 1999; Halliwell, 2007).



It has been demonstrated that the thiol groups of the cysteines involved in the zinc-finger motif as part of the metal-binding, DNA-intercalating fingers (Kadonaga et al., 1987; Desjarlais and Berg, 1992) confer gene regulation by ROS (Cimino et al., 1997). These zinc finger structures are potentially very sensitive redox targets in DNA binding motifs of many DNA transcription factors and DNA repair enzymes (Berg, 1992; Rhodes and Klug, 1993; Wu et al., 1996; Webster et al., 2001; Wilcox et al., 2001). Specifically, when redox iron displaces zinc ions in zinc-finger structures of DNA repair enzymes, it generates more aggressive free radicals.

Over 100 oxidative DNA adducts have been identified thus far; however, whether each of these adducts are produced in measurable amounts *in vivo* to be biologically relevant is unclear (von Sonntag, 1987b; Dizdaroglu, 1992; Demple and Harrison, 1994; Cadet et al., 2003). Among the oxidative DNA lesions, one of the major classes of DNA damage leads to at least 20 modifications in purine and pyrimidine bases, together with oligonucleotide strand breaks, DNA-protein cross-links and abasic sites, possibly leading to mutagenesis and cell death (Aitken et al., 1998a; Lopes et al., 1998; Halliwell and Gutteridge, 1999; Kemal Duru et al., 2000; Dizdaroglu et al., 2002; Sawyer et al., 2003; Sedelnikova et al., 2010). For instance, the number of oxidative lesions to DNA per cell per day, even without excessive exposure to DNA damaging agents, is estimated to be about 100,000 in rats and greater than 20,000 in humans (Fraga et al., 1990; Ames et al., 1993; Lindahl, 1993; Lindahl and Barnes, 2000; De Bont and van Larebeke, 2004) and is thought to contribute to carcinogenesis, aging and tissue damage following ischemia (Jackson and Loeb, 2001; Ma et al., 2008; Klaunig et al., 2010; Ralph et al., 2010; Sedelnikova et al., 2010). An analysis of the mutation spectrum suggests that there are at least four different pathways by which oxidative DNA damage leads to mutations (Feig et al., 1994): (i) chemical modification of nucleotide moieties in DNA causing an

alteration in their hydrogen bonding or "coding" specificity; (ii) damage-mediated exacerbation of polymerase-specific hot spots; (iii) damage-induced conformational change in the DNA template that prevents accurate replication by DNA polymerases (Hsu et al., 2004); (iv) induction of a DNA polymerase conformation that is error-prone. To overcome the potential problems to the functionality of DNA, essentially all organisms use a battery of DNA repair enzymes that identify the damaged site, and remove it with restoration of the original DNA sequence (Friedberg et al., 2006). Several DNA repair pathways are involved in maintaining cell genomic stability; these include direct repair (DR), base-excision repair (BER), nucleotide-excision repair (NER), mismatch repair (MMR), DNA double-strand break repair (DSBR), and post replication repair (PRR). More than 150 proteins are involved (Miles and Sancar, 1989; Luo M et al., 2010). Eukaryotic cells repair DNA double-strand breaks (DSBs) by at least two pathways, homologous recombination (HR) and non-homologous end-joining (NHEJ) (Shinohara and Ogawa, 1995). The best-studied transcriptional response to DNA damage is the bacterial SOS response (Friedberg et al., 1995; Walker, 1996; Storz and Hengge-Aronis, 2000; van der Veen et al., 2010). The SOS response involves two kinds of repair systems (Shapiro, 2011):

- A precise repair process that removes the UV-damaged DNA and does not introduce mutations. This "error-free" process operates very much like the mismatch repair proofreading system, except that the sensor protein recognizes the characteristic chemistry of UV damage in DNA rather than helix distortions. It is called excision repair because the result of damage sensing, as in mismatch correction, leads to excision of a section of the damaged DNA strand (Smith, 1978; Van Houten, 1990; Petit and Sancar, 1999).
- A mutagenic repair process that involves the synthesis of specialized "error-prone" DNA polymerases, which can replicate DNA that carries unrepaired damage. Without these specialized polymerases, mutations do not occur in response to DNA damage. Instead, the cells or molecules that cannot remove or replicate past the damage are simply doomed and produce no mutant progeny (Pham et al., 2001; Goodman, 2002; Wagner et al., 2002; Broyde et al., 2008).

A low concentration of H₂O₂ results in SOS gene induction in wild-type cells (Imlay and Linn, 1987; Goerlich et al., 1989). The regulon orchestrates cellular survival responses to a variety of stressors, mediates growth arrest, mutagenesis and resistance to DNA damage (Heininger, 2001; Aertsen and

Michiels, 2005). Environmental stress can alter the balance between stability/repair and mutagenesis/exploration/bet-hedging (Foster, 2005). Recombination frequency is markedly elevated by cellular stressors such as drugs, ionizing radiation, parasites, and heat shock, known activators of oxidative stress (Lebel et al., 1993; Lucht et al., 2002; Winn et al., 2003; Defoort et al., 2006). Stress-induced mutation mechanisms differ from those that produce classical spontaneous mutations, which occur with a definable relationship to cell generations in proliferating cells (Luria and Delbrück, 1943; Lea and Coulson, 1949). In an *E. coli* model, stationary-phase sigma factor RpoS (which encodes the stress response σ S transcription factor)-controlled switch from high-fidelity to mutagenic double-strand break repair activates stress-induced mutagenesis during stationary phase/starvation (Ponder et al., 2005). *B. subtilis* has similar stationary phase/starvation-dependent mutagenic programs (Robledo et al., 2007). Mutants that lack components of the SOS system are more sensitive to a variety of damaging agents (Imlay and Linn, 1987; Yonei et al., 1987; Escarceller et al., 1994; van der Veen et al., 2010). Higher levels of oxidative stress obviously favor mutagenesis (Greenberg and Demple, 1988; DeRose and Claycamp, 1991; McBride et al., 1991; Escarceller et al., 1994; Kato T et al., 1994; Blanco et al., 1995; Touati et al., 1995; Urios et al., 1995; Wang and Humayun, 1996; MacPhee, 1999; Ruiz-Laguna et al., 2000; Bjedov et al., 2003). Importantly, the repair/mutagenesis balance is modulated by interactions with heat shock proteins (Liu and Tessman, 1990a; b; Donnelly and Walker, 1989; 1992; Petit et al., 1994) which, in dependence of the cellular energy level may provide the regulatory feedback with cellular metabolic/oxidative homeostasis and its derangement during stress (MacPhee, 1985; 1994, 1996; Seetharam and Seidman, 1992; Keszenman et al., 2000). Oxidative stress is the final common pathway of responses to a multitude of biotic and abiotic stressors, including psychosocial stress (Lindquist, 1986; Sanchez et al., 1992; Finkel and Holbrook, 2000; Heininger, 2001; Mittler, 2002; Mikkelsen and Wardman, 2003; Sørensen et al., 2003; Apel and Hirt, 2004; Ardanaz and Pagano, 2006; Rollo, 2007; Miller et al., 2008; Slos and Stoks, 2008; Jaspers and Kangasjärvi, 2010; Steinberg, 2012; Choudhury et al., 2013).

4.2 Stress and microbial transformation

Bacteria multiply asexually by binary fission. Hence, bacteria are essentially clonal organisms. Under stressful conditions, mechanisms that increase genetic

variation can bestow a selective advantage. Bacteria have several stress responses that provide ways in which mutation rates can be increased (Bjedov et al., 2003; Hastings et al., 2004; Miller, 2005; Galhardo et al., 2007). These include the SOS response, the general stress response, the heat-shock response, and the stringent response, all of which impact the regulation of error-prone polymerases. Two classes of genes are known to accelerate mutation and/or recombination rates in bacterial populations: stress-inducible wild-type genes, usually part of the SOS regulon, and genes whose functional loss, or downregulation, increases the rate of genetic variability (mutator and/or hyper-rec mutants) (Radman et al., 2000). Stress-induced mutation appears to be a process by which cells can respond to selective pressure specifically by producing mutations (Foster, 2005; Miller, 2005). Many bacterial species are capable of exchanging genetic material by three parasexual mechanisms: conjugation, transduction, and transformation. Parasexuality is any process in which more than one parent participates, without meiosis and fertilization, which gives as a result a new cell (Heitman, 2006). The induction of genetic competence, the ability of cells to bind to and to take up exogenous DNA for food (Redfield, 1993b), evolved as a strategy used by bacteria to increase their genetic repertoire. Bacterial transformation, in which cells take up and recombine free strands of DNA, is a general response of bacteria to stress (Storz and Hengge-Aronis, 2000; Claverys et al., 2006; Singh et al., 2008). The heritable incorporation of this genetic information is a powerful mechanism of horizontal gene transfer. Genetic transformation is a widespread both natural and inducible feature of bacteria (Carlson et al., 1983; Dubnau 1991; Palmen et al., 1993; Lorenz and Wackernagel, 1994; Ogunseitán, 1995; Baur et al., 1996; Tortosa and Dubnau, 1999; Birdsell and Wills, 2003; Claverys et al., 2006; Singh et al., 2008). Competence for genetic transformation is under control of the SOS regulon, the bacterial master stress regulator (Yasbin et al., 1991; 1992; Cheo et al., 1993; Storz and Hengge-Aronis, 2000; Erill et al., 2007; Chiang and Schellhorn, 2010). As shown in computer simulations, bacterial transformation, which has been dubbed 'sex with dead cells' (Redfield, 1988), can increase the fitness of the recombinant progeny at equilibrium although the DNA taken up may be from cells killed by selection against mutations and may be of inferior genetic quality (Redfield, 1988; Hoelzer and Michod, 1991). The competence-regulatory apparatus senses and interprets environmental information and via an elaborate signal transduction system passes this information to the competence-specific

transcriptional machinery. Remarkably, these regulatory pathways play also a role in the expression of other post-exponential phenomena such as motility, sporulation, autolysis (Weinrauch et al., 1990; Dubnau, 1991; Grossman, 1995; Solomon and Grossman, 1996; Azoulay-Dupuis et al., 1998), stress resistance (Yasbin et al., 1991; 1992), recombination (Lovett et al., 1989) and "adaptive" mutagenesis (Radicella et al., 1995). Many stress responses are only pursued by discrete subpopulations of cells in a given bacterial community and are regulated as mutually exclusive events coordinated by integrated molecular switches and threshold phenomena (Msadek, 1999; Heininger, 2001; Tenaillon et al., 2001; Booth, 2002; Aertsen and Michiels, 2005; Foster, 2005; 2007; Fehér et al., 2012). However, conflict between these adaptive strategies may arise (Tenaillon et al., 2000; 2001). For example, stationary phase adaptive responses engage a highly interconnected network of signal transduction pathways which regulate motility (to exploit other carbon sources, flight), sporulation (differentiation to highly resistant, metabolically dormant spores), antibiotic production (cytocide), cannibalism, competence for DNA uptake (mating responses), stress resistance and mutagenesis (Love et al., 1985; Yasbin et al., 1991; 1992; Nunoshiba, 1996; Loomis et al., 1998; Perego, 1998; Msadek, 1999; Heininger, 2012). A stress-induced, fratricide-associated predatory mechanism may dramatically increase the efficiency of lateral gene transfer in *Streptococcus pneumoniae* and related commensal species (Prudhomme et al., 2006; Claverys and Håvarstein, 2007; Johnsborg et al., 2008; Johnsborg and Håvarstein, 2009). In a stressed *B. subtilis* colony only a minority of approximately 10-20% cells becomes competent (Somma and Polsinelli, 1970; Dubnau, 1982). Importantly, in subsequent starvation episodes, organisms carrying stress-induced genomic rearrangements exhibited a fitness advantage relative to the parental strain (Coyle and Kroll, 2008).

Sexual reproduction and eukaryotes probably evolved together (Cavalier-Smith, 2002), about 2.0–3.5 billion years ago (Miyamoto and Fitch, 1996; Gu, 1997). The frequency of sexual reproduction generally depends on the condition of an individual, called fitness-associated sex, a pattern found broadly across both facultatively sexual prokaryotes and eukaryotes (Bell, 1982; Hadany and Beker, 2003b; Hadany and Otto, 2007; 2009). Thus, organisms that are poorly adapted to the current environmental conditions, as part of a variety of stress-related responses, gamble with their genome hoping to boost their fitness (Dubnau and Losick, 2006; Veening et al., 2008a). Mutational alteration of genotype enables a sampling

of the 'sequence space' of the organism and increases the chances of natural selection acting on better adapted alleles (Sundin and Weigand, 2007). Individuals that are starved or deprived of other vital resources undergo sex in a wide variety of microorganisms, including bacteria (Dubnau, 1991; Redfield, 1888; 1993b; Jarmer et al., 2002; Foster, 2005), yeast (Kassir et al., 1988; Mochizuki and Yamamoto, 1992; Mai and Breeden, 2000; Abdullah and Borts, 2001; Davis and Smith, 2001; van Werven and Amon, 2011), and *Chlamydomonas reinhardtii* (Harris EH, 1989; Quarmby, 1994; Goodenough et al., 2007). In a variety of unicellular eukaryotic organisms e.g. *Dictyostelium*, asexual and mating behavior are alternative responses to metabolic stress (Saga and Yanagisawa, 1982; Cornillon et al., 1994). Evidence suggests, however, that mating responses are restricted to less harsh environmental conditions. Sexual reproduction may also be induced by crowding as social stressor (Harvell and Grosberg, 1988; Harris EH, 1989; Gilbert, 2003). In *V. carteri* a brief exposure to elevated temperatures generates egg-bearing sexual daughters (Kirk and Kirk, 1986). The same set of genes triggered by the sexual pheromone was also inducible in *V. carteri* by wounding (Amon et al., 1998). Mating behavior is favored by unfavorable and fluctuating environmental conditions (Frank and Swingland, 1988, Hoffman and Parsons, 1991; Nelson, 1996; Robson et al., 1999; Becks and Agrawal, 2010; 2012; Schoustra et al., 2010). In soil microfungi, sex is more common under stressful environmental conditions associated with drought severity and high salinity (Grishkan et al., 2003).

Cells with DNA damage have also been shown to undergo sex in viruses (Bernstein, 1987), bacteria (Wojciechowski et al., 1989), and yeast (Bernstein and Johns, 1989). In plants and benthic marine animals there is relatively greater allocation to sexual than to vegetative reproduction at high density (competitive stress) (Harvell and Grosberg, 1988; van Kleunen et al., 2001; van Kleunen and Fischer, 2003). The external signals may include pheromones that act as quorum-sensing signals and induce competence under a wide variety of conditions (Morrison and Baker, 1979; Zhang et al., 1993; Gomer, 1994; Hwang et al., 1994; Morrison, 1997, Tortosa and Dubnau 1999). Intriguingly, these pheromones and their transduction pathways may function as sexual isolation mechanism (Tortosa and Dubnau, 1999). These findings link the microbial mating behavior with population density as representing the cost of finding a mating partner (Bernstein et al., 1985a; b). The pheromone-induced conjugational transfer of plasmids has an immense importance for the acquisition of virulence and

antibiotic resistance (Wirth, 1994; Dunny et al., 1995; Zatyka and Thomas, 1998). The finding that plasmids (Goodman et al., 1993) or chromosomal DNA from other bacterial species can also be taken up and integrated, supports the adaptive concept but is not compatible with the concept that the ingested DNA may serve as template for recombinational repair (Lorenz and Wackernagel, 1994; Nielsen, 1998). For instance, 'adaptive' mutation was substantially mitigated when conjugational behavior was inhibited in starving bacteria (Radicella et al., 1995).

Fungi and yeast, facultatively sexual/asexual eukaryotes, exhibit sexual reproduction under various stressors such as nutritional and nitrogen starvation and following oxidative stress (Bernstein and Johns, 1989; Mochizuki and Yamamoto, 1992; Nelson, 1996). This mating behavior may also be induced by pheromones (Konopka and Fields, 1992; Kurjan, 1992; Bardwell et al., 1994; Spellig et al., 1994) which also require stress factors to induce their synthesis (Moore and Edman, 1993; Jee and Ko, 1998). Remarkably, pheromones induce growth arrest in G1 (Kurjan, 1992; Bardwell et al., 1994; Oehlen and Cross, 1994) the starting point of another stress response, differentiation (Heininger, 2001; 2012). Entry into stationary phase, differentiation, stress and conjugation responses are regulated in yeast by the same signaling pathways and transcription factors (Ammerer, 1994; Takeda et al., 1995; Wu and McLeod, 1995; Kato et al., 1996; Shiozaki and Russell, 1996; Madhani and Fink, 1998; Widmann et al., 1999). These pathways also implicate the expression of hsp (Danjoh and Fujiyama, 1999). That this phylogenetically ancient mechanism is highly conserved throughout eukaryotes is indicated by a striking conservation from yeasts to humans of a gene controlling stress-induced sexual development in yeast (Okazaki et al., 1998). The spontaneous mutation rate for some, though not all, mutations in cells of *Saccharomyces cerevisiae* undergoing meiosis is 3 to 30 times that of cells reproducing mitotically (Magni and von Borstell, 1962; Magni, 1963; Lawrence, 1982).

Another feature of conjugational behavior is the formation of polyploid giant cells which can be formed by algae, yeasts and other protozoans under various stress conditions (Rink and Partke, 1975; Urushihara, 1992; Mares et al., 1993) again facultatively mediated by pheromones (Urushihara, 1992). Even bacteria may be able to exhibit this type of conjugational behavior in stationary phase (Akerlund et al., 1995).

Three non-mutually exclusive models can account for the evolution of DNA uptake systems (Mehr and

Seifert, 1998; Dubnau, 1999):

- DNA for genetic diversity and innovation — the acquisition of potential useful genetic information, such as novel metabolic functions, virulence traits or antibiotic resistance (Dubnau, 1999; Ochman et al., 2000).
- DNA repair — environmental DNA from closely related bacteria might serve as templates for the repair of DNA damage (Bernstein et al., 1981; 1985a; b; Michod et al., 1988; Solomon and Grossman, 1996).
- DNA as food — DNA can be used as a source of carbon, nitrogen and phosphorous (Redfield, 1993b; 2001; Finkel and Kolter, 2001; Palchevskiy and Finkel, 2006).

4.3 Stress and multicellular reproductive behavior

During metazoan phylogeny many aspects of reproductive physiology including the biosynthesis, structure and function of steroid hormones show a remarkable degree of conservation arguing for the maintenance of shared origins and rationales (Dawson, 1998). In simple metazoans, the impact of environmental challenges on the preference of sexual reproduction can still be observed (Curtis, 1902; Hyman, 1939; Burnett and Diehl, 1963; Bell, 1982; Bell and Wolfe, 1985; Harvell and Grosberg, 1988; Schierwater and Hadrys, 1998). Volvocine algae switch from their principal, asexual mode of reproduction to a sexual mode when life-threatening conditions approach such as heat shock (Kirk and Kirk, 1986; Kirk, 1998; Harris et al., 2009), indicating drying up of the pond. The sexual cycle produces heavily walled, dormant zygotes (zygospores) that can resist tough conditions like drought, heat, and cold for a long period of time (Hallmann, 2011). Individuals that are starved also undergo sex in cladocera (Stuart et al., 1931; D'Abramo, 1980) and daphnia (together with inductive photoperiod and crowding) (Kleiven et al., 1992). Competitive stress also favors sexual reproduction in *Daphnia* and a rotifer (Kleiven et al., 1992; Berg et al., 2001; Gilbert, 2004). Sex in the nematode, *Strongyloides ratti*, is induced in response to a host immune response (Gemmill et al., 1997; West et al., 2001). Plants and sessile aquatic animals often exhibit labile sex expression but turn to sexual reproduction under moderate environmental challenges (Harvell and Grosberg, 1988; Kimmerer, 1991; Romme et al., 1997; Korpelainen, 1998; van Kleunen et al., 2001). Likewise, biotic and abiotic stress increase plant homologous recombination (Filkowski et al., 2004; Molinier et al., 2006; Boyko et al., 2010).

Environmental stress is known to initiate sexual

reproduction in a broad range of species that normally undergo asexual reproduction (Bell, 1982; Harris PD, 1989; Dubnau, 1991; Kleiven et al., 1992; Gemmill et al., 1997; Dacks and Roger, 1999; Mai and Breeden, 2000). Some enchytraeid species (pot worms) reproduce asexually by fragmentation and subsequent regeneration (Bell 1959; Christensen 1959; Bouguenec and Giani 1989; Dózsa-Farkas, 1995; Schmelz et al., 2000; Yoshida-Noro and Tochinai, 2010) but reproduce sexually under environmental stressors such as starvation (Christensen 1959; Dózsa-Farkas 1996; Myohara et al., 1999; Tadokoro et al., 2006). Likewise, facultative outcrossing may enhance the adaptive response of highly selfing populations in the face of environmental and genetic stress (Morran et al., 2009a; b).

In multicellular unitary organisms with their increasing independence from environmental changes, a special variation of the environmental challenge leitmotif is the change to and maintenance of sexual reproduction in hosts to counter the pressure of parasitic coevolution (the Red Queen hypothesis) (Hamilton, 1980; Hamilton and Zuk, 1982; Hamilton et al., 1990; Howard and Lively, 1994; Møller and Saino, 1994; Able, 1996; John, 1997; Ooi and Yahara, 1999; Martins, 2000; Salathé et al., 2008; Lively, 2010). The coevolutionary models have been extended to interactions with other species in the biotic space (Otto and Nuismer, 2004). Climatic change has been suggested to be a comodulating factor to the host-parasite coevolution (Atkinson, 1991). The same appears to be true for parasite reproduction. A parasitic nematode reproduces sexually in immune-competent hosts but may propagate clonally in the less challenging environment of immune-deficient hosts (Gemmill et al., 1997). In fact, random mating is the by far favored reproduction type of a pathogenic fungus in a natural immune-competent environment (Chen and McDonald, 1996). As further support of the coevolution concept, genetic diversity of viruses is substantially higher in sexual than asexual hosts (Ooi and Yahara, 1999). The modulation of sexual reproduction appears to be even exploited as strategy in the parasite-host arm race. Bacteria induce parthenogenesis in infected female wasps (Huigens et al., 2000) thus putatively reducing the hosts' evolutionary adaptability and immune competence. Both circumstantial evidence (Clark, 1996) and theoretical calculations (Cui et al., 2000) suggest that aging may contribute to the maintenance of sexual reproduction. Conversely, asymmetric, both asexual and sexual, reproduction are coselected with senescence and death (Heininger, 2002; 2012).

Oxidative stress is the final common pathway of responses to a variety of biotic and abiotic stressors (Lindquist, 1986; Sanchez et al., 1992; Finkel and Holbrook, 2000; Heininger, 2001; Mittler, 2002; Mikkelsen and Wardman, 2003; Sørensen et al., 2003; Apel and Hirt, 2004; Ardanaz and Pagano, 2006; Rollo, 2007; Miller et al., 2008; Slos and Stoks, 2008; Jaspers and Kangasjärvi, 2010; Steinberg, 2012; Choudhury et al., 2013). And in this capacity, oxidative stress is a general inducer of sexual reproductive activity (Bernstein and Johns, 1989; Heininger, 2001; Nedelcu and Michod, 2003; Nedelcu et al., 2004; Nedelcu, 2005; McInnis et al., 2006). In fungi, deletion or mutagenesis of NADPH oxidases that are used deliberately to produce ROS, specifically block differentiation of sexual fruit bodies, without affecting asexual development (Lara-Ortiz et al., 2003; Malagnac et al., 2004; Takemoto et al., 2007).

5. Mutagenesis and fitness

Summary

The Modern Synthesis posited that (1) mutations occur independently of the environment, (2) mutations are due to replication errors, and (3) mutation rates are constant. Since the vast majority of new mutations are likely to be neutral or deleterious for fitness, organisms should evolve as low mutation rates as possible. Contrary to this prediction, there are situations in nature, e.g. in stressful conditions that by definition are associated with impaired fitness, in which being a mutator confers a selective advantage (condition-dependent mutagenesis). The mutation rate of an organism is subject to heritable variation, and therefore evolves. Mathematical models suggested that mutation rates adapt up (or down) as the evolutionary demands for novelty in variable environments (genetic innovation) or memory in stable environments (genetic conservation) increase. Nature selected for those organisms with a mutation rate that compromises between adaptability and adaptedness. Stressful conditions can lead to a genetically controlled increase in bacterial and eukaryote mutagenesis that is genome-wide. The evolutionary fate of mutators, however, is inextricably linked to their effective population size: only with a large population size chances are substantial that some individuals may create beneficial mutations that confer a competitive advantage to cells, allowing them to take over the population. Based on the

nearly universal inverse relationship between body mass/size and population size and density, increased multicellularity is generally associated with a reduction in effective population size, and this in turn reduces the efficiency of natural selection. Given the deleterious effects of most mutations, theory predicts that increasing the mutation rate should generate progressively larger reductions in fitness, assuming that the mutations accumulate in the genome and that the effects of the mutations are additive or act synergistically. However, efficiency of artificial selection can be enhanced due to the increased genetic variation induced by mutagenesis. An efficient selection regime that is able to pick the “pearl(s)” of beneficial or at least neutral mutations out of the “pebbles” of deleterious ones may fundamentally change the course of evolution.

5.1 Are mutations genetic “accidents”?

In this paper, mutagenesis and mutation, when not specified otherwise, will refer in the broadest sense to any permanent, and consequently heritable, change of DNA sequence including transposable elements activity and recombination. Homologous recombination by itself does not generate sequence polymorphisms. However, recombination does prevent the reduction in variability caused by selective sweeps and sequential bottlenecks, thus increasing the polymorphism in a population (Suerbaum et al., 1998).

The Modern Synthesis posited that (1) mutations occur independently of the environment, (2) mutations are due to replication errors, and (3) mutation rates are constant (Lenski and Mittler, 1993; Brisson, 2003). Mutation is a double-edged sword. On one side, it is the ultimate source of genetic variation and the basis of evolution, the material upon which natural selection works (Punnett, 1911, p. 139; Mayr, 2001). Yet, the vast majority of new mutations are likely to be neutral or deleterious for fitness (Bridges, 1919; Fisher, 1930; 1958; Falconer and Mackay, 1996; Kibota and Lynch, 1996; Elena and Moya, 1999; Lynch et al., 1999; Wloch et al., 2001a; Keightley and Lynch, 2003; Sanjuán et al., 2004a; Eyre-Walker and Keightley, 2007; Sawyer et al., 2007; Soskine and Tawfik, 2010; King, 2012a). For example, for *Escherichia coli* K-12, the rate of deleterious mutations per genome per replication is, at least, $2-8 \times 10^{-4}$ (Kibota and Lynch, 1996; Boe et al., 2000), while that of beneficial mutations is, at least, 2×10^{-9} (Imhof and Schlotterer, 2001). As Calvin Bridges, one of the pioneers of *Drosophila* genetics, put it (1919): “Any organism as it now exists must be regarded as a very complex physicochemical machine with delicate adjustments of

part to part. Any haphazard change made in this mechanism would almost certainly result in a decrease of efficiency... Only an extremely small proportion of mutations may be expected to improve a part or the interrelation of parts in such a way that the fitness of the whole organism for its available environments is increased.” It is generally assumed that beneficial effects are ~1,000-fold less common than neutral and deleterious ones (Miralles et al., 1999; Keightley and Lynch, 2003; Orr, 2003), although large differences exist between taxa (Eyre-Walker and Keightley, 2007). Applying an extended McDonald-Kreitman test (McDonald and Kreitman, 1991; Charlesworth, 1994; Fay et al., 2001; Smith and Eyre-Walker, 2002; Loewe and Charlesworth, 2006) to polymorphism data from *D. melanogaster*, the fraction of deleterious newly arising mutations was estimated to be ~94% at amino acid sites, ~81% in untranslated regions, ~56% in introns, and ~61% in intergenic regions (Andolfatto, 2005). Any variant that has increased mutation rates is expected to have reduced fitness due to increased production of deleterious mutations. Sturtevant (1937) asked: “why does the mutation rate not become reduced to zero?” And gave the reply: “In short, mutations are accidents, and accidents will happen”. Without mutation, evolution would not be possible, and life itself could never have arisen in the first place. Thus, as Baer (2008) noted “deleterious mutations are the price living organisms pay for the ability to evolve”. Naively one may think that organisms should evolve as low mutation rates as possible. It has been concluded that “natural selection of mutation rates has only one possible direction, that of reducing the frequency of mutation to zero” (Williams, 1966a). Thus, there should be a strong selective pressure to eliminate mutation altogether, due to the high probability that any particular mutation will have deleterious effects. Accordingly, theory indicates that under most conditions, selection puts a premium on the faithful maintenance and transmission of genetic information and is expected to favor alleles that reduce the mutation rate (Karlin and McGregor, 1974; Feldman and Liberman, 1986; Kondrashov, 1995; Sniegowski et al., 2000; Sniegowski, 2004). In fact, DNA replication can have a remarkable fidelity, estimated to produce 10^{-9} – 10^{-11} mutations/nucleotide, achieved by multiple mechanisms of error avoidance and correction (Kunkel, 2004). Eigen (1992) argued that replication error rates established themselves near an error-threshold where the best conditions for evolution exist. However, analyzing the genomes of a bacterium, a yeast, and a nematode, Ackermann and Chao (2006) found that codons are used to encode proteins in a way that avoids the emergence of

mononucleotide repeats, suggesting that selection for genetic stability may be more important than selection for the generation of variation. In well-adapted populations in stable environments the rate of mutation will evolve towards lower values (Leigh, 1973; Karlin and McGregor, 1974; Liberman and Feldman, 1986; Drake, 1991; Kunkel, 2004) until further improvements in replication fidelity and DNA repair become too costly (André and Godelle, 2006) reflecting the combined metabolic and temporal costs of perfection in replication and transcription fidelity (Kimura, 1967; Sniegowski et al., 2000). Another theory suggests that if the mutation rate is reduced to a very low level, a point will eventually be reached at which the small advantage of any further reduction is overwhelmed by the power of drift (Lynch, 2011).

Measurements of mutation rates, however, show that organisms have copying fidelities much lower than what could be expected from this assumption (Drake, 1993; 1999; Drake et al., 1998). A genotype with a null mutation rate would be sentenced to extinction because of its inability to respond to environmental perturbations. Dobzhansky (1950), in a seminal statement on adaptation to diverse environments, wrote 'Changeable environments put the highest premium on versatility rather than on perfection in adaptation'. In changing environments, the potential benefit of generating a few adaptive variants may outweigh the cost of many deleterious mutations (Muller, 1928; Sturtevant, 1937; Radman, 1999). Also for host-parasite interactions, it has been shown that mean fitness is optimized by high or non-zero mutation rates, in a manner similar to that found with fluctuating abiotic environments (Nee, 1989; Sasaki, 1994; Haraguchi and Sasaki, 1996; M'Gonigle et al., 2009). Mathematical analyses have shown that evolution yields optimal, positive mutation rates under certain conditions (Kimura, 1967; Leigh, 1970; 1973; Eschel, 1973a; b; Gillespie, 1981; 1991a; Holsinger and Feldman, 1983; Liberman and Feldman, 1986; Bedau and Packard, 2003; Clune et al., 2008; Dees and Bahar, 2010). In fact, contrary to Williams' intuitive prediction, strains having high mutation rates (mutators) are not rare in natural bacterial populations (Giraud et al. 2001a; Denamur and Matic, 2006). They have been found in populations of *Escherichia coli* (LeClerc et al., 1996; Matic et al., 1997; Denamur et al., 2002; Baquero et al., 2004), *Salmonella enterica* (LeClerc et al., 1996), *Neisseria meningitidis* (Richardson et al., 2002), *Haemophilus influenza* (Watson et al., 2004), *Staphylococcus aureus* (Prunier et al., 2003), *Helicobacter pylori* (Björkholm et al., 2001), *Streptococcus pneumoniae* (del Campo et al., 2005) and *Pseudomonas aeruginosa* (Oliver et al.,

2000; Ciofu et al., 2005; Maciá et al., 2005), with frequencies ranging from 0.1% to above 60%. Experimental (Mao et al., 1997; LeClerc et al., 1998) and theoretical (Boe et al., 2000) studies indicate that the frequency of mutators observed among natural isolates is much higher than expected from mutation/selection equilibrium, which suggests that there are situations in nature where being a mutator confers a selective advantage (Giraud et al. 2001a; Tanaka et al., 2003; Denamur and Matic, 2006; Ram and Hadany, 2012). Enrichment of spontaneously originated mutators in microbial populations undergoing adaptation to a new environment has been shown in laboratory experiments (Sniegowski et al., 1997; Miller et al., 1999; Notley-McRobb et al., 2002a; b). In long-term experiments with *E. coli*, 3 of 12 populations spontaneously evolved into mutators in 10,000 generations (Sniegowski et al., 1997) and a fourth by 20,000 generations (Cooper and Lenski, 2000). Also antimutator strains, with a significantly lower mutation rate, can be found (Fijalkowska et al., 1993). This suggests that mutation rates are adjustable and subject to selection (Taddei et al., 1997; Sniegowski et al., 2000; De Visser, 2002).

5.2 May mutagenesis be adaptive?

Environments never remain static. They continuously undergo changes that alter the fitness landscapes, displacing populations towards suboptimal fitness regions, where the amount of mutations with positive effects increases. These poorly-adapted populations could benefit from having higher than standard mutation rates (Stich et al., 2010). The variation of mutation effects with fitness, together with the fact that error rates can be easily modified as a consequence of mutations producing genotypes with variable capacity to cause errors, suggest that mutation rates are a character subjected to the action of natural selection (Drake et al., 1998; Sniegowski et al., 2000). Selection of mutation rates was studied by a variety of models (Taddei et al., 1997; Orr, 2000; Andre and Godelle, 2006; Sniegowski et al., 2000; Gerrish et al., 2007; Heo et al., 2009). The mutation rate of an organism is subject to heritable variation, and therefore evolves (Weber, 1996; Kirschner and Gerhart, 1998; Radman et al., 1999; Metzgar and Wills, 2000; Sniegowski et al., 2000; Earl and Deem, 2004; Aharoni et al., 2005; Pigliucci, 2008; Wagner, 2008a).

Fisher's fundamental theorem of natural selection (1930) states that the rate of increase in fitness of a population at any time is proportional to its genetic variance in fitness at that time. If there is no variation in survival and reproduction or if this variation has no genetic basis, then the composition of a population will

not evolve over time. The theorem has been confirmed experimentally in animals and plants. The degree of fitness evolved is greater when the initial amount of genetic variability is larger (Strickberger, 1965; Ayala, 1968a; Vrijenhoek, 1994; Reed and Frankham, 2003; Leimu et al., 2006). Populations with genetic variability increased by hybridization adapt to the environment at a faster rate than parental, genetically less variable populations (Strickberger, 1965; Ayala, 1965; 1968 a; b). Adaptation theory also assigns a central role to mutation (Orr, 2000a; Grenfell et al., 2004). Adaptation by natural selection occurs through the spread and substitution of mutations that improve the performance of an organism and its reproductive success in its environment. An important focus of evolution experiments using microorganisms has been to investigate the dynamics of this process (Elena and Lenski, 2003). It seems that nature selected for those organisms with a mutation rate that compromises between adaptability and adaptedness (Radman et al., 2000). Mathematical models suggested that mutation rates adapt up (or down) as the evolutionary demands for novelty in variable environments (genetic innovation) or memory in stable environments (genetic conservation) increase (Bedau and Packard, 2003; Buchanan et al., 2004; Clune et al., 2008; Dees and Bahar, 2010). Similarly, the optimal genomic mutation rate was found to depend only on the environmental change and its severity (Nilsson and Snoad, 2002; Ancliff and Park, 2009). Even in stable abiotic environments, relatively high mutation rates may be observed for traits subject to cyclical frequency-dependent population dynamics (Allen and Scholes Rosenbloom, 2012). Studies in bacteriophage T4 (Drake et al., 1969; Schapper, 1998), *E. coli* (Schapper, 1998) and *Drosophila* (Nöthel, 1987) have demonstrated that mutation rates can be driven lower than (or can increase above) wild type values under various external pressures, and can be restored to wild type when control conditions are re-established (Sniegowski et al., 1997).

Mutation rate variability is a key theme in current discussions of the need for an extended evolutionary synthesis (Pigliucci, 2007; Pennisi, 2008) under the name of "the evolution of evolvability", the tantalizingly recursive possibility that the ability of organisms to evolve is itself a trait, or spectrum of traits, under evolutionary control (Bedau and Packard, 2003; Earl and Deem, 2004; Bell, 2005; Pigliucci, 2008; Dees and Bahar, 2010). Genes which may cause elevated rates of mutation ('mutator genes') have been identified in many species (Demerec, 1937; Neel, 1942; Ives, 1950; Smith, 1992; Goho and Bell, 2000). Mutator bacterial strains are more antibiotic resistant than non-mutator

strains, and thus have a clear selective advantage, potentially leading to an increase in the overall mutation rate within a population (Maciá et al., 2005; Denamur and Matic, 2006). In 115 replicate populations to characterize the genetic response of *E. coli* to high temperature (42.2°C), during 2000 generations one of the lines had evolved a mutator phenotype, many more mutations, and a higher fitness (Tenaillon et al., 2012). Overall, stressful conditions can lead to a genetically controlled increase in bacterial and eukaryote mutagenesis that is genome-wide (Taddei et al., 1995; Torkelson et al. 1997; Rosche and Foster, 1999; Goho and Bell, 2000; Shaver et al., 2002; Bjedov et al., 2003; Tenaillon et al., 2004; Saint-Ruf and Matic, 2006; Foster, 2007). These stresses include nutritional deprivation, DNA damage, temperature shift, or exposure to antibiotics. All of these global stress responses include functions that can increase genetic variation. In particular, up-regulation and activation of error-prone DNA polymerases, down-regulation of error-correcting enzymes, and movement of mobile genetic elements are common features of several stress responses. The result is that under a variety of stressful conditions, bacteria are induced for genetic change (Foster, 2007). Transformation is only one of several bacterial stress responses that advance genetic variation (Msadek, 1999; Merlin et al., 2000; Storz and Hengge-Aronis, 2000). Several authors have proposed that some form of stress-induced increase in the mutation rate might be favored by natural selection (Echols, 1981; Wills, 1984; McDonald, 1987). According to Thoday's fitness definition (1953) "increase of fitness,..., must be brought about largely by changes which increase either genetic stability or variability without bringing about corresponding decrease in the other component. A progressive change is thus one that increases the sum of these components". Microorganisms achieve this goal by balancing robustness and evolvability (Lenski et al., 2006).

At the end of 31 days of cocultivation for 320 generations of 69 *E. coli* mutants with polymerase fidelities varying by more than 6 orders of magnitude, all surviving strains were moderate mutators with 10 to 47 lower fidelity than the wild type, whereas antimutators and extreme mutators had been outcompeted (Loh et al., 2007; Loeb et al., 2008). Under specific conditions, selective pressure favors mutator strains of bacteria over nonmutator strains in both natural (Gross and Siegel, 1981; Leclerc et al., 1996; 1998; Matic et al., 1997; Oliver et al., 2000; Bjorkholm et al., 2001; Denamur et al., 2002; Giraud et al., 2002; Richardson et al., 2002; Blázquez, 2003;

Prunier et al., 2003; Watson et al., 2004; del Campo et al., 2005; Labat et al., 2005; Denamur and Matic, 2006) and experimental populations (Cox and Gibson, 1974; Trobner and Piechocki, 1981; Chao and Cox, 1983; Chao et al., 1983; Mao et al., 1997; Sniegowski et al., 1997; Giraud et al., 2001a; Notley-McRobb et al., 2002; Shaver et al., 2002; Thompson et al., 2006; Pal et al., 2007). These situations are fulfilled under a variety of stressors (Gonzalez et al., 2008; Ram and Hadany, 2012). A generic thermodynamical analysis of genetic information storage suggests that an elevated stress level (i) reduces an organism's ability to deflect mutagenic influence and/or (ii) restricts or redistributes metabolic resources available to mutation suppression in an unstressed situation and/or (iii) impairs the means to utilize these resources. Vice versa, any influence exerting one or several of the aforementioned effects can be understood as stress (Hilbert, 2011). As the environment at the ecological extremes is stressful by definition, an increase in mutation rates as a stress response can play a fundamental role in adaptation to new conditions (Gostincar et al., 2010). This response has been seen in a variety of organisms, in the laboratory as well as in wild strains of, for example, *Escherichia coli* (Rosenberg et al., 1998; Bjedov et al., 2003; Hastings et al., 2004), *S. cerevisiae* (Heidenreich et al., 2003) and *Caenorhabditis elegans* (Rosenberg and Hastings, 2004). Mutators have an advantage against phages in the coevolutionary arms race (Pal et al., 2007) and play a role in the emergence of antibiotic-resistant bacteria (Chopra et al., 2003; Woodford and Ellington, 2007). Freezing can increase the mutation rates of mtDNA in *S. cerevisiae* (Stoycheva et al., 2007a), and activate retrotransposons (Stamenova et al., 2008). Frequencies of new spontaneous mutations of *Sordaria fimicola*, *Penicillium lanosum* and *Aspergillus niger* are clearly related to whether they had been isolated from a region of high or low microclimatic stress, being much lower in strains from the north-facing, less stressful "European" slope of "Evolution Canyon I", compared with strains from the south-facing "African" slope, which is a much more stressful environment (Lamb et al., 1998; 2008). Similarly, isolates of the ericoid mycorrhizal fungus *Oidiodendron maius* from stressed sites showed a significantly higher polymorphism in the Cu,Zn superoxide dismutase (Cu,ZnSOD) promoter region, suggesting that environmental stress may increase the rate of mutations in specific regions of the *Sod1* locus (Vallino et al., 2011). Mutator strains were found to have a fitness advantage over wild-type strains, which stemmed from the fact that the mutator generated more beneficial mutations. The advantage of the

mutator strain was shown to be frequency dependent, so that below a threshold level — $\sim 1/10,000$ of the population — the mutator went extinct, because then the probability of a beneficial mutation arising in the wild-type population was greater than in the much smaller mutator population. Above this level, however, the mutator was able to out-compete the wild-type because beneficial mutations had a greater chance of arising in the mutator strain and their selective advantage caused the linked mutator to hitchhike to high frequency (Gibson et al., 1970; Chao and Cox, 1983; Taddei et al., 1997; Rainey, 1999; Tenaillon et al., 1999; Elena and Lenski, 2003; Denamur and Matic, 2006). Mutational heritability in the asexual bacteria *Pseudomonas fluorescens* was estimated as 1×10^{-3} per generation in simple, single-substrate environments and 3×10^{-3} per generation in complex, four-substrate environments. Populations selected in complex environments evolved into genetically diverse communities that exhibited greater metabolic differentiation from other genotypes in their own population than to genotypes evolving in other populations, presumably as a result of resource competition. In populations selected in simple environments, little genetic diversity evolved, and genotypes shared very similar phenotypes (Barrett and Bell, 2006). Evolution in complex environments results in a genetically diverse population of overlapping generalists, each of which is adapted to a certain range of substrates but not all (Barrett et al., 2005).

Since too high a mutation rate has obvious negative consequences (Fisher, 1930; Crow, 1997b; Giraud et al., 2001a; Gerrish et al., 2012), there is evidence that evolution may have established brakes that ensure a "speed limit" to mutagenesis and select against high mutation rates when fitness gains no longer counterbalance the fitness loss due to continuous generation of deleterious mutations (Gerrish and Lenski, 1998; de Visser et al., 1999; Rainey, 1999; Sniegowski et al., 2000; Denamur and Matic, 2006; Pybus et al., 2007). High mutation rates help organisms to reach high fitness peak, after which they are no longer advantageous, and lower mutation rates get fixed to localize the population in the fitness peak (Heo et al., 2009). However, many bacteria can increase their mutation rates 10–100-fold without noticeable loss of fitness (Matic et al., 1997; Sniegowski et al., 1997; Shaver et al., 2002). A quantitative analysis revealed that evolution rates increase linearly with mutation rates for slowly mutating viruses. This relationship plateaus for fast mutating viruses (Sanjuán, 2012). The evolution of bacterial populations may happen through alternating

periods of high and low mutation rates (Giraud et al., 2001a; b). Highly illustrative is the behavior of bacteria kept under metabolic stress in stationary phase. To survive, cells must scavenge whatever becomes available through excretion or death in an otherwise starving population. After a period of mortality, mutants emerge that can survive and grow under such conditions (Zambrano et al., 1993; Finkel and Kolter, 1999; Zinser and Kolter, 2000). Null mutations in *rpoS* confer this advantage (Zambrano et al., 1993) (see chapter 12.1).

Binomial sampling error and background selection both generate random change in the frequency of a mutation across generations. The former is an inevitable consequence of finite population size and it causes the frequency of a mutation to change in a manner that is independent of direct selection on the mutation itself. Its magnitude is inversely proportional to population size, N . The latter causes additional noise due to a mutation's chance association with genetic backgrounds of different selective value. Its magnitude is proportional to the genetic standard deviation in genome-wide fitness, $\sigma_{W(\text{gen})}$. The dilution of direct selection on a mutation due to the additional noise generated by background selection can be expressed by a lowered effective population size, N_e , in comparison to the census size N (Hill and Robertson, 1966; Felsenstein, 1974; Rice and Chippindale, 2001). The effective size of a population (N_e) is a fundamental determinant of nearly all aspects of evolution as it determines the probability of (and times to) fixation or removal of mutant alleles (Lynch, 2006; Charlesworth, 2009). N_e is generally much smaller than the actual size of a population, as a consequence of variation in family size, nonrandom mating, sex-ratio bias, and many other aspects of population structure (Crow and Morton, 1955; Frankham, 1995). Comprehensive estimates of the N_e/N ratio (that included the effects of fluctuation in population size, variance in family size and unequal sex-ratio) ranged from 0.11 (Frankham, 1995) to 0.25 and 0.75 (Nunney, 1993; 1996) to but can also be much smaller (Hedgecock, 1994; Waples, 1998; Hedrick, 2005). Response to selection is dependent on population size for both new mutations (Hill, 1982 a; b; Caballero et al., 1991; López and López-Fanjul, 1993; Mackay et al., 1994; Samani and Bell, 2010) and standing genetic variation (Jones et al., 1968; Weber, 1990; Weber and Diggins, 1990; Agashe et al., 2011; Lachapelle and Bell, 2012). Thus, the rate of adaptive evolution is positively correlated to N_e (Wright, 1931; Kimura, 1983; Keightley, 2004; Leimu et al., 2006; Willi et al., 2006). Small effective population sizes, on the other hand, are believed to have an

increased risk of extinction (Lande, 1994; Kondrashov, 1995a; Lynch et al., 1995a; b; Willi et al., 2006; Bell and Gonzalez, 2009; Willi and Hoffmann, 2009). The ability of a population to incorporate beneficial mutations and to purge deleterious mutations should scale positively with population size, assuming that N_e scales positively with N (Lynch, 2006; 2007a). However, associations between population size and genetic variance may be complex (Barton and Turelli, 2004). Muller (1964) proposed that an asexual organism will inevitably accumulate deleterious mutations, resulting in an increase of the mutational load and an inexorable, ratchet-like, loss of the least mutated class. In large populations, Muller's ratchet occurs more slowly, and even lower rates of recombination will effectively arrest mutation accumulation (Charlesworth et al., 1993). Large populations more rapidly produce variants carrying multiple mutations that can evade constraints such as fitness valleys (Weinreich and Chao, 2005). As the rate of long-term adaptive evolution appears to be limited by the supply of new mutations (Gossmann et al., 2012), species with larger N_e are expected to undergo more adaptive evolution than species with small N_e because a greater number of advantageous mutations appear in the population and a higher proportion of these mutations are effectively selected (Jensen and Bachtrog, 2011; Gossmann et al., 2012; Phifer-Rixey et al., 2012). Accordingly, mathematical models observe a low mean population size for low values of the maximum possible mutation size μ , a sharp rise in population size for intermediate values of μ , and a plateau in the population size for high values of μ (Dees and Bahar, 2010). For low μ , new organisms remain in tight clusters, unable to explore the fitness landscape far beyond the locations of their parents. This results in overcrowding, followed by a decrease of the population and eventual extinction. For high μ , the population cannot grow indefinitely, constrained by both the overpopulation limit and the finite fitness landscape size, which combine to play a role analogous to the carrying capacity in logistic population models (Dees and Bahar, 2010).

Levels of genetic diversity in plant and animal wildlife are related to population size (Frankham, 1996; 1997; Spielman et al. 2004; Leimu et al., 2006; Willi et al., 2007; Hoffmann and Willi, 2008; Charlesworth, 2009). Under assumptions of neutrality and additive gene effects, equilibrium additive genetic variance of a quantitative trait increases linearly with effective population size (Chakraborty and Nei, 1982; Lynch and Hill, 1986). On the other hand, the amount of genetic diversity a population contains has been shown to correlate with current fitness and, in the case

of heritabilities, with evolutionary potential (Fisher, 1930; Falk and Holsinger, 1991; Frankham, 1995; Falconer and Mackay, 1996; Franklin and Frankham, 1998; Reed and Frankham, 2003; Johnson et al., 2006; Leimu et al., 2006). A certain amount of genetic load is considered the necessary cost of evolutionary responsiveness (Crow and Abrahamson, 1965). Literature suggests that allozyme heterozygosity is a good measure of population fitness and adaptive potential (Garten, 1976; Soulé and Wilcox, 1980; Beardmore, 1983; Allendorf and Leary, 1986; Houle, 1989; Merilä and Crnokrak, 2001) although the association between neutral diversity and population fitness is highly variable across studies (Arden and Lambert, 1997; Calero et al., 1999; Booy et al., 2000; Noel et al., 2007). Moreover, estimates of variation within natural populations often do not support the prediction that quantitative genetic variation declines at small N_e (Willi et al., 2006).

Bigger animals not only live longer but they also display a set of correlated life-history traits (Stearns, 1983; 1989; Promislow and Harvey, 1990; Promislow et al., 1992; Hendriks and Mulder, 2008; Jeschke and Kokko, 2009). Specifically, they mature more slowly and breed for the first time at a later age. Their reproductive rates are lower (longer intervals between reproductive events) and their productivity at each breeding event is also reduced (lower litter or clutch sizes) (Speakman and Król, 2010). Body mass can be taken as a proxy for N_e (Berlin et al., 2007; Popadin et al., 2007; Nabholz et al., 2008b; 2009), based on the nearly universal inverse relationship between body mass/size and population size and density (Damuth, 1981; 1987; Peters, 1983; Griffiths, 1998; Ackerman et al., 2004; Arim et al., 2011). Thus, increased multicellularity is generally associated with a reduction in N_e , and this in turn reduces the efficiency of natural selection (Lynch, 2010a). The nearly neutral theory predicts that the rate and pattern of molecular evolution will be influenced by N_e , because in small populations more slightly deleterious mutations are expected to drift to fixation (Ohta and Kimura, 1971; Ohta, 1992; 1993). As predicted by theory, island lineages have significantly higher ratios of non-synonymous to synonymous substitution rates than mainland lineages (Johnson and Seger, 2001; Woolfit and Bromham, 2005). The higher supply of beneficial mutations allows large microbial populations to adapt more rapidly to new environments compared to small populations (Gillespie, 1999; Orr, 2000a; Wilke, 2004; de Visser and Rozen, 2005). The adaptive walk of asexually reproducing populations can be described as travelling wave whose speed is determined by population size and mutation rate

(Fisher, 2011; Hallatschek, 2011).

Similarity of mutation rates among lineages with vastly different generation lengths and physiological attributes points to a much greater contribution of replication-independent mutational processes to the overall mutation rate (Kumar and Subramanian, 2002). Species with long generation times, and small effective population size, appear to have higher rates of mutation per generation (Keightley and Eyre-Walker, 2000; Piganeau and Eyre-Walker, 2009). Direct estimates are limited, but suggest that the nuclear mutation rate per generation ranges over 100-fold, from 3.3×10^{-10} per site in *Saccharomyces cerevisiae* to 3.5×10^{-9} in *Drosophila melanogaster*, 2×10^{-8} in *Homo sapiens*, and 3.8×10^{-8} in *Mus musculus* (Keightley et al., 2009; Lynch, 2010a). Estimates of human germline base substitution rates range from 0.97 to 3.8×10^{-8} per base per generation (Haldane, 1935; Kondrashov and Crow, 1993; Crow, 1993; Nachman and Crowell, 2000; Kondrashov, 2003; Xue et al., 2009; Lynch, 2010b; Roach et al., 2010; The 1000 Genomes Project Consortium, 2010; Awadalla et al., 2011; Conrad et al., 2011; Kong et al., 2012; Sun et al., 2012). A human mutation rate of $\sim 2.5 \times 10^{-8}$ mutations per nucleotide site corresponds to 175 (range 91–238) mutations per diploid genome per generation (Nachman and Crowell, 2000). Assuming that (i) there is no selective bottleneck between gametogenesis and offspring (but see chapter 8) and (ii) 95 to 100% of all mutations have either neutral ($\sim 30\%$ of amino-acid changing mutations in humans, $\sim 16\%$ in *Drosophila* [Eyre-Walker, 2002], and $\sim 2.8\%$ in enteric bacteria [Charlesworth and Eyre-Walker, 2006]) or deleterious effects on fitness (Eyre-Walker and Keightley, 2007) this ratio would mean that with each generation, fitness of human populations should decline. A recent study revealed a gradual decline in the proportion of nonsynonymous single nucleotide polymorphisms (SNPs) (considered deleterious) from tip to root of the human population tree. Up to 48% of nonsynonymous SNPs specific to a single genome were regarded deleterious in nature (Subramanian, 2012). It was estimated that at least 1.6 harmful new mutations per individual per generation have been arising in our lineage for the last several million years (Crow, 1999; Eyre-Walker and Keightley, 1999). Due to the effects of smaller N_e on the force of natural selection (Frankham, 1995; Lynch, 2010a), natural selection is deemed insufficient to deal with this mutational load (Eyre-Walker and Keightley, 1999; Eyre-Walker et al., 2002; Harris, 2010). It has been concluded that taking into account the human low reproductive rate it is difficult to envisage how such a high load can be tolerated by hominid populations

(Kondrashov, 1995a; Crow, 1997b; Eyre-Walker and Keightley, 1999; Sunyaev et al., 2001; Eyre-Walker et al., 2002; Eöry et al., 2010). On the basis of genome-wide sequencing it has been estimated that, on average, each person carries approximately 250 to 300 loss-of-function variants in annotated genes and 50 to 100 variants previously implicated in inherited disorders (The 1000 Genomes Project Consortium, 2010).

Fisher (1930) concluded that sexual populations may have a more rapid rate of evolution than would an otherwise equivalent group of asexual organisms. Fisher's conclusion depends on the rate of mutation (Ridley, 2003):

- If favorable mutations are rare, each one will have been fixed in the population before the next one arises. New favorable mutations will always arise in individuals that already carry the previous favorable mutation. Sexual and asexual populations then evolve at the same rate.
- If favorable mutations arise more frequently, Fisher's argument works: the sexual population evolves faster. Each new favorable mutation will usually arise in an individual that does not already possess other favorable mutations; the greater speed with which the different favorable mutations combine together causes the sexual population to evolve faster. The higher the rate at which favorable mutations are arising, the greater the evolutionary rate of a sexual relative to an asexual population.

Given the deleterious effects of most mutations, it can be predicted that increasing the mutation rate should generate progressively larger reductions in fitness, assuming that the mutations accumulate in the genome and that the effects of the mutations are additive or act synergistically (Schultz and Lynch, 1997). This prediction has been confirmed by most studies that have examined the fitness effects of elevated mutation rates (Rosenbluth et al., 1983; Drake et al., 1998; Davies et al., 1999; Manoel et al., 2007; Morran et al., 2010). Ethyl methanesulfonate (EMS) mutagenesis experiments, in which controls are given identical treatment to mutagenized lines, other than a dose of mutagen, have also shown consistently strongly negative effects on fitness traits in *Drosophila* (Mukai, 1970; Ohnishi, 1977; Mitchell and Simmons, 1977; Temin, 1978; Keightley and Ohnishi, 1998; Yang et al., 2001) and *C. elegans* (Keightley et al., 2000). Similarly, transposable element insertional mutagenesis leads to reduced fitness in *Drosophila* (Mackay et al., 1992) and *E. coli* (Elena and Lenski, 1997). However, efficiency of artificial selection in agricultural plants can be enhanced following the

increased genetic variation induced by mutagenesis with irradiation (Gregory, 1955; Brock, 1971; Chavan and Chopde, 1982; Micke et al., 1987; Ahloowalla et al., 2004; Patade and Suprasanna, 2008). Ionizing radiation was also used to increase genetic variation in a variety of insects. The response to selection was dependent on the genetic background, size of the irradiated population and dose of radiation. After an initial decline, population fitness and other responses to artificial selection increased in the irradiated populations compared with controls (Wallace, 1958; Mukai, 1961; Crenshaw, 1965; Ayala, 1966; 1967; 1969; van Delden and Beardmore, 1968; Blaylock and Shugart, 1972; Maruyama and Crow, 1975). Thus, it is essential for the evolutionary significance of mutations to take population size, mutation rate and the action of selection into account.

Cancer arises from a Darwinian process of mutation and selection among somatic cells (Frank and Nowak, 2004). Theoretical models and clinical observations confirm that mutator mechanisms are generally more efficient routes to tumorigenesis than non-mutator mechanisms. Mutations, generated via a mutator phenotype, accelerate carcinogenesis (Loeb, 1998; Strauss, 1998; Beckman and Loeb, 2006; Bielas et al., 2006; Loeb et al., 2008; Beckman, 2009). In carcinogenesis, the size of the stem pool affects the spread of deleterious and advantageous mutations (Frank, 2003a; Michor et al., 2003). In a large stem pool, oncogene and tumor suppressor mutations with increased rates of proliferation almost always succeed, whereas mutator mutations with decreased rates of proliferation rarely succeed. Put another way, natural selection among cell lineages deterministically takes its course in a large population. In small stem pools, chance events can influence which cell lineages succeed or fail. Small pools increase the probability that deleterious mutator mutations spread and decrease the probability that advantageous mutations spread (Frank and Nowak, 2004). Thus, in a variety of evolutionary events mutation rate and population size are the crucial determinants of adaptive evolution dynamics (Gerrish and Lenski, 1998; Hallatschek, 2011).

From these relationships a general framework for the fitness effects of mutations in a variable environment can be sketched:

- Due to the unfavorable ratio of deleterious to beneficial mutations, only a high amount of mutations gives the chance to generate some beneficial mutations.
- There is both a lower and upper limit to mutagenesis intensity that may be beneficial for population fitness.

- Due to this ratio, populations with a low effective population size should invest heavily into DNA repair. Otherwise they are doomed. However, their evolvability in variable environments is poor.
- Populations with a high population size are able to engage in a mutagenic bet-hedging strategy.
- Thus, a high effective size of the mutating population is prerequisite for what I would like to call the “selecting the pearl(s) among the pebbles” approach: An efficient selection regime, either due to natural selection or an experienced breeder (like in the case of irradiated crop plants) that is able to pick the “pearl(s)” of beneficial or at least neutral mutations out of the “pebbles” of deleterious ones may change the course of evolution

6. Developmental and reproductive biology hold the clue

... one finds two very different areas, which may be designated functional biology and evolutionary biology. To be sure, the two fields have many points of contact and overlap. Any biologist working in one of these fields must have a knowledge and appreciation of the other field if he wants to avoid the label of a narrow-minded specialist.

Ernst Mayr, 1961

Summary

Intriguingly, the major theories on the evolutionary rationale for the origin and maintenance of sexual reproduction treated the very processes involved in sexual reproduction either as a black box or reduced its evolutionary potential to the process of recombination. However, to gauge the full evolutionary importance of sexual reproduction, its varied ontogenetic and gametogenetic processes have to be taken into account. To this end, I embark on an inventory of the molecular toolboxes of developmental and reproduction biology from a phylogenetic point of view. The earliest both ontogenetic and reproductive events were responses to metabolic stress that occurred cyclically during the feast and famine life cycles of microorganisms. The molecular events created dormant seeds/propagules as a bet-hedging strategy with the ability to enter a reversible state of low metabolic activity when faced with unfavorable environmental conditions but capable of being resuscitated following environmental change. The morphogens that induced microbial dormancy such as cyclic AMP and differentiation-inducing factors (DIFs) elicit

evolutionarily highly conserved ontogenetic events in metazoan cells. In this phylogenetic legacy, metazoan growth/differentiation factors induce cellular stress reactions. Cellular differentiation is associated with epigenetic reprogramming resulting, due to stochastic epigenetic instability, in significant epigenetic differences between differentiated cells. This variation impacts the cells' competitive abilities for limiting amounts of trophic factors. The losers of these cell competitions are eliminated. Specification of primordial germ cells proceeds via different pathways, i.e. preformation or epigenesis. Spermatogenesis, the sequence of male germ cell development, is a long, orderly, and well-defined process in vertebrates occurring in seminiferous tubules of the testis whereby undifferentiated spermatogonial germ cells evolve into maturing spermatozoa. The temporal course of oogenesis is highly variable across taxa. In most species, oocytes are much larger than sperm, requiring a larger investment of resources. Importantly, during gametogenesis at various stages of the process a huge amount of germ cells are eliminated by apoptosis. Thus, depending on the species, only a limited number of gametes are allowed to pass their genetic information to the next generation.

In 1975 Feldman and Lewontin wrote: “There is a vast loss of information in going from a complex machine to a few descriptive parameters. Therefore, there is immense indeterminacy in trying to infer the structure of the machine from those few descriptive variables, themselves subject to error. It is rather like trying to infer the structure of a clock by listening to it tick and watching the hands”. The fundamental implications of this insight extend to virtual any complex phenomenon of life such as aging (Heininger, 2012) and sexual reproduction. Intriguingly, the major theories on the evolutionary rationale for the origin and maintenance of sexual reproduction treated the very processes involved in sexual reproduction as a black box or to stay in the picture of Feldman and Lewontin (1975) as a clock whose working they tried to infer from its tick and tack. It was one of the strange realizations gained from my literature work that both evolutionary biology, trying to decipher the evolutionary rationale of sexual reproduction, and reproduction biology, investigating the molecular processes of sexual reproduction, obviously lead completely independent lives with minimal, if any, information exchange (ignoring the a.m. wise advice of Ernst Mayr). Scientists' specialization means that particular issues are looked at in isolation (sometimes called ‘silos’), rather than as

an integrated whole (Joffe, 2010). Yet, since Aristotle's time, scientists have maintained that to understand a phenomenon in a scientific way we must know its ultimate cause(s) (Ruse, 2003).

In 1896, extended in 1904, A. Weismann devised the theory of Germinal Selection as an additional, hierarchic level to natural selection: competition and selection among the hereditary units within the germplasm (Weissman, 2011). Stephen Gould in his epic book *"The Structure of Evolutionary Thought"* (2002) extensively covered Weismann's concept of germinal selection as an early hierarchical selection perspective. Selection means differential survival. What has often been overlooked when dealing with sexual reproduction is that it is invariably associated with death. I don't mean the death of the reproductive organism that has repeatedly been addressed (Ruffié, 1986; Clark, 1996; Reznick and Ghilambor, 1999; Partridge et al., 2005). I mean the death of genetic units that during sexual reproduction are denied to pass their genetic information to the next generation: e.g. unicellular *Dictyostelium discoideum* that are engulfed by giant cells to form a multinucleated giant cell but disappear at the early stage of development (Okada et al., 1986) or the sometimes billionfold death of gametes in higher taxa.

6.1 A primer on the evolutionary roots of multicellular development

Knowledge is the object of our inquiry, and men do not think they know a thing till they have grasped the 'why' of it (which is to grasp its primary cause).

Aristotle

A variety of models for the evolution of multicellularity are based on the concept of division of labor (Willensdorfer, 2009; Gavrillets, 2010; Rossetti et al., 2010; Ispolatov et al., 2012). Such a division of labor does not necessarily need to occur in the form of soma and germ cells (Ispolatov et al., 2012). However, the basic physiological trade-off underlying the transition to differentiated multicellularity is between reproduction and viability, hence the germ-soma division of labor (Bonner, 2003; Kirk, 2003; Michod, 2006; 2007; Gavrillets, 2010). Studying the environmental conditions and processes underlying cellular differentiation at the unicellular-multicellular transition should provide valuable clues to understand the evolutionary roots and processes related to differentiation and reproduction (Buss, 1987; Heininger, 2001; Bonner, 2003). Studies of deep homology are showing that new structures need not arise from scratch, genetically speaking, but can evolve by deploying regulatory circuits that were first established

in protists and early metazoans. The deep homology of shared genetic, biochemical, cellular and developmental mechanisms (Shubin et al., 1997; 2009; Gerhart, 2000; Gilbert and Bolker, 2001; Hall, 2003) is the "fossil record" (Runnegar, 1986; Buss, 1987) that each contemporary organism carries inside and that allows a glimpse into deep evolutionary time.

Cellular differentiation evolved as a stress response. Unicellular organisms have a "feast and famine" lifestyle, limiting amounts of nutrients being rather the rule than the exception and long periods of nutritional deprivation are punctuated by short periods that allow fast growth (Koch, 1971; Kolter et al., 1993, Morita, 1993; Msadek, 1999; Heininger, 2001). The evolutionary signature of persistent metabolic "feast and famine" cycling is still present in every eukaryotic cell (Johnston, 1999; Ravussin, 2002). The feast-to-famine transition is not merely a metabolic response to a drop in nutrient availability; this transition also involves cell-to-cell signaling pathways, the results of which range from sporulation to fruiting body and complex pattern formation (Shapiro and Dworkin, 1997; Shimkets, 1999). Arguably, the most ubiquitous and predictably recurrent environmental signal that triggers differentiation in unicellular organisms is nutrient shortage (Losick and Stragier, 1992; Hengge-Aronis, 1993; Yarmolinsky, 1995; Kaiser, 1996). At the crossroads of uni- and multicellularity, *Dictyostelium discoideum*, a non-metazoan social amoeba, is the model organism for the study of differentiation and development (Janssens and Van Haastert, 1987; Heininger, 2001; Williams, 2006; 2010; Bonner, 2009; Kawabe et al., 2009; Kessin, 2010), apoptosis/programmed cell death (Cornillon et al., 1994; Heininger, 2001; Bonner, 2009; Kessin, 2010), and both asexual and sexual reproduction (Godfrey and Sussman, 1982; Urushihara, 1992; Francis, 1998; Urushihara and Muramoto 2006; Bonner, 2009; Flowers et al., 2010; Amagai, 2011). In these life-cycle events, a variety of functional equivalences between proteins of *Dictyostelium* and other eukaryotic species were found (Annesley and Fisher, 2009). Intriguingly, metabolic stress is the trigger for *Dictyostelium* multicellular differentiation. Following nutrient deprivation, between 10^4 and 10^6 unicellular *Dictyostelium discoideum* aggregate into mobile slugs that are spatially heterogeneous with respect to cell fate. Upon extended starvation, slugs transform into stationary fruiting structures that consist of a round, spore-bearing sorus at the top of a long, thin stalk (Mohanty and Firtel, 1999; Williams, 2006). Differentiation to spores and apoptosis of the stalk cells are closely linked in a social stress response

(Christensen et al., 1998). The stress response not only represents a primordial differentiation/apoptosis event but is also regarded as primordial reproduction event (Heininger, 2001; 2012; Foster et al., 2004; Jack et al., 2008). Cumulative evidence argues for the phylogenetic conservation of these processes. Dictyostelium-derived morphogens such as cyclic AMP and differentiation-inducing factors (DIFs) elicit dose-dependent and context-specific effects (Thomason et al., 1999; Williams, 2006; 2010) that are evolutionarily highly conserved. The conservation and ambiguity of the signals has been ascertained through their effects on various mammalian cell lines causing both growth arrest, differentiation and apoptosis (Asahi et al., 1995; Kubohara et al., 1995a; b; 1998; Kubohara, 1997; 1999; Miwa et al., 2000; Takahashi-Yanaga et al., 2003). Likewise, in the spheroidal green alga *Volvox carteri*, the most fundamental and primordial differentiation event creates germline and somatic cells (Kirk, 1998; Bonner, 2003; Heininger, 2012). The evolutionary conservation of these processes can be traced throughout phylogenesis following their continuity of genetic programming and the “fossil record” of the genome (Heininger, 2012).

Cellular stress is the overarching principle underlying cellular differentiation in metazoan organisms. Oxygen levels in the atmosphere only reached its present level approximately 350 million years ago (carboniferous period), clearly showing that cellular life on earth was well adapted to hypoxic conditions a long time before the present oxygen-dependent organisms appeared on earth (Wayne, 1985). Hypoxic microenvironments occur in both the developing embryo and adult, and often create specific ‘niches’ that regulate cellular differentiation (Maltepe and Simon, 1998; Simon MC et al., 2003). Hypoxia is a potent suppressor of mitochondrial oxidation and appears to promote “stemness” in adult and embryonic stem cells (Rehman, 2010). In adult stem cells, hypoxia prolongs the lifespan of the stem cells, increases their proliferative capacity, and reduces differentiation in culture (Fehrer et al., 2007; Jang and Sharkis, 2007). Embryonic stem cells are able to retain their pluripotency for a longer period of time when cultured in hypoxic conditions (Ezashi et al., 2005; Prasad et al., 2009). Components of the hypoxia-inducible factor-regulated system play essential roles in embryonic development and cellular differentiation (see chapter 7.2.4). Interestingly, Oct4, a transcription factor essential for maintaining stem cell pluripotency (see chapter 7.2.4), is a hypoxia- and hypoxia-inducible factor-regulated gene (Covello et al., 2006). On the other hand, hypoxia can also induce

differentiation of cell lines (Short et al., 2004).

Mammal ontogeny occurs in a low oxygen environment (estimated to be roughly 1–6%; Guyton & Hall, 1966) during the initial stages of development similar to the environment in which early unicellular organisms lived (Jaffe, 1998). From fungi and plants to humans, oxidative stress is a trigger and marker of developmental events and cell differentiation (Sohal et al., 1986; Allen, 1991; 1998; Zs.-Nagy, 1992; Blackstone, 1999; 2009; Heininger, 2001; 2012; Orzechowski et al., 2002; Foyer and Noctor, 2005; de Magalhães and Church, 2006; Gapper and Dolan, 2006; Pitzschke et al., 2006; Hitchler and Domann, 2007; Covarrubias et al., 2008; Nasution et al., 2008; Scott and Eaton, 2008; Owusu-Ansah and Banerjee, 2009; Hernández-García et al., 2010; Vincent and Crozatier, 2010; Sardina et al., 2012). Generally, growth factors stimulate cellular growth and differentiation through the formation of reactive oxygen species (Burdon and Rice-Evans, 1989; Radeke et al., 1990; Thannickal et al., 1993; Lo and Cruz, 1995; Sundaresan et al., 1995; Bae et al., 1997; Zafari et al., 1998; Sattler et al., 1999; Sung et al., 2000; Suzukawa et al., 2000; Thannickal and Fanburg, 2000; Tolando et al., 2000; Sauer et al., 2001; Menon et al., 2003; Sturrock et al., 2006; Meng et al., 2008; Morgan and Liu, 2010). During cellular differentiation of two human embryonic stem cell lines, mitochondrial superoxide production and cellular levels of reactive oxygen species increased as result of increased mitochondrial biogenesis. The expression of major antioxidant genes was downregulated despite this increased oxidative stress and DNA damage levels increased during differentiation, whereas expression of genes involved in different types of DNA repair decreased (Saretzki et al., 2004; 2008).

The p53 protein family is activated by (Lu and Lane, 1993; Wang and Ohnishi, 1997; Vousden and Lu, 2002; Murray-Zmijewski et al., 2006; 2008; Berns, 2010; Hölzel et al., 2010; Marchenko et al., 2010; Lu et al., 2011) and integrates multiple cellular stress signals and assesses cellular damages to trigger different cellular outcomes — ranging from cell-cycle arrest (Aoubala et al., 2011; Blagosklonny, 2011; Smits, 2012), DNA repair (Götz and Montenarh, 1996; Albrechtsen et al., 1999; Seo et al., 2002; Sengupta and Harris, 2005), genome stability (Lane, 1992; Vousden and Lane, 2007; Riley et al., 2008; Dulic, 2011; Spinnler et al., 2011), tumor suppression (Barlev et al., 2010; Ho et al., 2010; Feldser et al., 2010; Junttila et al., 2010; Cheok et al., 2011; Madan et al., 2011), induction of autophagy (Crichton et al., 2006; Amaravadi et al., 2007), cell migration (Roger et al.,

2006), reproduction (Hu et al., 2007; Hu, 2009; Amelio et al., 2012), regulation of metabolism (Jones RG et al., 2005; Bensaad et al., 2006; Green and Chipuk, 2006; Matoba et al., 2006; Bensaad and Vousden, 2007; Olovnikov et al., 2009; Vousden and Ryan, 2009; Feng and Levine, 2010; Hu W et al., 2010; Madan et al., 2011; Maddocks and Vousden, 2011; Liang et al., 2013a), angiogenesis (Teodoro JG et al., 2006), and senescence, differentiation (Liu Y et al., 2009; Darzynkiewicz, 2010; Mallette et al., 2010; Manning and Kumar, 2010; Morselli et al., 2010; Horikawa et al., 2011; Lee et al., 2011; Vilborg et al., 2011; McGee et al., 2012; Tucci, 2012), to apoptosis (Mihara et al., 2003; Karlberg et al., 2010; Meley et al., 2010; Trinh et al., 2010; Hill et al., 2011; Koster et al., 2011; Nardinocchi et al., 2011; Vaseva et al., 2011). p53 is a key regulator of mitochondrial function, including ROS production and associated repair of mtDNA oxidative damage, as well as mtDNA replication and mitochondrial biogenesis (Ralph et al., 2010). Thus, p53 couples energy metabolism and ROS formation by modulating the transcription of target genes that control the fluxes through mitochondrial respiration, glycolysis, or the pentose phosphate shunt (Liu B et al., 2008; Maddocks and Vousden, 2011). ROS are potent activators of p53 function and, indeed, the redox balance is believed to be a key factor in the modulation of p53 activity (Jayaraman et al., 1997; Martindale and Holbrook, 2002).

How can the fascinating variety of cellular functions in differentiated cell lineages be generated from a single genome? Emerging biochemical, genetic, and functional evidence suggests that both genetic and epigenetic reprogramming is crucial for diverse biological processes, including primordial germ cell reprogramming, pluripotent stem cell differentiation, hematopoiesis, and cancerogenesis (Ficz et al., 2011; Wu and Zhang, 2011; Tan and Shi, 2012). So far, developmentally programmed genome rearrangement that leads to the elimination of portions of chromosomes or the loss of entire chromosomes during embryonic development has been described in protists, crustaceans, insects, and vertebrates (fishes, birds, marsupials) (Beermann, 1959; Nakai et al., 1991; 1995; Prescott, 1994; Kubota et al., 1997; 2001; Goto et al., 1998; Kohno et al., 1998; Watson et al., 1998; Sanchez and Perondini, 1999; Müller and Tobler, 2000; Goday and Esteban, 2001; Kloc and Zagrodzinska, 2001; Degtyarev et al., 2002; Bachmann-Waldmann et al., 2004; Matzke and Birchler, 2005; Pigozzi and Solari, 2005; Yao and Chao, 2005; Zufall et al., 2005; Drouin, 2006; Duret et al., 2008; Itoh et al., 2009; Smith et al., 2009; 2012; Kojima et al., 2010; Nemetschke et al., 2010; Nowacki et al., 2011; Sémon

et al., 2012; Wang et al., 2012; Bracht et al., 2013; Sabin et al., 2013). Intriguingly, the process of DNA elimination in *Tetrahymena* and *Paramecium* is orchestrated by small RNAs which are expressed during conjugation and direct chromatin modifications to mark internal eliminated segment sequences for elimination (Matzke and Birchler, 2005; Nowacki et al., 2011; Sabin et al., 2013). Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA-mediated regulatory events, are phylogenetically conserved to effect the long-lasting changes in gene expression during development and tissue differentiation of a variety of taxa (Wu and Sun, 2006; Hitchler and Domann, 2007; Singh et al., 2009; Feng et al., 2010; Hu B et al., 2010; Iorio et al., 2010; Mahapatra et al., 2010; Ficz et al., 2011; Wu and Zhang, 2011; Briones and Muegge, 2012; Hu et al., 2012; Sabin et al., 2013). Genome-wide dynamic DNA methylation changes occur during cellular differentiation (Lister et al., 2009; Geiman and Muegge, 2010; Nagae et al., 2011; Su et al., 2012). It has been estimated that the mitotic transmission fidelity of DNA methylation patterns is about three orders of magnitude lower than that of DNA sequence (an error rate of 1 in 10^6 and 1 in 10^3 for DNA sequences and DNA modification, respectively) (Ushijima et al., 2003; Laird et al., 2004; Riggs and Xiong, 2004; Genereux et al., 2005; Fu et al., 2010; Petronis, 2010). Errors in methylation pattern were mainly due to de novo methylations in unmethylated regions (Ushijima et al., 2003). This stochastic epigenetic instability can result in significant epigenetic differences accumulating over time across cells, despite the DNA sequence identity of these cells (Wong et al., 2005; Petronis, 2010). Thus, epigenetic reprogramming of embryonic stem cells and differentiating cells has a significant stochastic element (Ushijima et al., 2003; Reiss and Mager, 2007; Raj and van Oudenaarden, 2008; Mohn and Schübeler, 2009) resulting in genetic and epigenetic mosaicism (Rakyan et al., 2002; Petronis et al., 2003; Wong et al., 2005; Feinberg and Irizarry, 2010; Weinhouse et al., 2011). It can be expected that such genetic and epigenetic variation impacts the competitive abilities of cells, rendering them the raw material for selective events.

No tissue differentiates without the loss of cells by apoptosis. In a variety of tissues, competition for limiting amounts of trophic factors, e.g. nerve growth factor, determines life or death of cells (Hamburger and Oppenheim, 1982; Raff, 1992; Deckwerth and Johnson, 1993; McLean et al., 1997; Barres and Raff, 1999; Casaccia-Bonnel et al., 1999; Bonner-Weir, 2000; Meier et al., 2000; Lee FS et al., 2001; Li L et al., 2001; Frago et al., 2003; Imaizumi et al., 2004).

The losers of this cell competition die (Adachi-Yamada and O'Connor, 2004). Although this cellular selection has a stochastic and spatiotemporal component (Milán et al., 2002), predominantly the competitively inferior cells are eliminated (Adachi-Yamada and O'Connor, 2004; Igaki, 2009).

6.2 A primer on reproductive biology

Surprisingly, almost none of the numerous publications attempting to elucidate the evolutionary origin and maintenance of sex made reference to the molecular processes of sexual reproduction. In fact, these molecular processes allow telling inferences on the evolutionary rationale of sexual reproduction. A corollary of the lack of information exchange between evolutionary biology and reproduction biology is the strange phenomenon that, to my knowledge, the millionfold “waste” production of gametes so far was not taken into account in any one of the many theories about the evolutionary rationale of sexual reproduction. And, strangely, that reproduction biology failed to interpret this “waste” gamete production in an ecological-evolutionary context.

Primordial germ cells (PGCs) are the precursor cells to the eggs and sperm that comprise the germline. In many animals, a population of PGCs is set aside early in embryogenesis that is dedicated for the germ cell lineage while other cells in the embryo differentiate into soma giving rise to the organ systems of the adult. PGCs migrate to the somatically derived gonads and proliferate into germline stem cells that can self renew and differentiate into gametes. At least three general mechanisms are used to specify PGCs within the animal kingdom (Extavour and Akam, 2003; Johnson AD et al., 2003; 2011; Seydoux and Braun, 2006; Extavour, 2007; Rosner et al., 2009; Gustafson and Wessel, 2010). The germline can form (i) early in embryogenesis from an inheritance of maternal factors (maternally derived, also referred to as preformation) as used in flies and nematodes, (ii) by cell-cell interactions early in embryogenesis (inductive, also referred to as epigenesis) as seen in mice, and (iii) any time in the animal's life, even in adulthood, from a multipotent stem cell precursor (persistent multipotent cell-derived germ cells), such as in planaria and hydra (a mode of germ cell specification pathway that also occurs in plants) (Gustafson and Wessel, 2010). Despite these developmental differences, animals employ a group of conserved molecular determinants for PGC specification. The most common of these is the gene *Vasa* (Raz, 2000; Mochizuki et al., 2001; Noce et al., 2001; Gustafson and Wessel, 2010). Anisogamy or gamete dimorphism is the rule in multicellular animals and plants (Bell, 1982; Parker,

1982) — egg-producing females make a larger contribution to the zygote compared with the small contribution made by the sperm of males, but both males and females contribute 50% of the genes.

6.2.1 Male gametogenesis

Sperm cells are, arguably, the most differentiated cells, and spermatogenesis may very well be one of the most complex biological processes undergone by any organism. Spermatogenesis, the sequence of male germ cell development, is a long, orderly, and well-defined process occurring in seminiferous tubules of the testis whereby undifferentiated spermatogonial germ cells evolve into maturing spermatozoa. The functions of all of the cell types in the testis, the Leydig cells, the Sertoli (and/or peritubular) cells, the germ cells, and the vasculature, are interwoven in a highly organized manner (Sharpe et al., 1990). Mammalian spermatogenesis can be divided into two phases. The first round of spermatogenesis, which starts after birth, is characterized by the sequential appearance within seminiferous tubules of cells corresponding to each stage of germinal cell. The second phase is that of mature spermatogenesis, made up of the subsequent rounds of spermatogenesis which then occurs permanently in adult animals. Seminiferous tubules are composed of somatic cells (myoid cells, Leydig cells and Sertoli cells), and germ cells (spermatogonia, spermatocytes, and spermatids). During spermatogenesis, three distinct stages can be differentiated: spermatocytogenesis by mitotic proliferation of spermatogonia, meiotic development of spermatocytes, and spermiogenesis, the postmeiotic development of spermatids and maturation of the spermatozoon (Johnson, 1995; Johnson et al., 2000). Spermatogenesis is dependent on a specific microenvironment (niche) contributed by Sertoli, myoid, and Leydig cells for proper development.

The Sertoli cells (the somatic cells of the seminiferous epithelium) play a key role in regulation of spermatogenesis and altering rates of spermatozoa produced (Johnson et al., 1984b; Orth et al., 1988; Sharpe, 1994; Rato et al., 2012). Damages to Sertoli cells lead to severe disruption of spermatogenesis and male infertility (Sridharan et al., 2007; Papaioannou et al., 2009). Sertoli cells are the target for both the pituitary follicle stimulating hormone and testosterone (almost exclusively produced by Leydig cells), illustrating their crucial role in supporting germ cell maturation (Sharpe, 1994; Walker and Cheng, 2005; Walker, 2009). Sertoli cells provide a specialized, protected environment within the seminiferous tubules of the testis for germ cell development. Adjacent Sertoli cells form tight junctions with each other such

that nothing larger than 1000 daltons can pass from the outside to the inside of the tubule. This characteristic of Sertoli cells creates what is known as the blood-testis barrier. Serum macromolecules are effectively excluded from the adluminal section, which is an essential prerequisite for spermatogenesis, creating a microenvironment consisting exclusively of Sertoli cell secretions and germ cells (Dym and Fawcett, 1970; Russell and Peterson, 1985; Griswold, 1995). At the beginning of meiosis, germ cells located outside of the barrier pass through the tight junctions. Once beyond the blood-testis barrier, germ cells are dependent on Sertoli cells to supply nutrients and growth factors (Mruk and Cheng, 2004). Sertoli cells provide factors required to fuel germ cell metabolism (lactate, transferrin, androgen binding protein), growth regulatory factors (stem cell factor, transforming growth factors alpha and beta, insulin-like growth factor-I (IGF-I), fibroblast growth factor (FGF) and epidermal growth factor (EGF) and hormones that regulate the development of the male reproductive structures or feedback to regulate the hormonal signals affecting Sertoli cells (mullerian-inhibiting substance (MIS), and inhibin) (Jegou, 1992; Skinner, 2005). Sertoli cells are very active in elongation and desaturation of polyunsaturated fatty acids (PUFAs), while isolated germ cells are inefficient in synthesizing 22:5n-6 and 22:6n-3 (Retterstøl et al., 2001a; b). Thus, Sertoli cells appear to provide the bulk of PUFAs to pachytene spermatocytes and round spermatids (Retterstøl et al., 2001a; b). Glutathione levels (GSH) are a marker of oxidative stress susceptibility. GSH participates in diverse biochemical processes, including the maintenance of protein thiol groups, and protection of cells against peroxides, free radicals, and certain xenobiotics (Meister and Anderson, 1983). Sertoli cells are essential for the maintenance of spermatogenic cell GSH. The rate of GSH synthesis in isolated spermatogenic cells is insufficient to compensate for GSH turnover (Li et al., 1989). Sertoli cell functions include providing structural support and nutrition to developing germ cells, phagocytosis of degenerating germ cells and residual bodies, release of spermatids at spermiation and production of a host of proteins that regulate and/or respond to pituitary hormone release and that influence mitotic activity of spermatogonia (Amann, 1970; Dym and Raj, 1977; Feig et al., 1980; Jutte et al., 1982, 1983; Tres et al., 1986; Buch et al., 1988; Bellve and Zheng, 1989; Johnson, 1991; Russell and Griswold, 1993; Sharpe, 1994; Griswold, 1998; Walker and Cheng, 2005; Johnson et al., 2008).

In a germ cell's path to make a spermatozoon from a spermatogonium, a spermatogonium divides by

mitosis in the basal compartment of the seminiferous tubule, to produce either stem cells or committed spermatogonia that ultimately become primary spermatocytes. These cells pass through the blood-testis barrier of the Sertoli cell tight junctions as they move into the adluminal compartment. Germ cells continue their development in the immunologic-protected site of the adluminal compartment. In mammals, numerous (9 to 11) cell divisions of spermatogonia and 2 divisions of spermatocytes build the germ cell population of the testis. Spermatocytes undergo two meiotic divisions to form haploid spermatids. During meiosis, spermatocytes undergo chromosomal pairing, synapsis, and genetic exchange as well as transforming into haploid cells. Each cell progresses through a series of cytologically identifiable stages known as leptotene (chromosomes begin to condense), zygotene (pairing of homologous chromosomes is initiated), pachytene (complete synapsis of homologous chromosomes which undergo recombination), diplotene (homologous chromosomes begin to separate), diakinesis (chromosomes condense), metaphase I (separation of homologous chromosomes) and metaphase II (separation of sister chromatids). The germ cells at the end of meiosis produce round spermatids (de Kretser and Kerr, 1988; 1994; Holstein et al., 2003). During spermiogenesis, the nucleus of round haploid spermatids undergoes major chromatin restructuring (Meistrich, 1989; Wouters-Tyrou et al., 1998). The somatic and meiotic histones that remain in spermatids are replaced ~14 days before ejaculation in the mouse (~21 days in human) with basic transition proteins and then with protamines (Meistrich, 1989; Churikov et al., 2004; Kimmins and Sassone-Corsi, 2005), which are arginine-rich proteins that condense the chromatin and cause DNA to become transcriptionally inactive (Kierszenbaum and Tres, 1978). Sperm are then released into the seminiferous lumen and undergo a final process of maturation within the epididymis where they acquire motility and the ability to fertilize the egg (Khole, 2003; Gatti et al., 2004). The result of these elaborate processes is transcriptionally inert mature sperm DNA, the most highly condensed DNA structure known. During spermatogenesis, loss of a certain percentage of germ cells via apoptosis is normal in all species investigated, and it plays a critical role in determining spermatogenic efficiency (Roosen-Runge, 1973; Sharpe, 1994). Germ cell death occurs exclusively or preferentially in certain developmental stages, also varying in a species-specific manner in quality and quantity (Roosen-Runge, 1977). It takes approximately 35 days in mice (~64 days in humans)

for germ cells to develop from spermatogonia to spermatozoa. The last round of DNA synthesis occurs in preleptotene spermatocytes. Meiotic prophase lasts about two weeks in the mouse (less than 4 weeks in man) and is followed by the first and second meiotic divisions, which occur within 24 hr of each other, while spermiogenesis takes about three weeks (over 5 weeks in man). It has been calculated that, assuming that a man produces 100 million (10^8) mature sperm per day, during an average reproductive life of sixty years he would produce well over two trillion (2×10^{12}) mature sperm in his lifetime (Martin, 1991) (and a multiple of this figure of immature germ cells).

6.2.2 Female gametogenesis

The mature oocyte is one of the largest cell types in most eukaryotic species. While the nucleus of an oocyte contains the same amount of DNA as any other post-replication diploid cell in an organism, the cytoplasm is larger in volume and often contains much more RNA and protein than is found in most somatic cells. The mature oocyte is prepared to sustain the early development of the embryo immediately following fertilization. In some species the embryo develops externally, e.g. in frogs or sea urchins. Thus the oocyte must contain sufficient yolk reserves to sustain the embryo until it begins feeding. In the mouse, the embryo develops internally, is nourished by the mother and little or no yolk is stored in the oocyte (Bakken and McClanahan, 1978). In most teleosts, all amphibians, most reptiles and relatively few mammals, oogenesis appears to continue either uninterruptedly or cyclically throughout reproductive life. The other variant is that the oogenesis occurs only in fetal gonads, and oogonia neither persist nor divide mitotically during sexual maturity - e.g. cyclostomes, elasmobranchs, a few teleosts, perhaps some reptiles, all birds, mono-tremes, and with a few possible exceptions, all eutherian mammals (Zuckerman, 1951; 1971; Franchi et al., 1962). Others maintain that neo-oogenesis and follicular renewal during the prime reproductive period exists throughout the animal kingdom, including higher vertebrates (Bukovsky et al., 2005). In the developing mouse fetus, primordial germ cells (PGCs) that have colonized the developing ovaries (the germ cells are now referred to as oogonia) continue to proliferate and thus expand the female germline. Peak numbers of germ cells are reached by around e13.5, at which time many of the oogonia have left the mitotic cell cycle and initiated the first steps of meiosis (Byskov, 1986). After passing through the leptotene, zygotene, pachytene, and diplotene stages of meiosis I, the oocytes become arrested in diakinesis coincident with their enclosure by a specialized

population of somatic (pregranulosa) cells to form nongrowing primordial follicles (Byskov, 1986). An identical situation is believed to proceed in human fetal ovaries (Briggs et al., 1999), with peak germ cell numbers of around 7×10^6 reached by approximately the 20th week of gestation (Block, 1952; Baker, 1963; Tilly and Ratts, 1996). In humans, it has been estimated that the ~7 million germ cells in the fetal ovaries at around week 20 of gestation are decimated to 1–2 million viable oocytes in early neonatal life (Baker, 1963). A proportion of oocytes and follicles either do not become, or do not stay, arrested (probably by escaping local inhibitors, Wandji et al., 1997; Yang and Fortune, 2008), or they initiate growth during prenatal or prepubertal life. These growing follicles are a consistent feature of ovaries during childhood (Peters et al., 1976). They always become atretic due to the prevailing immaturity of the hypothalamo-pituitary axis (Djahanbakhch et al., 2007). By menarche, the time of in-principle commencement of reproductive competence, the number of primordial follicles is down to about 300,000 (Block, 1952; Faddy et al., 1999; Jansen and Burton, 2004). Comparable proportions of germ cells are lost during fetal ovarian development in other vertebrate species (Beaumont and Mandl, 1961). In all vertebrate species examined to date, females are born with far fewer oocytes than the peak numbers present during early oogenesis. In fact, it has been estimated that over two-thirds of the potential female germ cell pool is lost by the time of birth in rats (Beaumont and Mandl, 1961), mice (Borum, 1961; Bakken and McClanahan, 1978), and humans (Pinkerton et al., 1961; Baker, 1963; Forabosco et al., 1991), resulting from attrition of both oogonia and oocytes (Borum, 1961; Bakken and McClanahan, 1978). In the follicular phase of the reproductive cycle, a cohort of primordial follicles are recruited for further development and maturation, with the end result being ovulation of one or more dominant mature follicles. Folliculogenesis is a process starting from primordial follicles, through primary, secondary, and antral stages to the largest Graafian or preovulatory follicles. Less than 0.1% of follicles present at the beginning of puberty develop into follicles capable of being ovulated (Tilly et al., 1997; Marti et al., 1999). It has been estimated that the duration of time required for the growth of a human follicle from the primordial stage to the large preantral stage takes in excess of 150 days (Gougeon, 2004). Thus, a follicle which ovulates in any given menstrual cycle will actually have begun to grow at least five menstrual cycles earlier. At ovulation, the human egg has entered its second meiotic division. The secondary oocyte just before fertilization lies within a

comparatively massive, cystic structure, approximately 2 cm in diameter, the preovulatory Graafian follicle. This follicle is composed of up to about one million follicular (granulosa) cells, a fluid-filled antrum that accounts for most of the follicle's volume, and an eccentrically placed egg that is surrounded by a specialized group of closely applied granulosa cells, the cumulus oophorus. In response to the luteinizing hormone surge, the preovulatory follicles ovulate and release oocytes. After ovulation, the granulosa cells and theca cells remaining within the follicles differentiate into a transient endocrine gland, the corpus luteum (Murphy, 2000). The corpus luteum is critical for successful maintenance of pregnancy in mammals because it is the primary source of the progestational hormone progesterone. Granulosa cells play a nurturing role in supporting oocyte development and follicle maturation by providing essential nutrients and estrogen (Buccione et al., 1990; Binelli and Murphy, 2010). However, during follicular growth and development, more than 99% of follicles become atretic and regress, primarily due to apoptosis of granulosa cells (Baker, 1963; Hughes and Gorospe, 1991; Tilly et al., 1991; Faddy et al., 1992; Kaipia and Hsueh, 1997; Jiang JY et al., 2003). Thus, in each cycle of folliculogenesis most primordial follicles undergo a process of regression known as atresia and only one or a few (depending on the species) numbers of them are destined to become preovulatory follicles (McGee and Hsueh, 2000). Considering that a woman will generally ovulate a single egg during each monthly cycle, between 400 and 500 oocytes advance to the point of ovulation in adult life. In summary, of the 7 million or so oocytes formed in human fetal ovaries, fewer than 500 will ever ovulate. A quick calculation thus reveals that greater than 99.99% of fetal germ cells and 99.9% of the oocytes endowed in the human ovaries at birth face death as their ultimate fate, a process which, when completed, leads to exhaustion of the follicle reserve and to menopause (Morita and Tilly, 1999; Tilly, 2001). Follicular atresia is also a common feature of nonmammalian vertebrate ovaries although the mode of atresia may differ in different species (Saidapur, 1978).

If there is any meaning to evolutionary theory and to MacArthur and Wilson's notion (1967, p. 149): "Evolution ... favours efficiency of conversion of food into offspring". this "waste" female and male gamete overproduction **must** bear an evolutionary meaning, since otherwise these organisms should have been replaced by organisms that deal with their resources more economically. In a world of limited resources (Heininger, 2012), "The best competitor in an environment will be that population that is able to

persist using the lowest level of resource supply" (Sears et al., 2004).

7. Sex: Proactive mutagenesis

It would be very strange indeed to believe that everything in the living world is the product of evolution except one thing – the process of generating new variation!

Jablonka and Lamb, 2005 p.101

Summary

The environmental signals that resulted in the reactive bacterial transformation were both accommodated and assimilated in eukaryotes as proactive bet-hedging tools. The oxidative stress was "domesticated" by higher taxa as "fire in the hearth" to institutionalize the generation of genetic variation. To this end both male and female gametogenesis proceed in a stressful milieu. The poor vascularization of the testes and the maturing follicle together with the high metabolic investment particularly for spermatogenesis result in functional hypoxia and metabolic and oxidative stress. Hypoxia-inducible factors are constitutionally expressed in male and female germ cells. Various molecular and structural features such as cytokines and nuclear factor-kappaB, heat shock proteins, germ granules, mitochondrial uncoupling and aquaporin-8, and upregulated, but poorly coordinated DNA repair are footprints of the (epi-)mutagenic, DNA instability-fostering milieu. Importantly, germ granules are the germline-specific version of stress granules, the stress-dependent assembly of ribonucleoproteins. In essence, sexual reproduction evolved a gender-dimorphic "division of labor". The smaller male gametes are exposed to high oxidative stress resulting in male-biased (epi-)mutagenesis and innovation of genetic information. The larger female gametes, affording a higher investment of resources, rather are the elements of information conservation. Germline cell differentiation is controlled by a specific set of genes whose expression is tightly locked into the repressed state in somatic cells. Large-scale epigenome alterations, now evidenced in nearly all cancers, lead to aberrant activation of these normally silenced genes, known as cancer/testis genes. The observation of shared characteristics between germline cells and tumor cells has led to the concept that recapitulation of

portions of the germline gene-expression programme might contribute characteristic features to the neoplastic phenotype, including immortality and DNA instability.

Evolution is opportunistic and favors the prepared (Caporale, 1999). Due to its blindness and purposelessness, evolution does not "know" in advance which evolutionary path will lead to the increase of fitness (or at least avoid the loss of fitness) in fluctuating often unpredictable environments. Therefore, retrospectively, the best "strategy" to increase fitness is to take every possible path at every next step, sampling the 'sequence space' with as many lottery tickets as is reasonable in a bet-hedging strategy. As a result, no fit configurations will be missed. In contrast, if the evolutionary entity only takes a part of paths at the current location, only configurations downstream of these paths can be reached: all other configurations will be missed. From the angle of blind evolution the greater the incompleteness in configuration sampling, the smaller is the probability for blind evolution to increase fitness (Fu, 2007). Evidently, bacteria respond to stress resorting to a bet-hedging strategy, seeking new genetic material that might help them to survive (Johnsborg and Håvarstein, 2009). Three main bet-hedging strategies have been described: conservative bet-hedging (play it safe), diversified bet-hedging (don't put all eggs in one basket) and adaptive coin flipping (choose a strategy at random from a fixed distribution) (Cohen, 1966; Cooper and Kaplan, 1982; Seger and Brockmann, 1987; Olofsson et al., 2009). Bet-hedging is found in organisms ranging from bacteria to humans (Cohen, 1966; Gillespie, 1973; 1974a; Slatkin, 1974; Tonegawa, 1983; Hairston and Munns, 1984; Seger and Brockmann, 1987; Moxon et al., 1994; Danforth, 1999; Meyers and Bull, 2002; Friedenber, 2003; Balaban et al., 2004; Kussell and Leibler, 2005; Wolf et al., 2005; Venable, 2007; Acar et al., 2008; Ackermann et al., 2008; Beaumont et al., 2009; Olofsson et al., 2009; Childs et al., 2010; Gremer et al., 2012; Morrongiello et al., 2012; Starrfelt and Kokko, 2012).

7.1 Sexual reproduction: domesticating the fire

It has been argued that exchange of genetic material can only speed up evolution if donors and recipients use the same system to encode, store and process genetic information. Consequently, prokaryotic "sex" must have played a significant role in preserving the near universality of the genetic code (Johnsborg et al., 2007). Exchange of genetic materials by two individual members of the same species is considered to be the origin of primitive sex. Genetic assimilation occurs

when an acquired trait loses its dependency on environmental triggers and becomes an inherited trait (Masel, 2004). Already at the level of bacteria, genetic assimilation of competence and transformation is observed (Majewski, 2001; Birdsell and Wills, 2003). *Neisseria gonorrhoeae*, *Helicobacter pylori*, and *Thermus thermophilus* are some of at least 44 species of bacteria that are naturally competent for genetic transformation and are able to take up DNA independently of their growth phase (Sparling, 1966; Hidaka et al., 1994; Lorenz and Wackernagel, 1994; Israel et al., 2000; César et al., 2011). Another Gram-negative bacterium, *Haemophilus influenzae* becomes competent under defined physiological conditions, but is not sensitive to external signaling (Lorenz and Wackernagel, 1994). Transformation in the pathogenic *Neisseria* has fuelled high rates of recombination (Smith et al., 1993) that has been estimated to change an allele of the *Neisseria meningitidis* genome ten times more likely than point mutation (Feil et al., 1999; Jolley et al., 2005). In gonococci, transformation has been harnessed as a powerful mechanism for generating genetic diversity, spreading advantageous alleles and mediating some forms of antigenic variation (Hobbs et al., 1994; Fudyk et al., 1999; Snyder et al., 2004). Analyses of the four published neisserial genomes revealed high densities of repeated elements (Parkhill et al., 2000; Tettelin et al., 2000; Achaz et al., 2002; Bentley et al., 2007). Intrachromosomal recombination between these repeats is a major source of variability in *Neisseria*, resulting in frequent adaptive changes in gene expression profiles (Moxon et al., 1994; Saunders et al., 2000) and even reoccurring states of hypermutability (Richardson et al., 2002; Davidsen et al., 2007). Transformation in *Neisseria* spp. and *H. influenzae* requires the presence of a specific DNA uptake sequence (Scoocca et al., 1974; Danner et al., 1980; 1982; Goodman and Scoocca, 1988; Elkins et al., 1991) in the incoming DNA. These signals allow discrimination between DNA from closely related strains or species and foreign/unrelated DNA. When exposed to a mixture of homologous and foreign DNAs, these human pathogens show preferential uptake of DNA uptake sequence-containing DNA (Scoocca et al., 1974; Elkins et al., 1991; Duffin and Seifert, 2010). In *Neisseria meningitidis*, *Neisseria gonorrhoeae* and *Haemophilus influenzae* by far the most frequent 9- or 10mer repeat genomic sequences residing within coding regions are the DNA uptake sequences required for natural genetic transformation. A significantly higher density of DNA uptake sequences was found within genes involved in DNA repair, recombination, restriction modification and

replication than in any other annotated gene group in these organisms (Davidsen et al., 2004). Increased DNA uptake sequences density is expected to enhance DNA uptake and the over-representation of DNA uptake sequences in genome maintenance genes might reflect facilitated recovery of genome preserving functions. For example, transient and beneficial increase in genome instability can be allowed during pathogenesis simply through loss of antimutator genes, since these DNA uptake sequences-containing sequences will be preferentially recovered. Furthermore, uptake of such genes could provide a mechanism for facilitated recovery from DNA damage after genotoxic stress (Davidsen et al., 2004). Evidence was also presented that DNA uptake sequences are implicated in genome stability rather than in generating adaptive variation (Treangen et al., 2008). This dual evidence for a role of DNA uptake sequences in DNA repair and diversity may reflect the ambiguity of sexual reproduction in generating both genetic conservation and innovation depending on the evolutionary demands of an organism (Bedau and Packard, 2003; Buchanan et al., 2004; Clune et al., 2008; Dees and Bahar, 2010). During evolution, this primitive form of molecular sex has been transformed into a complex biological function involving specialized sexual structures and multiple hormonal interactions (Roy et al., 1996). While genetic recombination is a key feature of meiosis, it is not unique to this process. Recombinational capacity is found throughout the prokaryotes and therefore must considerably predate eukaryotes and meiosis (Levin, 1988; Cavalier-Smith, 2002; Marcon and Moens, 2005; Wilkins and Holliday, 2009). A crucial set of molecules for genetic recombination, the *recA* family of proteins, is utilized for recombination in both prokaryotes and eukaryotes (Shinohara et al., 1992; Wilkins and Holliday, 2009).

Genetic assimilation is the evolutionary process by which a phenotype that is produced specifically in response to some environmental stimulus, such as a stressor, becomes stably expressed independently of the evoking environmental effect (Waddington, 1942; 1953a; 1956; 1957; Scharloo, 1991; Masel, 2004; Braendle and Flatt, 2006; Pigliucci et al., 2006). Genetic assimilation is a special case of a more general phenomenon, called genetic accommodation (West-Eberhard, 2003; Braendle and Flatt, 2006). This scenario of phenotypic evolution posits that (1) a mutation or environmental change triggers the expression of a novel, heritable phenotypic variant, (2) the initially rare variant phenotype starts to spread (in the case of an environmentally induced change, due to the consistent recurrence of the environmental factor), creating a subpopulation expressing the novel trait,

and (3) selection on existing genetic variation for the regulation or form of the trait causes it to become (a) genetically fixed or to remain (b) phenotypically plastic (West-Eberhard, 2003). According to Braendle and Flatt (2006), only process (3) represents genetic accommodation in the strict sense as it was defined by West-Eberhard (2003) but, for the sake of conceptual simplicity, they refer to genetic accommodation as the entire sequence of steps (1) to (3). Genetic assimilation describes only scenario (3a), i.e. the fixation of the response leading to environmental insensitivity, also called “environmental canalization” (West-Eberhard, 2003), whereas genetic accommodation can describe both the evolution of environmentally insensitive (3a) and sensitive (3b) trait expression (Braendle and Flatt, 2006). Another difference between the two concepts is that the model of genetic accommodation assumes that the trigger uncovering previously cryptic or novel phenotypes is either genetic or environmental, whereas the concept of genetic assimilation typically assumes only an environmental trigger. Thus, genetic accommodation is a generalization of genetic assimilation (Braendle and Flatt, 2006). Sexual trait expression can be both environmentally insensitive, i.e. genetically assimilated, as in birds and mammals, and environmentally sensitive, i.e. genetically accommodated, as in cyclically parthenogenetic taxa like daphnia and aphids and geographically parthenogenetic taxa.

Co-option, exaptation, and preadaptation are related terms referring to shifts in the function of a trait during evolution. For example, a trait can evolve because it served one particular function, but subsequently it may come to serve another. Time and again evolution had to master an arduous task: what had evolved as a facultative response of unicellular organisms to environmental cues had to be fixed after the multicellular transition in an obligate developmental context (Heininger, 2001; 2002; 2012). What had been an environmental challenge evolved to be relayed by signaling molecules as a cellular message in the internal milieu of a multicellular organism.

In the same way fire is dangerous and humans learned how to control and use it, cells control and use ROS (de Magalhães and Church, 2006). Sexual reproduction evolved as stress response and the “wildfire” that had served to generate genetic diversity was “tamed” as “domestic fire in the hearth” to constitutively generate genetic variation. What evolved as reactive process became a proactive evolutionary motor. Importantly, by no means this implies that evolution may be foresighted.

7.2 The oxidative stress of gametogenesis

That oxidative stress represents an essential feature of gametogenesis is widely acknowledged (Riley and Behrman, 1991; Aitken, 1995; Tilly and Tilly, 1995; Chainy et al., 1997; Fisher and Aitken, 1997; Kugu et al., 1998; Knapen et al., 1999; Behrman et al., 2001; Gil-Guzman et al., 2001; Orozco et al., 2003; Ford, 2004; Juan et al., 2005; Aitken and Roman, 2008; Gupta et al., 2008). However, so far the focus of scientific interest was rather on the detrimental, pathophysiological, aspects of oxidative stress, particularly in mammalian gametogenesis, largely ignoring its physiological implications. Oxidative stress is an inherent feature of gametogenesis in all taxa. Importantly, from lower to higher taxa there is a substantially incremental use of this general principle, culminating in human male gametogenesis that balances at the verge of mutational error catastrophe (see chapter 14.1). Scientific focus has been on mammalian gametogenesis. Thus, evidence for the relevance of oxidative stress in gametogenesis is most compelling in mammals while it is often rather circumstantial in other taxa. One of the main difficulties relates to the absence of generally agreed methodologies to measure ROS, especially in vivo (Taylor and Moncada, 2010). But the fire develops enough smoke to be detected indirectly. For instance, DNA and RNA oxidation as indicators of cellular damage from free radicals (Halliwell and Gutteridge, 1999; Joyner-Matos et al., 2007), and up-regulated expression of specific stress proteins, such as heat shock proteins, are biomarkers of a homeostatic cellular response to a stressor (e.g. Hofmann and Somero, 1995; Downs et al., 2001; Abele and Puntarulo, 2004; Joyner-Matos et al., 2007).

A multitude of cellular stress-related features witnesses the pronounced developmental stress during gametogenesis:

- metabolic and replicative stress
- functional hypoxia with constitutive expression of hypoxia-inducible factors
- oxidative stress markers
- expression of heat shock factors and heat shock proteins
- RNA granules
- epigenetic reprogramming
- recombination requiring double-strand breaks
- membrane lipid unsaturation
- mitochondrial aquaporin-8
- DNA repair
- autophagy and apoptosis

During mammalian gametogenesis, at least 3 major periods with increased oxidative stress can be delimited:

- period of epigenetic reprogramming in PGCs and ensuing quality selection
- recombination during meiosis requiring double strand breaks
- sperm maturation or follicle selection

7.2.1 Functional hypoxia

7.2.1.1 Testis

Whereas ambient air contains 21% O₂, most tissues maintain O₂ tensions between 2% and 9%. The resistance in the unusually long and narrow testicular artery is high, leaving pressure in the unfenestrated testicular capillaries lower than in all other organs, only marginally higher than venous pressure (Sweeney et al., 1991). Since blood vessels are located exclusively between the tubuli, oxygen reaches the lumen of the tubuli seminiferi only by diffusion. The poor vascularization of the testes means that oxygen tensions in this tissue are low (Cross and Silver, 1962; Setchell and Waites, 1964; Free et al., 1976; Setchell, 1978, p. 300; Setchell et al., 1994; Klotz et al., 1996; Zheng and Olive, 1997; Lysiak et al., 2000a; b; Giaccia et al., 2004; Wenger and Katschinski, 2005; Reyes et al., 2012). The safety margin for disturbances in the testicular blood flow is particularly narrow (Damber and Bergh, 1992; Bergh et al., 2001; Lissbrant et al., 2006). The capacity of the testis to autoregulate its blood flow is limited (Lissbrant et al., 2006), and reductions in systemic blood pressure are, therefore, accompanied by reductions in testicular blood flow (Free, 1977; Lissbrant et al., 1997a). In line with this, circulatory shock is followed by damage to the spermatogenic epithelium (Pfitzer et al., 1982). Reported mean interstitial oxygen tensions in mammalian testes ranged from 10.6 to 15.2 mmHg (Cross and Silver, 1962; Massie et al., 1969; Free et al., 1976; Lysiak et al., 2000a), close to the brink of hypoxia (Setchell, 1978; Collin et al., 2000). Even pO₂ values as low as 2 mmHg have been reported, which are among the lowest values found in the body and otherwise occur only in the vicinity of oxygen consuming mitochondria (Max, 1992). Even if other groups reported higher testicular pO₂ values, the pO₂ values within the tubuli seminiferi are clearly below the pO₂ values outside of the tubuli (Wenger and Katschinski, 2005). Moreover, testicular microvascular pO₂ (which represents the driving force for transcapillary O₂ flux; Behnke et al., 2001) was found reduced by ~50% with old age (Dominguez et al., 2011). As an adjustment of mammalian testes to low O₂ pressure in the seminiferous tubules, testicular mitochondria seem to consume less oxygen to generate the same electrical membrane potential when compared to mitochondria from other tissues

(Moreira et al., 2005; 2006; Teodoro J et al., 2006). Cytochrome c oxidase is the terminal complex of the mitochondrial respiratory chain responsible for about 90% of oxygen consumption in mammals (Babcock and Wikström, 1992). Inhibition by NO of O₂ binding to cytochrome c oxidase (Brown and Cooper, 1994; Cleeter et al., 1994; Schweizer and Richter, 1994; Brown, 2001; Cooper et al., 2008; Taylor and Moncada, 2010) might be responsible for the inability of mitochondria to consume O₂ readily at low O₂ concentrations (Clementi et al., 1999). Inhibition of cytochrome c oxidase has been linked to increased ROS release (Kowaltowski and Vercesi, 1999; Echtaý et al., 2002; Inoue et al., 2003; Turrens, 2003; Facundo et al., 2006; Kowaltowski et al., 2009). Moreover, endogenous NO mediates ROS production at low oxygen concentrations by modifying the redox state of cytochrome c oxidase (Moncada and Erusalimsky, 2002; Palacios-Callender et al., 2004; Mason et al., 2006). NO production in rat liver and heart mitochondria increases under hypoxic conditions (Schild et al., 2003; Valdez et al., 2004). Mitochondria from a variety of eukaryotes are capable of reducing NO₂⁻ to NO when incubated at low oxygen concentrations (Kozlov et al., 1999; Nohl et al., 2000; Tiravanti et al., 2004; Tischner et al., 2004; Planchet et al., 2005; Castello et al., 2006) and this reaction has been shown to be catalyzed by cytochrome c oxidase in a pH-dependent fashion (Castello et al., 2006; 2008; Poyton et al., 2009a). In the testis, NO regulates various functions, including Leydig cell steroidogenesis (Del Punta et al., 1996), spermatogenesis and germ cell apoptosis (Zini et al., 1996; El-Gohary et al., 1999; Lue et al., 2003), Sertoli cell tight-junction dynamics (Lee and Cheng, 2004) and regulation of testicular blood flow (Lissbrant et al., 1997b). In addition to its mitochondrial generation, NO is synthesized from L-arginine by three different nitric oxide synthases: inducible NOS (iNOS), constitutive neuronal nitric oxide synthase (nNOS) and constitutive endothelial nitric oxide synthase (eNOS). Endothelial and neuronal NOS are Ca²⁺-dependent and often produce NO at the nanomolar level every few hours. Inducible NOS produces more NO (micromolar levels) and its productive activity can last for days. In the mammalian testis, all three isoforms of NOS are constitutively expressed and they play important roles in the biology of Sertoli and Leydig cells as well as in spermatogenesis and germ cell apoptosis (Zini et al., 1996; O'Bryan et al., 2000; Wang Y et al., 2002; Ha et al., 2004; Kim HC et al., 2007; Costur et al., 2012; Doshi et al., 2012). It has been shown that iNOS can be induced by factors released from round spermatids, implicating a regulatory role of germ cells on Sertoli

and Leydig cell NOS function (Lee and Cheng, 2004; Türker et al., 2004).

Testicular blood flow exhibits vasomotion, the rhythmic dilation and constriction of precapillary sphincters, which in turn results in cyclical variations in blood flow through capillaries (Damber et al., 1982; 1983; Collin et al., 1993; 2000; Turner et al., 1996). Mean rat testicular interstitial pO₂ was 12.5 ± 2.6 mm Hg, which displayed a cyclical variation of 11.9 ± 0.4 cycles per minute with a mean amplitude of 2.8 ± 0.8 mm Hg (Lysiak et al., 2000a). Vasomotion is testosterone-dependent (Damber et al., 1987; 1992; Collin et al., 1993), is induced by local factors (Bergh et al., 1999), is not seen prior to puberty (Damber et al., 1990) and is inhibited by stress, hyperthermia, hypoxia, cryptorchidism, and varicocele (Setchell et al., 1995; Collin et al., 1996; 2000; Collin and Bergh, 1996b). There is evidence for an increase in oxidative stress as a consequence of cycling hypoxia in tumors (Kalliomäki et al., 2008).

Oxygen consumption in the testis is high because of the energetic demands of spermatogenesis (Setchell and Waites, 1964; Wenger and Katschinski, 2005). Hypoxia occurs when the metabolic demand for oxygen exceeds the supply and both low oxygen tension and high oxygen consumption together result in functional hypoxia (Abele et al., 2007). Cells detect decreases in oxygen concentrations to activate a variety of responses that help cells to adapt to low oxygen levels. Oxidative stress may be induced not only by a rise but also by a fall in oxygen tension. Paradoxically, hypoxic tissues generate a high amount of oxidative stress (Chandel et al., 1998; 2000; Waypa and Schumacker, 2002; Schumacker, 2002; Turrens, 2003; Guzy and Schumacker, 2006; Cash et al., 2007; Bell et al., 2007; Clanton, 2007; Kulkarni et al., 2007), at least in part mediated by NO (Palacios-Callender et al., 2004; Mason et al., 2006). Mitochondria have been implicated as potential oxygen sensors by increasing the generation of ROS, which regulate a variety of hypoxic responses (Chandel et al., 1998; 2000; Agani et al., 2000). Both in *Saccharomyces cerevisiae* (Dagsgaard et al., 2001) and mammals (Brunelle et al., 2005; Guzy et al., 2005; Klimova and Chandel, 2008) the mitochondrial respiratory chain is required for hypoxic gene expression independent of oxidative phosphorylation. The transcriptional response to hypoxia activates a microtubule-dependent and dynein motor-driven mechanism that redistributes mitochondria from the central cytoplasm to the perinuclear region (Gutsaeva et al., 2008; Liu and Hajnóczky, 2011; Al-Mehdi et al., 2012; Murphy, 2012). Perinuclear clustering of mitochondria is also a

reponse of cells to oxidative stress (Hallmann et al., 2004). This perinuclear mitochondrial clustering is associated with accumulation of nuclear ROS that is required for hypoxia-induced transcription (Al-Mehdi et al., 2012; Murphy, 2012; Sena and Chandel, 2012). In a multitude of taxa throughout phylogenesis, clusters of perinuclear mitochondria have been identified during gametogenesis (Fukuda et al., 1975; Guraya, 1979; D'Herde et al., 1995; Eckelbarger et al., 1998; Dabiké and Preller, 1999; de Smedt et al., 2000; Pepling and Spradling, 2001; Wilding et al., 2001; Eckelbarger and Young, 2002; Kloc et al., 2004a; Pepling et al., 2007; Zelazowska et al., 2007; Taguchi et al., 2012) mimicking the perinuclear distribution of mitochondria of hypoxic tissues. Intriguingly, perinuclear redistribution of mitochondria is an early event of cell death pathways in many cell types (De Vos et al., 1998; Desagher and Martinou, 2000; Wakabayashi and Spodnik, 2000; Li J et al., 2004; Golstein and Kroemer, 2007), facilitating the transfer of apoptosis initiating factor (AIF), which activates caspases in the nucleus, Endonuclease G, an apoptotic DNase that degrades nuclear DNA, and ROS directly from the mitochondria to the nucleus to promote genomic destruction (Ferri and Kroemer, 2001; Li LY et al., 2001; Li J et al., 2004; Aslan and Thomas, 2009). Disrupted expression of beta-actin reduced TNF-induced mitochondria clustering, ROS production and apoptosis dramatically (Li J et al., 2004).

7.2.1.2 Ovary

The ovary is one of the best vascularized organs of the body (Banwell, 2009). However, the large pre-ovulatory follicle, where the oocyte undergoes maturation, remains avascular with all capillaries being excluded from the basal lamina and the oocyte is removed from any direct oxygen supply (Hazzard and Stouffer, 2000; Plendl, 2000; Tamanini and De Ambrogi, 2004; Banwell, 2009). Hypoxia of the granulosa cells is a normal event during the growth of ovarian follicles (Tropea et al., 2006). Follicular fluid oxygen partial pressure is reported to decrease with increasing follicular size in mammals (Fischer et al., 1992; Basini et al., 2004a). A positive correlation between glucose utilization and lactate production exists, and it is postulated that, as the follicle grows, energy requirements increase with decreasing O₂ availability (due to thickening of the avascular epithelium), leading to an increase in glycolysis and increased lactate production (Boland et al., 1993; Gull et al., 1999). This is accompanied by a 2-fold decrease in O₂ tension (59.8 mmHg in follicular fluid versus 102 mmHg in maternal blood) and higher CO₂

tension (46.9 mmHg in follicular fluid versus 38.3 mmHg in blood), resulting in a lower pH of follicular fluid compared with blood (7.33 and 7.41, respectively) (Fischer et al., 1992; Sutton et al., 2003). Theoretical modeling also suggested that the follicle becomes increasingly hypoxic (Gosden and Byatt-Smith, 1986; Redding et al., 2007; 2008). Oxygen limitation is known to stimulate follicular angiogenesis, which is important for follicular growth and development. Impairment of angiogenesis within ovarian follicles contributes to follicular atresia (Greenwald and Terranova, 1988). ROS may act as signal transducers (Schroedel et al., 2002) or intracellular messengers (Pearlstein et al., 2002) of the angiogenic response.

7.2.2 Metabolic and replicative stress

Metabolic activity is a primary source of free radicals, which are unavoidable by-products of ATP synthesis. Commoner et al. (1954) published the first direct evidence that free radicals were produced in living cells and found that free radical levels were higher in tissues that were more metabolically active (Swartz, 1998; Gomez-Cabrera et al., 2009). Endotherms exhibit generally a higher metabolic activity (Else et al., 2004) and 10 to 100 fold higher ROS production in different tissues compared to invertebrates and fishes (Wilhelm Filho et al., 2000; 2007; Abele and Puntarulo, 2004), and this difference corresponds roughly to differences in specific metabolic rates (Schmidt-Nielsen, 1977). Typically, a cell becomes mitochondria-rich when it is subjected to high levels of metabolic demand (Lane, 2002). The 'germinal cytoplasm' of a variety of organisms is crowded with mitochondria (Czolowska, 1969; Fukuda et al., 1975; Guraya, 1979; D'Herde et al., 1995; Eckelbarger et al., 1998; Dabiké and Preller, 1999; de Smedt et al., 2000; Pepling and Spradling, 2001; Wilding et al., 2001; Eckelbarger and Young, 2002; Kloc et al., 2004a; Pepling et al., 2007; Zelazowska et al., 2007; Taguchi et al., 2012). An increased mass-specific metabolic rate elevates the generation of reactive oxygen and nitrogen species (RONS) both at the cellular (Sohal et al., 1990; Mohanty et al., 2000) and organismal level (Adelman et al., 1988). Mitochondrial ROS generation correlates well with metabolic rate (Sohal and Allen, 1995; Perez-Campo et al., 1998), suggesting that a faster metabolism simply results in more respiratory chain electron leakage. Conversely, dietary restriction results in a decrease in mitochondrial substrate oxidation activity, a concomitant decrease in the production rate of ROS and oxidative DNA damage (Simic and Bergtold, 1991; Chung et al., 1992; Sohal and Weindruch, 1996; Yu, 1996; Dandona et al., 2001; Heilbronn and Ravussin, 2003; Bevilacqua et al., 2004;

Lambert and Merry, 2004; Masoro, 2005). Likewise, a dietary restriction mimetic, the glucose antimetabolite 2-deoxy-D-glucose, that competitively inhibits the uptake and utilization of glucose thereby suppressing glycolysis and reducing energy production in mitochondria, leads to a decrease in production of ROS (Halicka et al., 1995; Lee J et al., 1999a; Roth et al., 2005) and oxidative DNA damage (Tanaka et al., 2006a). Various intraindividual, intraspecies and interspecies comparative data revealed that the rate of ROS generation, oxidative DNA damage and DNA evolution is directly related to the mass-specific metabolic rate (Adelman et al., 1988; Shigenaga et al., 1989; Cutler, 1991; Simic and Bergtold, 1991; Avise et al., 1992a; Cortopassi et al., 1992; Adachi et al., 1993; Martin and Palumbi, 1993; Loft et al., 1994; Rand, 1994; Martin, 1999; Gillooly et al., 2001; 2005; 2007; Cooke et al., 2003; Foksinski et al., 2004; Olinski et al., 2006; Rosa et al., 2008).

Quite obviously, for sexually reproducing taxa reproduction affords a high investment for gamete production in terms of resource and energy utilization (Williams, 1966b; Calow, 1979; Bell, 1980; Reznick, 1985; Bell and Koufopanou, 1986; Berglund and Rosenqvist, 1986; Loudon and Racey, 1987; Gittleman and Thompson, 1988; Reiss, 1989; Geber et al., 1999; Rocheleau and Houle, 2001; Barnes and Partridge, 2003; Lester et al., 2004; Wheelwright and Logan, 2004; Roff et al., 2006; Speakman, 2008; Szymanski et al., 2009; Bergeron et al., 2011). In the oviparous lizard, *Sceloporus undulatus*, for instance, the metabolic rate of females when gravid was elevated by 122% compared with that when non-gravid (Angilletta and Sears, 1999). In birds, reproduction is associated with significant metabolic costs. Because most avian species maintain atrophied reproductive organs when not active, reproduction requires major tissue remodeling in preparation for breeding. Females undergo rapid (days) recrudescence and regression of their reproductive organs at each breeding attempt, while males grow their organs ahead of time at a much slower rate (weeks) and may maintain them at maximal size throughout the breeding season. Egg production leads to a 22%–27% increase in resting metabolic rate over non-reproductive values. In male birds, gonadal recrudescence may lead to a 30% increase in resting metabolic rate (Vézina and Salvante, 2010). In free-ranging reproductive male North American red squirrels (*Tamiasciurus hudsonicus*) mean energy expenditure of males approximately doubled during the breeding season (from 290 ± 7 to 579 ± 73 kJ/day) (Lane et al., 2010).

Testis-specific morphogenetic events suggest that male gonads have a higher energy requirement than ovaries (Matoba et al., 2008). Approximately 4×10^6 sperm cells are produced every day by the male mouse (Thayer et al., 2001). Between age 20 and 50 years, the human testes produce approx. 2,000 spermatozoa per second each day with wide ranges (Amann and Howards, 1980; Amann, 2010). For 50% of healthy men, 21–50 years old, their daily output of mature sperm is between 68 and 250×10^6 (i.e. 2.8 to 10.4×10^6 sperm/h), but for 25% of men daily sperm production is $<68 \times 10^6$ and for another 25% of men is between 251 and $>600 \times 10^6$ (Johnson et al., 1984a). In addition, almost half of the potential sperm production in men is lost by apoptosis during postprophase of meiosis (Johnson et al., 1983a) and around two-thirds to three-quarters of spermatogonia are eliminated during mitotic proliferation (Oakberg, 1956; Clermont, 1962; Huckins and Oakberg, 1978; Allan et al., 1992; Dym, 1994; Blanco-Rodríguez et al., 2003). Daily sperm production per gram of testicular parenchyma varies between species but appears to be generally high, and as far as comparisons can be carried out (Clermont, 1972; Berndtson, 1977; 2011), is significantly higher in other mammalian species than in humans (Amann et al., 1976; Berndtson, 1977; Johnson et al., 1980; 1983b; 1992; 2000; Johnson, 1986; Gopalkrishnan et al., 1987). Thus, given that daily output of mature sperm is only the peak of the iceberg of daily spermatogenetic activity, there is a huge energetic investment into mammalian male gametogenesis. It has been calculated that, assuming that a man produces 100 million (10^8) mature sperm per day, during an average reproductive life of sixty years he would produce well over two trillion (2×10^{12}) mature sperm in his lifetime (Martin, 1991) (and a multiple of this figure of immature germ cells). In mice it has been estimated that if all the cells produced as spermatogonia were to become sperm, there would be a two- to fivefold increase in sperm production (de Rooij and Lok, 1987). Mammalian male germ cells produce ATP in the mitochondria at a close to maximal rate (Grootegoed et al., 1984). Spermatogenesis in vivo is impaired by lowered germ cell ATP levels after inhibition of the citric acid cycle and uncoupling of oxidative phosphorylation. Fluoroacetate is converted to fluorocitrate and then inhibits the enzyme aconitase. Gossypol acts as an uncoupling agent on oxidative phosphorylation in different cell types. The more or less specific effects of fluoroacetate and gossypol on spermatogenesis in vivo (Sullivan et al., 1979; Qian and Wang, 1984) may be related to a high sensitivity of spermatogenic cell types, as compared to other cell types, to compounds which interfere with

mitochondrial energy metabolism and respiratory control (Grootegoed et al., 1984).

Oscillations in oxygen consumption, energy metabolism, and redox state are intimately integrated with cell cycle progression, establishing the redox control of the cell cycle (Menon and Goswami, 2007; Burhans and Heintz, 2009; Sarsour et al., 2009). Because signaling pathways play specific roles in different phases of the cell cycle and the hierarchy of redox-dependent regulatory checkpoints changes during cell cycle progression, the effects of ROS on cell fate vary during the cell cycle. ROS navigate cells between Scylla and Charybdis. A role for oxidative stress has been demonstrated in the stimulation of cell proliferation (Burdon, 1995; Irani et al., 1997; Cotgreave and Gerdes, 1998; Shackelford et al., 2000; Thannickal et al., 2000; Sauer et al., 2001; Ushio-Fukai et al., 2002; Kreuzer et al., 2003; Immenschuh and Baumgart-Vogt, 2005; Rhee, 2006; Buggisch et al., 2007; Matés et al., 2008). Regarding cellular proliferation, oxidative stress affects several biochemical pathways (from epidermal growth factor receptor to mTOR) that involve key signaling proteins, such as nuclear factor erythroid 2-related factor 2 (Nrf2), kelch-like protein 19 (Keap1), Ras, Raf, mitogen activated protein kinases (MAPK) such as ERK1/2, MEK, p38alpha, c-Jun N-terminal kinase (JNK), c-myc, p53 and PKC (Matsuzawa and Ichijo, 2008; Nguyen et al., 2009; Wiemer, 2011; Sosa et al., 2013). And oxidative stress is the key orchestrator of cellular deletion by apoptosis (Buttke and Sandstrom, 1994; Jacobson, 1996; Tan et al., 1998; Jabs, 1999; Kannan and Jain, 2000; Simon et al., 2000; Jones, 2001; Ueda et al., 2002; Kern and Kehrer, 2005; Le Bras et al., 2005; Orrenius, 2007; Matés et al., 2008; Trachootham et al., 2008; Circu and Aw, 2010; Doyle et al., 2010). Intriguingly, thyroid hormones that increase the metabolic rate, calorogenesis, and exacerbate oxidative stress due to the acceleration of aerobic metabolism, trigger reproductive activity in response to environmental cues as phylogenetically highly conserved signals (see chapter 14.2.2).

Mammalian spermatogenesis balances at a very narrow edge in relation to cell proliferation on one hand and lipid peroxidation, DNA damage and cell death on the other. Progression to a more prooxidant state whilst initially leading to enhanced proliferative responses results subsequently in increased cell death (Burdon, 1995). Increased mitochondrial metabolic activity has been shown to enhance oxidative stress (Commoner et al., 1954; Hagen et al., 1998; Swartz, 1998; Gomez-Cabrera et al., 2009). Accordingly, the high metabolic effort during the reproductive period is

reflected by increased systemic prooxidant state, susceptibility to stress and oxidative stress (Boonstra et al., 2001; Salmon et al., 2001; Wang Y et al., 2001; Wingfield and Sapolsky, 2003; Alonso-Alvarez et al., 2004a; 2006; Koochmeshgi et al., 2004; Wiersma et al., 2004; Bertrand et al., 2006; Klose et al., 2006; Delaporte et al., 2007; Harshman and Zera, 2007; Rush et al., 2007; Samain et al., 2007; Bizé et al., 2008; Costantini, 2008; Dowling and Simmons, 2009; Monaghan et al., 2009; Bergeron et al., 2011; Isaksson et al., 2011; Heiss and Schoech, 2012).

Many observations have demonstrated the greater vulnerability of single-stranded DNA as occurs during DNA replication and transcription (Cohen et al., 1991). For example, in vitro single-stranded DNA exhibits a >100-fold greater rate of depurination (Lindahl and Neiberg, 1972) or of deamination (Lindahl and Neiberg, 1974) than double-stranded DNA. Similarly, a review of chemical mutagenesis that is often associated with oxidative stress stated that "Most, if not all, mutagens are much more reactive in single-stranded nucleic acids, so that these regions are probably preferentially modified in replicating DNA" (Singer and Kusmierek, 1982). The occurrence of nonrandom distribution/clustering of oxidative DNA damage sites in the genome of highly proliferative cells indicates that there may be regions in the genome with an increased vulnerability to ROS damage (Chastain et al., 2006; Redon et al., 2010). These vulnerable regions are in areas undergoing replication, transcription, and/or between nucleosomes (Hanawalt et al., 1979; Friedberg et al., 1995; MacLeod, 1995; Chastain et al., 2006). DNA synthesis is a remarkably vulnerable phase in the cell cycle. In addition to introduction of errors during semi-conservative replication, the inherently labile structure of the replication fork, as well as numerous pitfalls encountered in the course of fork progression, make the normally stable double stranded molecule susceptible to collapse and recombination. Estimates of the extent of endogenous DNA damage due to oxidants produced during metabolic activity vary widely (Nohl, 1994; Beckman and Ames, 1997; Vilenchik and Knudson, 2003; Barzilai and Yamamoto, 2004; Møller and Loft, 2004; Tanaka et al., 2006b). According to one of the relatively low estimates, during a single cell cycle approximately 5,000 DNA single-strand lesions are generated per nucleus by endogenous ROS (Vilenchik and Knudson, 2003; Tanaka et al., 2006b). Approximately 1% of these single-strand lesions become converted to DSBs, predominantly at the time of DNA replication, while the remaining 99% are repaired by essentially error-free mechanisms. Thus, on average, about 50 DSBs per nucleus (~0.8 DSBs

per 10⁸ bp) are generated during a single cell cycle in human cells (Vilenchik and Knudson, 2003). Cellular demand for DNA repair correlates with the cell's potential to replicate. gamma-H2AX-enriched regions (that mark DSBs, see chapter 7.2.8) of endogenous origin in replicating cells include sub-telomeres and active transcription start sites, apparently reflecting replication- and transcription-mediated stress during rapid cell division (Seo et al., 2012). Activated oncogenes including ras, myc, cyclin E, mos, cdc25A, and E2F1, result in the continuous formation of mitochondrial ROS and endogenous DSBs (Denko et al., 1994; Karlsson et al., 2003; Bartkova et al., 2005; 2006; Di Micco et al., 2006; Halazonetis et al., 2008; Ralph et al., 2010; González et al., 2013) due to increased replication stress (Bartkova et al., 2006; Di Micco et al., 2006). Male spermatogonia and spermatocytes have an extreme replication activity compared with any other cell type (humans produce approximately 50–200 million spermatozoa per individual per day). This huge energetic investment, coupled with testicular high oxygen consumption and low oxygen tension generates substantial oxidative stress (Agarwal et al., 2003; Fujii et al., 2003) and associated DNA damage (Tanaka et al., 2006a; b).

7.2.3 Oxidative stress

Oxidative stress is a constitutive feature of male (Riley and Behrman, 1991; Aitken, 1994; 1995; Chainy et al., 1997; Fisher and Aitken, 1997; Gil-Guzman et al., 2001; Aitken et al., 2003; Orozco et al., 2003; Ford, 2004; Juan et al., 2005; Aitken and Roman, 2008) and female gametogenesis (Riley and Behrman, 1991; Tilly and Tilly, 1995, Kugu et al., 1998, Knapen et al., 1999; Behrman et al., 2001; Agarwal et al., 2005; Gupta et al., 2008; Ruder et al., 2008; Lázár, 2012). A thorough examination of the available literature suggests the general tendency that in female gametogenesis the physiological role of ROS is appreciated while in male gametogenesis rather the pathophysiological role of ROS is emphasized. Particularly, the oxidative stress within the seminiferous tubules is often treated as black box, in part because the massive ROS-dependent carnage of germ cells is highly cryptic due to the fast phagocytosis of cell debris by Sertoli cells (Maeda et al., 2002) and in part because oxidative stress during the various later stages of sperm maturation is highly visible and may have a detrimental impact for male fertility. On the other hand the high sensitivity of spermatogenic cells to oxidative stress may explain their extremely limited viability in cell culture (Chapin and Phelps, 1990). Testosterone has been shown to have pro-oxidant properties in a variety of animal

tissues (e.g. Chainy et al., 1997; Royle et al., 2001; Pansarasa et al., 2002; Aydilek et al., 2004; Gil et al., 2004; Rutkowska et al., 2005; Prasad et al., 2006; 2008; Alonso-Alvarez et al., 2007; Iliescu et al., 2007; Chignalia et al., 2012) while in other tissues, particularly in the brain, anti-oxidant actions have been described (Ahlbom et al., 1999; 2001; Calderón Guzmán et al., 2005; Chisu et al., 2006). Testosterone also induces testicular oxidative and nitrosative stress (Peltola et al., 1996; Chainy et al., 1997; Aydilek et al., 2004; Guo et al., 2009) that, on the other hand, is indispensable for spermatogenesis (Chainy et al., 1997; Aydilek et al., 2004). Androgens may cause oxidative stress via cytochrome P450 4A and NADPH oxidase-dependent mechanisms (Iliescu et al., 2007; Singh et al., 2007; Ojeda et al., 2012) that was considered causal to the sexual dimorphism of blood pressure dysregulation (Chen and Meng, 1991; Bowles, 2004; Dantas et al., 2004; Iliescu et al., 2007; Miller et al., 2007; Singh et al., 2007; Ojeda et al., 2012). Testosterone also stimulated NADPH-oxidase activity in a variety of tissues (Brown et al., 1976; Lu JP et al., 2010; Chignalia et al., 2012).

Oxidative and nitrosative stress, at least in part mediated by gonadal hormones (Chainy et al., 1997; Felty et al., 2005; Guo et al., 2009), is not only a hallmark of gametogenesis but of other sexual reproduction-related events as well (Riley and Behrman, 1991; Heining, 2001; Agarwal et al., 2003; 2005; Lue et al., 2003; Nedelcu, 2005; Aitken and Roman, 2008; Metcalfe and Alonso-Alvarez, 2010; Lázár, 2012). In vitro, male germ cells at various stages of differentiation were found to spontaneously generate hydrogen peroxide as they progressed through the epididymis, maximal activity being observed on the release of mature cells from the caudal region into a modified Krebs-Ringer's solution. Superoxide production could be dramatically enhanced by the addition of exogenous NADPH, in a manner that was closely correlated with the stage of epididymal development being maximal for immature cells recovered from the caput epididymis in all species. Precursor germ cells (pachytene spermatocytes, round and elongate spermatids) similarly generated chemiluminescent signals compatible with the low level generation of ROS. Superoxide generation in these cells could again be stimulated by NADPH, via mechanisms that were inversely related to the stage of germ cell differentiation, the greatest activity being observed in pachytene spermatocytes. These results demonstrate that differentiating male germ cells have the potential to generate ROS, and have implications for the redox regulation of gonadal function and the development of

reproductive pathologies involving oxidative stress (Fisher and Aitken, 1997).

As will be discussed in more detail in chapter 10, a multitude of processes related to gametogenesis require oxidative stress: mutagenesis, epimutagenesis, reprogramming, recombination, and apoptosis. Testicular germ cells are intimately associated with the free radical generating phagocytic Sertoli cells (Bauché et al., 1994). Compared to Sertoli cells, germline cells are much more susceptible to oxidative stress resulting in germ cell-specific apoptosis following oxidative stressor challenge (Turner et al., 1997; Lysiak et al., 2000a; Lue et al., 2002; Payabvash et al., 2008). A strong mutational bias from G/C to A/T nucleotides implicates oxidative DNA damage as a major endogenous mutagenic force in a variety of eukaryotes (Petrov and Hartl, 1999; Haddrill and Charlesworth, 2008; Lynch et al., 2008; Denver et al., 2009; Keightley et al., 2009; Lynch, 2010b; Ossowski et al., 2010). 5-Hydroxyuracil (resulting from the oxidative deamination of cytosine) and 8-oxoguanine (8-oxoG) are the two most common types of oxidative DNA damage in animal genomes and they cause G:C→A:T transitions and G:C→T:A transversions, respectively. 8-oxoG is unevenly distributed in the normal human genome and the distribution pattern is conserved among different individuals. Regions with a high frequency of recombination and SNPs are preferentially located within chromosomal regions with a high density of 8-oxoG (Ohno et al., 2006). This evidence suggests that 8-oxoG is one of the main causes of frequent recombinations and SNPs in the human genome, which largely contribute to the genomic diversity in human beings (Ohno et al., 2006). Management of ROS to prevent excessive damage, yet enabling its signaling function is achieved through numerous enzyme systems e.g. peroxidases, superoxide dismutases etc., and small molecules e.g. glutathione that collectively form the cellular anti-oxidant system (Hoogeboom and Burgering, 2009). The key role of glutathione in protecting various cells against free radical injury or chemically induced damage is now well established (Meister and Anderson, 1983; Vina, 1990; Sies, 1999).

The nuclear factor erythroid 2-related factor 2 (Nrf2), a Cap'n'Collar basic leucine zipper transcription factor, activates expression of cytoprotective genes that protect against oxidative stress (Banning et al., 2005; Kohle and Bock, 2007; Sporn and Liby, 2012; Cui et al., 2013). Nrf2 modulates the expression of hundreds of genes, including not only the familiar antioxidant enzymes but also a large number of genes that control

several processes, including immune and inflammatory responses, tissue remodeling and fibrosis, carcinogenesis, and metastasis (Hybertson et al., 2011; Sosa et al., 2013). ROS levels are tightly controlled and predominantly regulated by Nrf2 and its repressor protein Keap1. When treated with oxidation-inducing drugs, mice that lack Nrf2 develop more severe intestinal inflammation than controls, with increased aberrant crypts, suggesting a function for Nrf2 in the prevention of inflammation and carcinogenesis (Khor et al., 2006). Similarly, Nrf2-deficient mice display an increased susceptibility to oxidative stress with a disrupted spermatogenesis in an age-dependent manner (Nakamura et al., 2010). A recent report described a strong association between functional polymorphisms in Nrf2 promoters with defective spermatogenesis in humans and lower Nrf2 mRNA expression and decreased levels of antioxidant gene glutathione S-transferaseM1 and SOD2 mRNA in spermatozoa (Yu et al., 2012).

In mammals, antioxidant enzymes such as Sod1, Sod2, and Gpx are present during different stages of oogenesis (El Mouatassim et al., 1999). All known peroxiredoxins are expressed in the oocytes; particularly, Prx6 is upregulated during in vitro maturation (Leyens et al., 2004a; b). Interestingly, Sod1-deficient female mice have drastically compromised fertility, with oogenesis halted at the middle of follicle development (Matzuk et al., 1998). The lack of Sod1 in *Drosophila* also causes reduction in female fertility (Phillips et al., 1989). Infertility is often the only abnormality in unstressed animals with knock-out of genes for antioxidant enzymes (Ho et al., 1998; Matzuk et al., 1998). On the other hand, transgenic male mice that express higher levels of mitochondrial MnSOD exhibit a decreased fertility (Raineri et al., 2001). At puberty, a number of primary oocytes begin to grow each month. One primary oocyte outgrows the others and resumes meiosis I. Interestingly, resumption of meiosis I is induced by an increase in ROS and inhibited by antioxidants (Takami et al., 1999, 2000; Kodaman and Behrman, 2001). Attendant to the increase in steroid hormone production of developing follicles is an increase in the activity of cytochrome P450, which in turn generates ROS such as H₂O₂ (Ortega-Camarillo et al., 1999). On the other hand, large goat ovarian follicles (>6 mm) exhibited greater catalase activity than granulosa cells from small (<3 mm) or medium (3–6 mm) sized follicles. After a uniform dose of FSH (200 ng/ml), both catalase activity and estradiol release were greater in large follicles than in medium or small follicles (Behl and Pandey, 2002). Since the dominant follicle will be the follicle with the highest estrogen concentration, the

concomitant increases in catalase that is able to metabolize H_2O_2 , and estradiol in response to FSH suggest a role for catalase in follicular selection and prevention of apoptosis (Behl and Pandey, 2002). Moreover, antioxidants are beneficial for meiosis II (Yoshida et al., 1993; Eppig, 1996; Behrman et al., 2001), which suggests a complex role for ROS indicating that regulated generation of ROS by the pre-ovulatory follicle is an important promoter of the ovulatory sequence (Ruder et al., 2008). An investigation of ROS regulation by the preovulatory follicle in response to LH indicated that a gonadotrophin-stimulated, protein kinase C-activated, NADPH/NADH oxidase-type superoxide generator in the preovulatory follicle exists and may be a regulating factor in ROS production during ovulation (Kodaman and Behrman, 2001). In females, oxidative stress is not limited to gametogenesis but is involved in virtually every aspect of female reproductive activity from oogenesis to parturition (Heininger, 2001; Rizzo et al., 2012). Oxidative stress is involved in granulosa cell estrogen production (LaPolt and Hong, 1995) and estrogen-mediated oocyte maturation (Tarin et al., 1998; Behrman et al., 2001) but, on the other hand, may contribute to ovarian senescence (Tarin et al., 1998; Behrman et al., 2001). Oxidative stress-responsive NF-kappaB modulates the expression of an androgen receptor (Roy et al., 1996) which further stresses the links between sex and oxidative stress. On the other hand, mild oxidative stress as trigger of reparative events may be the mechanism (similar to tolerance induction) which ensures the DNA repair (Schwartz et al., 1988; Dutta et al., 1996; Zhang et al., 1996; Fabisiwicz and Janion, 1998; Korzets et al., 1999) and thus rejuvenation and essential immortality of germ cell lines. Control of intracellular redox balance has emerged as a primary function of the p53 network (Trinei et al., 2002; Holley et al., 2010; Pani and Galeotti, 2011). Strong immunoreactivity for p53, the guardian of the genome, was observed in the nuclei of a number of spermatogonia, of some premeiotic spermatocytes and probably in all spermatids (Sjöblom and Lähdetie, 1996; Stephan et al., 1996). p53 physically interacts with key factors of homologous recombination: the human RAD51 protein and its prokaryotic homologue RecA (Stürzbecher et al., 1996). p53 is the link both between oxidative stress-generated DNA repair, recombination (Sjöblom and Lähdetie 1996, Schwartz et al., 1999), and quality control (Yin et al., 1998; 2002) during spermatogenesis.

7.2.4 Hypoxia-inducible factors

The increase in mitochondrial ROS formation during hypoxia modulates the activation of one or more hypoxia-inducible factors (Agani et al., 2000; Chandel et al., 2000; Schroedl et al., 2002; Brune and Zhou, 2003; Zhou et al., 2003; Guzy et al., 2005; Kietzmann and Görlach, 2005; Mansfield et al., 2005; Poyton et al., 2009a; b; Kuphal et al., 2010; Majmundar et al., 2010). The key transcription factor, hypoxia-inducible factor (HIF), originally identified in erythropoietin producing hepatoma cells (Semenza and Wang, 1992), is expressed very widely (probably universally) in mammalian cells (Wang and Semenza, 1993; Firth et al., 1994). The HIF system is phylogenetically highly conserved, even in primitive animal species that lack erythropoietin, red blood cells or even any specialized oxygen-delivery apparatus (Nagao et al., 1996; Huang and Bunn, 2003; Chuang et al., 2011; Loenarz et al., 2011; Ratcliffe, 2013). Under normoxic conditions, HIF-1alpha is rapidly degraded which is mediated by the ubiquitin–proteasome pathway and the von-Hippel Lindau protein (Salceda and Caro, 1997; Huang et al., 1998; Semenza, 1999; Tanimoto et al., 2000). Acute cellular hypoxia stabilizes and activates both the ubiquitous HIF-1alpha and the more tissue-specific HIF-2alpha (also known as EPAS1) transcription factors. Once stabilized by hypoxia, HIF-1alpha forms a heterodimer with HIF-1beta (also known as ARNT) on hypoxic responsive elements (HREs) within target gene promoters to drive the expression of HIF-1alpha targets (Williams and Benjamin, 2000; Powell et al., 2002). Inhibition of mitochondrial electron transport in hypoxia leads to increased production of ROS and this, rather than lack of molecular oxygen itself, is responsible for the reduction in HIF hydroxylase activity that signals hypoxia (Chandel et al. 1998; Bell et al., 2007; Ratcliffe, 2013). ROS produced by the redistributed mitochondria cause oxidative modification of the promoter regions of HIF-1 target genes. The introduction of oxidative modifications in these promoters enhanced HIF-1alpha association and gene expression (Al-Mehdi et al., 2012; Murphy, 2012). The expression of glutathione peroxidase or catalase (that convert hydrogen peroxide into water), but not superoxide dismutases 1 or 2 (that convert superoxide into hydrogen peroxide), prevented the hypoxic stabilization of HIF-1alpha in mammalian cells (Brunelle et al., 2005). Intriguingly, a pattern of antioxidant enzymes (normal SOD levels but low GPx and catalase levels) that enhances the stabilization of HIF-1-alpha by H_2O_2 (Brunelle et al., 2005) is exactly what Bauché et al. (1994) and others (see chapter 7.3) found in male germ cells. HIFs regulate the expression of genes involved in the adaptation to hypoxic conditions (Chandel et al., 1998; Semenza, 1999;

2009; Kaelin and Ratcliffe, 2008; Kaluz et al., 2008; Ratcliffe, 2013). HIF-1 is considered a key regulator of the ROS-mediated response to metabolic, hypoxic, or inflammatory stress (Seagroves et al., 2001; Zagórska and Dulak, 2004; Kietzmann and Görlach, 2005; Lum et al., 2007; Aragonés et al., 2009; Chen D et al., 2009; Görlach, 2009; Semenza, 2009; Kuphal et al., 2010; Shay and Simon, 2012). In mammalian cells, HIF-1 α mRNAs are induced by the ubiquitous redox sensitive transcription factor nuclear factor-kappaB (NF-kappaB), the cellular 'sensor' for oxidative stress (Li and Karin, 1999; Mercurio and Manning, 1999; Storz and Toker, 2003; Gloire et al., 2006), so that NF-kappaB regulation plays an important role in the response to hypoxia (Jung et al., 2003; BelAiba et al., 2007; Bonello et al., 2007; Görlach and Bonello, 2008; van Uden et al., 2008; Görlach, 2009). HIF targets include members of stress-response gene families that mediate acute and chronic hypoxic adaptations, such as glucose transporters (Bashan et al., 1992; Ebert et al., 1995), glycolytic enzymes (Firth et al., 1994; 1995; Semenza et al., 1994), angiogenic factors such as vascular endothelial growth factor (VEGF) (Shweiki et al., 1992; Levy et al., 1995; 1996; Liu et al., 1995; Shima et al., 1995) and platelet-derived endothelial cell growth factor (Griffiths et al., 1997), haematopoietic growth factors such as erythropoietin (Semenza and Wang, 1992; Bunn and Poyton, 1996), and molecules that affect cell growth, survival, and motility. ROS are dose- and time-dependent inducers of VEGF gene and protein expression in vascular smooth muscle cells, human retinal pigment epithelial cells, human melanoma cells and glioblastoma cells (Bassus et al., 2001; Kuroki et al., 1996) while the antioxidant N-acetylcholine can suppress VEGF induction (Chua et al., 1998; Redondo et al., 2000). VEGF stimulates the expression of a cluster of nuclear-encoded mitochondrial genes, suggesting a role for VEGF in the regulation of mitochondrial biogenesis (Wright et al., 2008). On the other hand, HIF-1 actively represses mitochondrial function and O₂ consumption by inducing pyruvate dehydrogenase kinase 1, which inactivates the tricarboxylic acid cycle (TCA) for cell survival (Kim et al., 2006; Papandreou et al., 2006). Therefore, energy conservation, in addition to energy generation, is an integral part of the hypoxic response. Under conditions of limited oxygen supply, anaerobic glycolysis becomes the predominant form of cellular ATP generation (Pasteur effect). HIF-1 is a necessary mediator of the Pasteur effect in mammalian cells (Seagroves et al., 2001). Many genes involved in glucose uptake and glycolysis were identified as HIF-1 target genes (Wenger, 2000; Zhong et al., 2010).

Importantly, the Pasteur effect was observed in the adult rat testes whereas the Crabtree effect (the occurrence of anaerobic glycolysis despite aerobic conditions [Crabtree, 1929]) appeared only in immature testes (Leiderman and Mancini, 1968). HIF is also important for the establishment of the Warburg effect (Warburg et al., 1924; Sosa et al., 2013). In this metabolic shift from aerobic respiration, the machinery of glycolysis is upregulated in cancer cells and other rapidly proliferating cells (Wang et al., 1976; McKeenan, 1982), giving them a metabolic advantage for surviving and thriving in the oxygen poor microenvironment (Gladden, 2004; Sola-Penna, 2008). Aerobic glycolysis is an inefficient way to generate ATP. Under standard conditions, in which oxygen (O₂) is abundant, and for long-term maintenance, healthy cells choose aerobic respiration. In aerobic respiration, which takes place in the cytoplasm and mitochondria, oxygen and glucose are used to generate 38 ATP molecules and carbon dioxide (CO₂) is released and O₂ is absorbed. In anaerobic respiration, which occurs only in the cytoplasm, 2 molecules of ATP are synthesized in the electron transport chain, using inorganic molecules other than O₂; CO₂ is released, but O₂ is not required. Glycolytic enzymes are evolutionarily older and have reached catalytic perfection, thus suggesting that glycolysis may be the pathway of choice if glycolytic substrates are plentiful and oxygen is low. Anaerobic glycolysis generates lactate, and due to the low levels of energy produced only low levels of ROS are produced (Sosa et al., 2013). The major role of glycolysis in highly proliferating cells is to provide substrates to the pentose phosphate pathway for nucleotide synthesis, a great priority considering their high division rate (Kondoh et al., 2007; Weinberg and Chandel, 2009). Hence, the metabolism of proliferating cells is adapted to facilitate the uptake and incorporation of nutrients into the biomass (e.g., nucleotides, amino acids, and lipids) needed to produce a new cell (Vander Heiden et al., 2009; Shlomi et al., 2011; Krisher and Prather, 2012). Stem cells are more glycolytic than primary cells and possess reduced mitochondrial oxygen consumption, which helps these cells to control oxidative stress (Iyer et al., 1998; Kondoh et al., 2005; Funes et al., 2007; Diehn et al., 2009). Proliferating spermatogonia exhibit high glycolytic activity and fit into this metabolic pattern (Warburg et al., 1924; Roosen-Runge, 1953; Sosa et al., 2013). During spermatogenesis, the dependence of germ cells on lactate/pyruvate and glucose for energy metabolism keeps changing. Sertoli cells metabolize various substrates, preferentially glucose, the majority of which is converted to lactate and not

oxidized via the TCA cycle (Rato et al., 2012). A gradient in mitochondrial activity has been described in testicular germ cells with stem cell spermatogonia presenting the least active mitochondria (Meinhardt et al., 1999). In *Xenopus*, mitochondria in the germ plasm have lower respiratory activity than mitochondria destined for the soma (Kogo et al., 2011). After passage to the luminal compartment germ cells rely on the breakdown of lactate and pyruvate provided by Sertoli cells (Boussouar and Benhamed, 2004; Rato et al., 2012). A high concentration of exogenous lactate apparently is required for spermatocytes and spermatids to use endogenous pyruvate as the predominant energy-yielding substrate via the TCA cycle (Grootegeod et al., 1984). The use of lactate as their primary substrate for producing ATP (Nakamura et al., 1982; 1984a) protects spermatocytes and spermatids against apoptotic cell death (Bustamante-Marín et al., 2012). Spermatogonia, mature spermatozoa and the somatic Sertoli cells exhibit high glycolytic activity, whereas spermatocytes and spermatids produce ATP mainly by oxidative phosphorylation (Mann and Lutwak-Mann, 1981; Robinson and Fritz, 1981; Grootegeod et al., 1984; Nakamura et al., 1984b; Trejo et al., 1995; Bajpai et al., 1998; Meinhardt et al., 1999; Harris, 2002; Marin et al., 2003; Ramalho-Santos et al., 2009). Interestingly, inhibition of ATP synthase decreased ATP levels and suppressed cell death, an effect not seen with inhibition of glycolysis, indicating that mitochondrial ATP production plays a role in regulating male germ cell apoptosis (Erkkila et al., 2006; Ramalho-Santos et al., 2009).

HIF-1 is known to have bimodal effects on cell physiology because it can activate either cell survival or cell death genes depending on the extent and duration of oxygen debt (Piret et al., 2002; Wiesener and Maxwell, 2003; Wang Y et al., 2004; Kilic et al., 2007). p53 has been implicated in the expression and degradation of HIF-1 (Blagosklonny et al., 1998; Ravi et al., 2000; Schmid et al., 2004) and, on the other hand, is HIF-dependent in hypoxic cells (An et al., 1998; Carmeliet et al., 1998; Chen et al., 2003b).

Hypoxia can drive genomic instability and alter DNA damage repair pathways. Intriguingly, hypoxic cells can acquire a mutator phenotype that consists of decreased DNA repair, an increased mutation rate and increased chromosomal instability (see chapter 10.1), a phenomenon which has been well established in carcinogenesis (Ralph et al., 2010) and tumor progression (Huang LE et al., 2007; Bristow and Hill, 2008). This might be particularly true in proliferating cells that have adapted to low O₂ levels and continue

to proliferate in the context of compromised DNA repair (Blais et al., 2006). Components of the HIF-1 system play essential roles in embryonic development and cellular differentiation (Ke and Costa, 2006; Cicchillitti et al., 2012). A clear link has been demonstrated between hypoxia, HIFs and molecules that are crucial for the regulation of the differentiation of stem and/or progenitor cells, including Notch, beta-catenin, Sox2, Oct4 and c-MYC (Simon and Keith, 2008; McCord et al., 2009; Bussolati et al., 2012). HIF-1alpha expression increased between embryonic days 8.5 and 9.5 in normal mouse embryos (Iyer et al., 1998). Knockout of either HIF-1alpha (Iyer et al., 1998; Ryan et al., 1998; Kotch et al., 1999), HIF-2alpha (Tian et al., 1998; Peng et al., 2000), or HIF-1beta (Maltepe et al., 1997) resulted in abnormal vascular development and lethality in mice. Embryos deficient in HIF-1alpha died by embryonic day 11 as a consequence of lack of blood vessel formation, defective formation of the neural fold, and cardiovascular malformation (Iyer et al., 1998; Ryan et al., 1998). OCT4 can be directly activated by HIF-1alpha and HIF-2alpha (Covello et al., 2006; Bussolati et al., 2012). OCT4 is essential for maintaining the undifferentiated state of embryonic stem cells, inner cell mass cells, the embryonic epiblast and PGCs (Scholer et al., 1990; Nichols et al., 1998). OCT4 expression is tightly controlled during embryogenesis and adult life, and its downregulation is required for differentiation of the trophectoderm lineage and subsequent gastrulation by the epiblast; however, OCT4 expression is maintained in PGCs. In the adult, outside the stem-cell populations OCT4 is exclusively expressed in germ cells (Simon and Keith, 2008). OCT4 is essential for germ-cell maintenance, but dispensable for somatic stem-cell self-renewal (Kehler et al., 2004; Lengner et al., 2007). HIF-1alpha directly inhibits the transcription factor c-Myc, causing de-repression of its targets p21 and p27 (Koshiji et al., 2004; Dang et al., 2008). c-Myc targets involved in mismatch repair are also modulated by HIF-1alpha, suggesting a role for HIF in hypoxia-induced genetic instability (Koshiji et al., 2005; To et al., 2006; Huang LE, 2008).

Hypoxia induces specific microRNAs collectively referred to as hypoxamirs (Chan and Loscalzo, 2010). HIF-1 expression is also controlled by specific microRNAs and, in turn, controls the expression of other microRNAs, which fine-tune adaptation to low oxygen tension (Loscalzo, 2010). miR-210 is the master hypoxamir (Chan et al., 2012). miR-210 is consistently upregulated in both normal and transformed hypoxic cells (Kulshreshtha et al., 2007; Camps et al., 2008; Corn, 2008; Giannakakis et al.,

2008; Ivan et al., 2008; Pulkkinen et al., 2008, Crosby et al., 2009; Huang et al., 2010; Devlin et al., 2011; Gorospe et al., 2011; Mutharasan et al., 2011; Pocock, 2011; Voellenkle et al., 2012). miR-210 is involved in repressing mitochondrial respiration (Chan et al., 2009; Chen et al., 2010; Favaro et al., 2010; Puisségur et al., 2011), exaggerates production of mitochondrial ROS (Favaro et al., 2010) and impairs DNA repair (Crosby et al., 2009; Fasanaro et al., 2009; Devlin et al., 2011). miR-210 appears to be able to bypass hypoxia-induced cell cycle arrest and partially reverse the hypoxic gene expression signature (Zhang et al., 2009). In these particular cells, miR-210 activates the proto-oncogene *myc* pathway, via downregulation of the *c-Myc* antagonist MNT, and loss of MYC abolished miR-210-mediated override of hypoxia-induced cell cycle arrest. Importantly, miR-210 expression has been identified in gametogenesis of *Drosophila*, *Xenopus*, fishes and mammals (Grün et al., 2005; Madison-Villar and Michalak, 2011; Torley et al., 2011; Ambady et al., 2012; Bizuayehu et al., 2012; El Naby, 2012; Miles et al., 2012).

The hypoxic response is characterized by a rapid inhibition of protein synthesis which occurs through the repression of the initiation step of mRNA translation (Wouters et al., 2005; Buchan and Parker, 2009; Spriggs et al., 2010). However, regulation of translation also results in a specific increase in the synthesis of a subset of hypoxia-induced proteins (e.g. heat shock proteins; Borger and Essig, 1998; Yueh and Schneider, 2000; Koritzinsky and Wouters, 2007). These regulatory pathways link hypoxia with the stress granules (see chapter 7.2.7), the site of RNA triage (Anderson and Kedersha, 2002b; 2006; 2008; Kedersha and Anderson, 2002).

7.2.4.1 Male gametogenesis

Decreased O_2 levels and HIF-1 α activation are critical components of spermatogenesis (Gruber et al., 2010). Various HIF-1 isoforms are expressed constitutively by spermatocytes, spermatids, spermatozoa and Leydig cells (Marti et al., 2002; Powell et al., 2002; Depping et al., 2004; Wenger and Katschinski, 2005; Turner and Lysiak, 2008; Lysiak et al., 2009; Palladino et al., 2011), reflecting the stressful conditions under which spermatogenesis takes place. In cancer cells, constitutive HIF-1 α protein expression and activity is mediated by ROS and the NF κ B pathway (Kuphal et al., 2010). Under normoxic conditions, the von Hippel-Lindau tumor suppressor protein (VHL) targets the HIF-1 α subunit for rapid ubiquitination and proteasomal degradation (Maxwell et al., 1999). The significance of stringent regulation of HIF-1 α in the testis is supported by findings in male mice with

conditional inactivation of the VHL gene (Wenger and Katschinski, 2005). These animals show oligospermia, reduction in testicular weight and infertility, suggesting that impaired regulation of HIF-1 α results in defects in spermatogenesis (Ma et al., 2003). Because HIF-1 α knock-out mice die during embryogenesis (Iyer et al., 1998), the role of HIF-1 α in testis cannot be investigated in this animal model. However, HIF-2 α knock-out mice suffer among others from azoospermia (Scortegagna et al., 2003). Postnatal HIF-1 α ablation leads to male infertility, with reduced testis size and weight. While immature spermatogonia and spermatocytes are present in HIF-1 α ^{-/-} testes, spermatid and spermatozoan numbers are dramatically reduced. This is not due to germ cell-intrinsic defects. Rather, HIF-1 α ^{-/-} Sertoli cells exhibit decreased ability to form tight junctions, thereby disrupting the blood-testis barrier necessary for proper spermatogenesis (Gruber et al., 2010). Hypoxia may also be a physiological signal for testosterone production by Leydig cells (Gonzales et al., 2009; 2011). The promoter of the mouse 3 β -hydroxysteroid dehydrogenase type 1 gene, which encodes a key enzyme in testosterone production, is a potential target of HIF-1 (Lysiak et al., 2009). Intermittent hypoxia increased testosterone secretion from Leydig cells *in vivo* and *in vitro* through the activation of adenylate cyclase, enhanced activities of P450_{scc}, 3 β -hydroxysteroid dehydrogenase, and 17 β -hydroxysteroid dehydrogenase, increased levels of calcium ion, and influx into Leydig cells (Hwang et al., 2007; 2009). Many HIF-1 target genes, especially the glycolytic enzymes, are also expressed in the testis (Gold et al., 1983; McCarrey et al., 1996; Li et al., 1998; Welch et al., 2000). Various testis-specific isoforms of glycolytic enzymes are expressed in the haploid stages of spermatogenesis and are still active in mature spermatozoa, including phosphoglycerate kinase 2 (Gold et al., 1983; McCarrey et al., 1996), glyceraldehyde 3-phosphate dehydrogenase-2 (Welch et al., 2000) and lactate dehydrogenase C (Li et al., 1998). Interestingly, all four genes encoding the bifunctional enzymes 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB-1 to -4) are highly expressed in the testis in a hypoxia-inducible manner (Minchenko et al., 2003; 2004). PFKFB-1 to -4 regulate the levels of fructose-2,6-bisphosphate, a potent allosteric regulator of 6-phosphofructo-1-kinase and hence a key regulator of the glycolytic flux. Indeed, sperm capacitation, motility changes, acrosome reaction and fertilization are exclusively dependent on anaerobic glycolysis and can occur under strictly anaerobic

conditions (Fraser and Quinn, 1981).

While somatic Sertoli and Leydig cells produce VEGF-A, a VEGF isoform (Ergün et al., 1997; Liu and Yang, 2004; Reddy et al., 2012), VEGF receptors (VEGF-R1 and VEGF-R2) are expressed on testicular blood vessels (Shweiki et al., 1993; Collin and Bergh, 1996a; Ergün et al., 1997; Korpelainen et al., 1998; Marti and Risau, 1998) and testicular germ cells in humans (Ergün et al., 1997), rats (Rudolfsson et al., 2004), mice (Nalbandian et al., 2003), and cattle (Caires et al., 2009). The presence of VEGF receptors on Sertoli and Leydig cells suggests an autocrine regulatory effect of VEGF on the activity of both cell types (Ergün et al., 1997). In this context it is of interest that intermittent hypoxia (that could result from the autocrine negative feedback of VEGF) increased Leydig cell testosterone secretion *in vivo* and *in vitro* (Hwang et al., 2007; 2009) while chronic hypoxia leads to decreased testosterone and reproductive dysfunction (Fahim et al., 1980; Semple et al., 1980; Aasebo et al., 1993; Soukhova-O'Hare et al., 2008; Liao et al., 2010) possibly in conjunction with testicular vascularization and hyperthermia (Fariás et al., 2005; Madrid et al., 2012). Intriguingly, an intermittent hypoxic training regimen consisting of 14 consecutive days with four repetitions of 5–7 min each of induced hypoxia interspersed with 5 min periods of ambient inspiration produced a stimulatory effect on male reproductive function and remedied male subfertility (Swanson and Serebrovska, 2012). VEGF, however, had no effect on testicular vasomotion (see chapter 7.2.1) (Rudolfsson et al., 2004). VEGF expression is conserved in vertebrate testes of fish, reptiles and mammals (Reddy et al. 2012). VEGF increases the number of proliferating testicular endothelial cells (Rudolfsson et al., 2004). Seasonal regression and regrowth of the white-footed mouse testes positively correlated with VEGF expression (Young and Nelson, 2000). Adult roe deer males show VEGF mRNA expression dependent on season, reaching its highest level at the peak of spermatogenesis during the pre-rutting period and had its nadir at the end of the rut when involution already began (Wagener et al., 2010; Schön et al., 2010). These and other findings (Dolci et al., 2001; Guo R et al., 2004; Schmidt et al., 2006; 2007) suggested that VEGF may directly affect the proliferation and differentiation of germ cells, an effect that may, at least in part, be independent from the formation of testicular microvasculature (Korpelainen et al., 1998; Wagener et al., 2010). Ischemia-reperfusion injury of rat testis significantly increased VEGF protein and mRNA in a time-dependent manner in testicular vascular endothelial cells and germ cells (Hashimoto et al.,

2009). Overexpression of VEGF has harmful effects on spermatogenesis in transgenic mice (Korpelainen et al., 1998; Huminiecki et al., 2001) and in human testes with varicocele (Shiraishi and Naito, 2008) implicating VEGF in male fertility (Korpelainen et al., 1998; Huminiecki et al., 2001; Bott et al., 2006; Shiraishi and Naito, 2008).

7.2.4.2 Female gametogenesis

Low oxygen tension during meiotic arrest improves the developmental competence of mammalian oocytes (Eppig and Wigglesworth, 1995; Hashimoto et al., 2000; 2002). The functional hypoxia and the growing-follicle HIF signaling is involved in follicular differentiation and luteinization (Tam et al., 2010). Within non-atretic follicles, HIF-1alpha mRNA was highly expressed in the granulosa cell layer, while weaker labeling was evident in the theca interna. These results suggest that HIF-1alpha may play a role in the regulation of cellular metabolism during follicular growth (Boonyaparakob et al., 2005). Significant differences in dissolved oxygen content occur in follicular fluids aspirated from follicles of equivalent size and ultrasonographic appearance. Oocytes from severely hypoxic follicles were associated with high frequencies of DNA damage. Oocytes with cytoplasmic and chromosomal disorders and embryos with multinucleated blastomeres and limited developmental ability were derived predominantly from underoxygenated follicles (Van Blerkom, 1998). HIF-1 alpha expression appears to be the signal that provides trophic support and competitive advantage to growing follicles: human oocytes collected from follicles that contain a higher concentration of VEGF have a higher viability (Van Blerkom et al., 1997; Van Blerkom, 2000; Monteleone et al., 2008).

Initiation and maintenance of follicular growth depends on development of the follicular microvasculature (Clark, 1900; Andersen, 1926). The density of capillaries surrounding the dominant, maturing follicle is greater than that of other smaller follicles. Preovulatory follicles of monkeys were found to have similar concentrations of gonadotropin-binding sites; however, only the follicle that was destined to ovulate became heavily labelled after intravenous injection of labelled gonadotropin consistent with an increased vascularity of the dominant follicle (Zeleznik et al., 1981). Follicles undergoing atresia have decreased vascularity (Zeleznik et al., 1981; Moor and Seamark, 1986) and reduced DNA synthesis of follicular endothelial cells, in association with reduced follicular vascularity, is one of the earliest signs of atresia (Greenwald, 1989). Decreased vascularity may limit access of atretic follicles to nutrients, substrates, and

tropic hormones, thereby maintaining these follicles in an atretic state (Moor and Seamark, 1986). VEGF measurements of follicular fluid indicated a potentially important role for this factor both in perfollicular angiogenesis and in the regulation of intrafollicular oxygen levels (Van Blerkom et al., 1997). Metabolic/hypoxic stress that involves ROS in hypoxic signaling plays a pivotal role in the follicular angiogenic process and stimulates VEGF synthesis by granulosa cells (Neeman et al., 1997; Tempel-Brami and Neeman, 2002; Basini et al., 2004a; b; 2007). However, in contrast with solid tumors of similar size, the spatial and temporal discrepancy between VEGF expression and angiogenesis suggests that cumulus cells secrete to the follicular fluid, in addition to VEGF, material with antiangiogenic activity. Hyaluronan as a high molecular weight suppressor of angiogenesis, produced by the cumulus cells, can account for this antiangiogenic activity maintaining an avascular follicular antrum (Tempel et al., 2000; Tempel-Brami and Neeman, 2002). In addition to hypoxia, FSH and LH stimulate VEGF production by granulosa cells (Christenson and Stouffer, 1997). VEGF mRNA is expressed in large preantral follicles (Ravindranath et al., 1992). Direct injection of VEGF into the mouse ovary resulted in the development of an enhanced vascular network promoting follicular development and diminishing apoptosis (Quintana et al., 2004), acting as a survival factor for granulosa cells (Greenaway et al., 2004). Formation of antrum coincides with continued follicular angiogenesis resulting in the development of an intricate vascular mesh that secures an increasing supply of gonadotropins, growth factors, oxygen, steroid precursors, as well as other substances to the growing follicle (Geva and Jaffe, 2000a; b; Wulff et al., 2001). VEGF is essential for angiogenesis and the generation of healthy ovulatory follicles and corpora lutea. Even in the presence of gonadotropins, administration of substances that inactivate VEGF and its signaling, block the development and function of preovulatory follicles caused by arrests to both angiogenesis and antrum formation (Wulff et al., 2001; 2002; Zimmermann et al., 2001; 2002; 2003; Fraser et al., 2005; Taylor et al., 2007).

Elevated VEGF concentration in follicular fluid is a marker of follicular hypoxia, reduced perfollicular blood flow, and ovarian aging (Friedman et al., 1998; Battaglia et al., 2000; Ocal et al., 2004). Women of advanced reproductive age undergoing follicular aspiration after superovulation showed increased follicular fluid VEGF concentrations compared with younger women consistent with a hypoxic environment within follicles of older women (Friedman et al., 1997).

Taking into account that VEGF expression is associated with oxidative stress (Neeman et al., 1997; Basini et al., 2004a; b; 2007) these markers may also be related to oocyte DNA damage (Van Blerkom, 1998). Thus the complex causal relationship between follicular hypoxia and its timing make VEGF both a marker of oocyte high quality (Van Blerkom et al., 1997; Van Blerkom, 2000; Monteleone et al., 2008) and damage (Van Blerkom, 1998). Therefore, follicular blood flow is a better predictor for the outcome of in vitro fertilization than follicular fluid VEGF (Kim KH et al., 2004).

7.2.5 Cytokines and nuclear factor-kappaB

The cytokines interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF) exhibit a variety of stimulatory activities on maturation, differentiation and growth of many cell types involved in development and inflammation, such as fibroblasts, synovial cells, endothelial and epithelial cells, bone marrow cells, and T- and B-lymphocytes (Dinarello, 1985; Krakauer, 1986; Akahoshi et al., 1988; Chouaib et al., 1988; Bonavida and Granger, 1990; Le Hir et al., 1996; Muñoz-Fernández and Fresno, 1998; Azuma et al., 2000). Both cytokines have profound effects on inflammatory reactions (Beutler and Cerami, 1986; 1987; Billingham, 1987; Eastgate et al., 1988; Marx, 1988; Tracey et al., 1986; 1987; Fiers, 1991; Beutler, 1995). There seems to be an analogy between hematopoietic and spermatogenic systems (Huleihel and Lunenfeld, 2004). In the testes, cytokines are involved in the Sertoli-germ cell interaction, Leydig cells steroidogenesis, blood flow, and vascular permeability as well as in local control of immune cells (Spangelo et al., 1995). Macrophages are closely associated with Leydig cells in the testicular interstitium and comprise about 25% of the interstitial cell population in the testes of mammals including man, monkeys, rat and boar (Fawcett et al., 1973; Niemi et al., 1986). IL-1 and TNF are released by testicular macrophages, Sertoli and Leydig cells (Khan et al., 1987; Gérard et al., 1991; Söder et al., 1991; Wang et al., 1991; Hales et al., 1992; Hutson, 1992; Lin et al., 1993; Haugen et al., 1994; Kern et al., 1995; Cudicini et al., 1997). IL-1 receptors have been reported on Sertoli cells, Leydig cells, testicular macrophages, and germ cells suggesting both autocrine and paracrine functions. IL-1 was shown to promote proliferation and differentiation of spermatogonia and preleptotene spermatocytes (Pollanen et al., 1989; Parvinen et al., 1991) and is correlated with spermatogonial DNA synthesis in the rat seminiferous epithelium (Söder et al., 1991). Interleukin-1 and TNFalpha are also potent growth factors for immature rat Sertoli and Leydig cells

(Khan et al., 1992; Petersen et al., 2002; 2004) and stimulate testosterone biosynthesis and secretion in adult Leydig cells (Verhoeven et al., 1988; Warren et al., 1990; Svechnikov et al., 2001). IL-1 and TNF both induce oxygen radical formation in a variety of cell types (Klempner et al., 1979; Tsujimoto et al., 1986; Ferrante et al., 1988; Meier et al., 1989; Radeke et al., 1990; Feng et al., 1995; Lo et al., 1998; Lee FY et al., 1999; Bonizzi et al., 2000; Corda et al., 2001; Gloire et al., 2006; Ishikawa and Morris, 2006; Davies et al., 2008; Morgan and Liu, 2010), e.g. by the activation of NAD(P)H oxidases (De Keulenaer et al., 1998; Gauss et al., 2005; Ammons et al., 2007; Yang D et al., 2007). A key cytokine signaling pathway is through NF-kappaB (Schreck et al., 1991; Bonizzi et al., 2000; Baud and Karin, 2001; Janssens et al., 2002; Senftleben and Karin, 2002; Tian and Brasier, 2003; Gloire et al., 2006).

The metazoan transcription factor NF-kappaB signaling pathway shows some homology to the yeast mitochondrial retrograde response (Srinivasan et al., 2010). NF-kappaB activation is part of the cellular stress response to a variety of factors including cytokine stimulation, irradiation, and ischemia-reperfusion. NF-kappaB is a master regulator for inflammatory responses, mediating cellular defense against infectious agents and environmental and cellular stress (Mercurio and Manning, 1999; Wang et al., 2002; Piva et al., 2006), and is highly conserved in innate immunity (Silverman and Maniatis, 2001). Numerous studies have demonstrated that in cells subjected to oxidative stress there is a potent NF-kappaB response. As such, NF-kappaB is often referred to as the cellular 'sensor' for oxidative stress (Li and Karin, 1999; Mercurio and Manning, 1999; Storz and Toker, 2003; Oliveira-Marques et al., 2009; Morgan and Liu, 2011; Siomek, 2012) that is linked to ROS by reciprocal, both negative and positive controls (Bubici et al., 2006; Basak and Hoffmann, 2008; Morgan and Liu, 2011). Oxidative stress-sensitive NF-kappaB is upregulated during gamete maturation (Delfino and Walker, 1998; 1999a; b; Lilienbaum et al., 2000; Shalini and Bansal, 2007; Paciolla et al., 2011). Nuclear NF-kappaB is present in Sertoli cells and in the late meiotic and postmeiotic germ cells of the rodent testis (Delfino and Walker, 1998; Lilienbaum et al., 2000) at higher levels than in any other tissue assayed (Budde et al., 2002). Intense cytoplasmic staining for NF-kappaB was found in the spermatogonia and early meiotic germ cells of the human testis. In light of the importance of the stable pool of immature germ cells for continuous spermatogenesis, the extensive deposition of NF-kappaB in the cytoplasm of spermatogonia and

immature spermatocytes may be used for rapid nuclear translocation and transcriptional activation of protective genes on certain stimuli (Pentikäinen et al., 2002). In Sertoli cells, NF-kappaB elements in the androgen receptor promoter have been identified as being responsible for increased androgen receptor expression, representing an important (cell type-specific) regulatory mechanism required to maintain efficient spermatogenesis (Delfino et al., 2003; Zhang L et al., 2004).

7.2.6 Heat shock response

All organisms share a common molecular stress response that includes a dramatic change in the pattern of gene expression and the elevated synthesis of a family of stress-induced proteins called heat shock proteins (Craig, 1985; Lindquist and Craig, 1988; Kalmar and Greensmith, 2009). Genes encoding a variety of molecular chaperones, and proteins that catalyse ROS and disulfide bond metabolism are induced in response to oxidative stress (Barford, 2004). Cells react to stressful conditions by activation of heat-shock factors (HSFs), of which there are three mammalian (HSF1, HSF2, and HSF4) and one avian (HSF3) isoforms (Pirkkala et al., 2001; Kalmar and Greensmith, 2009). Functional conservation of HSFs among eukaryotes has been revealed by the finding that HSFs from various organisms, including insects, mammals and plants, can substitute for yeast HSF in *Saccharomyces* (Pirkkala et al., 2001; Abane and Mezger, 2010; Björk and Sistonen, 2010; Fujimoto and Nakai, 2010). Activated HSFs bind to heat-shock elements (HSEs) within the promoters of their target genes and induce synthesis of protective molecular chaperones called heat shock proteins (Hsps). Hsps are highly conserved proteins present in organisms ranging from bacteria to man. Hsps prevent protein misfolding and are required for stress resistance and healthy cell growth, development, and aging (Morimoto, 1993; 2008; Bukau et al., 2006; Prahlaad and Morimoto, 2009). In addition to extracellular stimuli, several 'nonstressful' conditions induce Hsps during normal cellular growth and development. The eukaryotic transcription factor that appears to be most directly redox regulated is HSF1, a highly conserved transcription factor which mediates the transcription of a complex of genes in response to heat, oxidative stress and a variety of other stressors (Fedoroff, 2006). Using HSF1-null mice, Izu et al. (2004) showed that apoptosis of pachytene spermatocytes was markedly inhibited in testes with a single exposure to heat and in cryptorchid testes, indicating that HSF1 promotes apoptotic cell death of pachytene spermatocytes exposed to thermal stress. In marked

contrast, HSF1 acts as a cell-survival factor of more immature germ cells, probably including spermatogonia, in testes exposed to high temperatures. These results demonstrate that HSF1 has two opposite roles in male germ cells independent of the activation of heat shock genes (Izu et al., 2004). HSF2 regulates the activity of heat shock genes under perceived non-stressful conditions, such as differentiation and development (Sistonen et al., 1994). Moreover, HSF2 modulates HSF1-mediated regulation of a variety of other hsp genes, clearly demonstrating a functional role for HSF2 in stress responses (Sistonen et al., 1994; Mathew et al., 2001; He et al., 2003; Åkerfelt et al., 2007; 2010; Östling et al., 2007; Sandqvist et al., 2009). The first indication of a role for HSFs in oogenesis was suggested by studies in *Drosophila*, which demonstrated that the unique *Drosophila* HSF is essential for oogenesis and implied that its role in oogenesis is mediated not only by the regulation of Hsp genes (Jedlicka et al., 1997; Abane and Mezger, 2010). HSF1 is highly expressed in mouse nonfertilized ovulated oocytes arrested at metaphase II and in pre-implantation embryos (Mezger et al., 1994; Christians et al., 1997). The deficiency in HSF1 provokes an oxidative stress to which oocytes are particularly sensitive (Liu L et al., 2000; Dumollard et al., 2007a). In gonads, HSF2 is abundantly expressed and plays a role in spermatogenesis (Sarge et al., 1994; Fiorenza et al., 1995; Kallio et al., 2002; Wang G et al., 2003; Åkerfelt et al., 2008) and oogenesis (Kallio et al., 2002; Wang G et al., 2003; Abane and Mezger, 2010). During mouse postnatal testis development, the HSF2-beta mRNA isoform (that is primarily expressed in the heart and brain) is switched to the HSF2-alpha isoform. HSF2-alpha protein, the predominant isoform expressed in testis cells, is a more potent transcriptional activator than the HSF2-beta isoform (Goodson et al., 1995). In contrast to *hsf1*^{-/-} mice, which exhibit normal spermatogenesis, targeted disruption of *hsf2* results in reduced testicular size but only a small impairment in male fertility. *Hsf2*^{-/-} mice displayed increased apoptosis at pachytene, meiotic M and type A spermatogonia stage (Kallio et al., 2002; Wang G et al., 2004). Meiosis is affected by HSF2 deficiency, in both males and females. Disruption of both *hsf1* and *hsf2* results in a more severe phenotype associated with male sterility due to severe defects in spermatogenesis. Earliest defects observed are the reduced number of germ cells in juvenile mice, and germ cells that enter the meiotic prophase fail to progress beyond the pachytene stage. This is associated with a reduction or absence of transcription of genes critically involved in spermatogenesis. The

findings suggest that additive or synergistic transcriptional activity of both *hsf1* and *hsf2* is required for normal mammalian spermatogenesis and male fertility (Wang G et al., 2004).

The Hsps are a group of highly conserved proteins that are induced in both prokaryotes and eukaryotes by elevated temperatures or a variety of cellular stressors (Samali and Orrenius, 1998; Feder and Hofmann, 1999; Kalmar and Greensmith, 2009). When cells are exposed to elevated temperatures the heat shock protein HSP70 is the most prominently expressed. Variation in Hsp70 gene expression and polymorphisms has been positively correlated with variation in thermotolerance in *Drosophila melanogaster*, in *Caenorhabditis elegans*, and in mammals (Hashmi et al., 1997; Maloyan et al., 1999; Sonna et al., 2002; Gong and Golic, 2004; Singh et al., 2006; Bernabucci et al., 2010). Hsps are constitutively expressed during both female and male germ cell maturation in invertebrates and vertebrates (Ambrosio and Schedl, 1984; Glaser and Lis, 1990; Ohsako et al., 1995; Paranko et al., 1996; Dix, 1997; Michaud et al., 1997; Sarge and Cullen, 1997; Joannis et al., 1998; Son et al., 1999; Neuer et al., 2000; Aguilar-Mahecha et al., 2001; Nonoguchi et al., 2001; Christians et al., 2003; Kamaruddin et al., 2004; Ma et al., 2007; Huo et al., 2008; Meistertzheim et al., 2009; Abane and Mezger, 2010; Åkerfelt et al., 2010; Lachance et al., 2010) and in plant male gametogenesis (Schöffl et al., 1998). Several HSPs have been found to be constitutively expressed in germ cells at specific stages of development. Two HSP70-related genes, Hsp70-2 and Hsp70t, are expressed at high levels in spermatocytes and spermatids, respectively, and at considerably lower or nondetectable levels in other tissues (Krawczyk et al., 1988; Zakeri et al., 1988; Matsumoto and Fujimoto, 1990; Rosario et al., 1992; Son et al., 1999; Fourie et al., 2001). Male mice deficient for Hsp70-2 are sterile due to a failure of spermatocytes to proceed through the first meiotic division and increased spermatocyte apoptosis (Dix et al., 1996), and a decreased level of Hsp70-2 mRNA in human testis has been associated with abnormal spermatogenesis and sterility (Son et al., 2000). Hsp70-2 is also expressed at moderate levels in a variety of tumor cells and controls tumor cell proliferation (Rohde et al., 2005). The temperature threshold for induction of HSP72 encoded by the *hsp70* gene is lower in male germ cells than in somatic cells (Sarge et al., 1995; Sarge, 1995). Similarly, Hspa41, a member of the heat shock protein 110 family that responds to a lower temperature heat shock rather than the traditional elevated temperatures is abundantly expressed from late pachytene

spermatocytes to postmeiotic spermatids (Kaneko et al., 1997a; b; Held et al., 2006; 2011). HSP90 and HSP60 are expressed in spermatogonia and spermatocytes (Gruppi et al., 1991; Meinhardt et al., 1995; Ohsako et al., 1995; Sarge and Cullen, 1997). Hsp90 is one of the most highly expressed cytosolic molecular chaperones, comprising 1% of the total cellular protein even in non-stressed conditions. It interacts with several hundred client proteins, simultaneously recruiting its own battery of co-chaperones, thus maintaining normal cellular functions in an ATP-dependent manner (Taipale et al., 2010; Echeverria and Picard, 2010). HSP90 is highly expressed in PGCs and continues to be expressed in both male and female pre-meiotic germ cells (Ohsako et al., 1995). Hsp90alpha is the major Hsp expressed by fully grown oocytes and markedly down-regulated by the absence of HSF1 (Metchat et al., 2009). Interestingly, Hsp90 is constitutively expressed at 2–10-fold higher levels in tumors compared to normal non-gonadal tissues (Ferrarini et al., 1992). Spermatogenesis is the developmental process most sensitive to the loss of Hsp90 function (Yue et al., 1999). Male KO mice without the Hsp90alpha isoform are sterile because spermatogenesis arrests specifically at the pachytene stage of meiosis I (Grad et al., 2010; Kajiwara et al., 2012). Birds are unique among homeothermic animals in developing spermatogenesis at the elevated avian internal body temperature of 40–41° C. While the expression of Hsp70 and ubiquitin did not change upon heat shock in mouse testicular cells, both the amount and polyadenylation of Hsp70 and ubiquitin transcripts increased when male germ cells from adult chicken testis were exposed to elevated temperatures (Mezquita et al., 1998).

Heme oxygenase (HO) is a heat shock protein and its induction occurs together with the induction of other HSPs during various physiopathological conditions (Shibahara et al., 1987; Keyse and Tyrrell, 1989; Mitani et al., 1990; Sharp et al., 1999). HO oxidatively cleaves heme (Fe-protoporphyrin IX) to produce CO, biliverdin, and free iron (Maines, 1997). Endogenously produced CO has been shown to possess intriguing signaling properties affecting numerous critical cellular functions including but not limited to inflammation, cellular proliferation, and apoptotic cell death (Ryter et al., 2006). Depending on the cellular milieu, HO activity can be considered as a proponent of oxidative stress with both pro-oxidant and anti-oxidant activities: (i) by liberating chelated iron from the heme molecule creating catalytically active free iron causing formation of ROS by Haber–Weiss chemistry (Mello-Filho and Meneghini, 1984; Maines and Gibbs, 2005) with

devastating effects in a cell or, (ii) as a means to generate the antioxidant bilirubin (Stocker et al., 1987; Maines, 1997; Baranano et al., 2002). Accordingly, numerous studies proposed that the activity of the HO system might provide cellular protection against oxidative stress (Stocker, 1990; Maines, 1997; Niess et al., 1999; Pomeranec et al., 2004; Shiraishi and Naito, 2005) and, on the other hand, may augment apoptosis (Liu XM et al., 2000; Ozawa et al., 2002; Harada et al., 2004a). HO-2 is the constitutive form of the stress inducible HO-1 gene and is abundantly expressed throughout spermatogenesis (Trakshel et al., 1986; Kurata et al., 1993; Ewing and Maines, 1995; McCoubrey et al., 1995; Aguilar-Mahecha et al., 2001) and in ovarian theca, granulosa cells, and corpora lutea as well as the ovarian stroma (Alexandreaanu and Lawson, 2003; Harada et al., 2004a; Malone and Michalak, 2008) suggesting that HO-2 plays an important role in germ cell development. Moreover, HO-1 expression in the ovary plays a pivotal role in the process of oocyte ovulation, fertilization, and corpora lutea maintenance (Zenclussen et al., 2012). Intriguingly, HO-2 levels in the testis are controlled by glucocorticoids and developmental and tissue-specific factor(s) determine generation of transcripts unique to the organ (Liu N et al., 2000). The glucocorticoid element is the only demonstrated functional response element in the promoter sequence of HO-2 (McCoubrey and Maines, 1994; Weber et al., 1994; Raju et al., 1997). Leydig cells play a key role in oxidative stress-induced downregulation of spermatogenesis (Ozawa et al., 2002). Under stress conditions, HO-1 is upregulated predominantly in Leydig cells coinciding with CO generation, and microsomal cytochromes P450 which are required for steroidogenesis are suppressed. Under these circumstances, diploid and tetraploid germ cells in peripheral regions of seminiferous tubules, suggesting involvement of spermatogonia and primary spermatocytes, exhibited apoptosis (Ozawa et al., 2002).

7.2.7 Stress and germ granules

In response to environmental stress (e.g. heat, hypoxia, hyperosmolarity and oxidative conditions), eukaryotic cells shut down protein synthesis in a stereotypic response that conserves anabolic energy for the repair of stress-induced damage, enhancing their ability to withstand stress (Holcik and Sonenberg, 2005; Lavut and Raveh, 2012). This results in a notable saving of cellular energy, which is mainly consumed in the process of translation (estimated as up to 50% of the cellular energy, depending on the organism) (Warner, 1999; Mathews et al., 2000; Rudra

and Warner, 2004). Cytoplasmic RNA granules in germ cells and somatic cells have emerged as important players in the posttranscriptional regulation of gene expression. RNA granules contain various ribosomal subunits, translation factors, decay enzymes, helicases, scaffold proteins, and RNA-binding proteins, and they control the localization, stability, and translation of their RNA cargo (Anderson and Kedersha, 2006). RNA-binding proteins and miRNAs can block translation by mobilizing mRNAs to subcytoplasmic domains where translation is inhibited; such sites include processing bodies (P-bodies), neuronal RNA granules, and stress granules (SGs). These are cytoplasmic foci that form transiently in response to cell stress and damage and harbor mRNAs that are typically stable and not translated (Gottschald et al., 2010; Gorospe et al., 2011). SGs have been observed in yeast (such as *Saccharomyces pombe*), protozoa (*Trypanosoma brucei*) and metazoa (such as *Homo sapiens* and *Caenorhabditis elegans*). They have also been observed in plants and in chloroplasts, suggesting that they may be assembled in prokaryotes as well (Anderson and Kedersha, 2009). In fact, stress induces the assembly of RNA granules in an organelle with bacterial ancestry, the chloroplast of *Chlamydomonas reinhardtii* (Uniacke and Zerges, 2008). SGs are phase-dense particles that appear in the cytoplasm of both plant and animal cells subjected to a wide variety of stresses (eg. heat, UV irradiation, oxidative conditions, hyperosmolarity) (Anderson and Kedersha, 2002a; b; Moeller et al., 2004; Kedersha and Anderson, 2007; Arimoto et al., 2008). SGs form during hypoxia both in vitro and in vivo and reoxygenation leads to disaggregation of these granules and restoration of protein synthesis (Moeller et al., 2004). SGs are hallmarks of stalled translational initiation (Brenques et al., 2005; Kedersha et al., 2005; Yamasaki and Anderson, 2008). SGs are a major adaptive defense mechanism that negatively regulates the stress-activated p38 and JNK MAPK apoptotic response (Arimoto et al., 2008; Tsai and Wei, 2010). The RNA silencing machinery redistributes into SGs in cells that go through mitosis after UV irradiation (Pothof et al., 2009). The involvement of oxidative stress in the causation of translational arrest and SG assembly has been shown in yeast, plants and animals (Anderson and Kedersha, 2002b; Kedersha and Anderson, 2002; 2007; Gilks et al. 2004; Cohen et al., 2005; McEwen et al., 2005; Shenton et al., 2006; Kedersha and Anderson, 2007; Kedersha et al., 2008, Uniacke and Zerges, 2008; Pothof et al., 2009; Wolf et al., 2010; Brown et al., 2011; Emara et al., 2012). The stress-induced phosphorylation of the eukaryotic translation initiation

factor 2 (eIF2) induces SG assembly by preventing or delaying translational initiation (Anderson and Kedersha, 2002a; 2009). SGs form when translation is initiated under conditions in which the concentration of the active eIF2–guanosine triphosphate (GTP)–transfer RNA for methionine (tRNA^{Met}) ternary complex is reduced. The assembly of translationally inactive initiation complexes lacking eIF2 allows the RNA-binding proteins TIA-1 or TIAR (or both) to redirect untranslated mRNAs from polyribosomes to SGs. By regulating the equilibrium between polysomes and SGs, TIA-1 and TIAR may influence the frequency with which individual transcripts are sorted for translation or triage in both stressed and unstressed cells (Anderson and Kedersha, 2002a; 2009). Sorting of mRNAs for future translation or decay by individual cells could generate potentially different phenotypes in a genetically identical population (Lavut and Raveh, 2012). The translational arrest that accompanies environmental stress is selective: whereas translation of constitutively expressed “housekeeping” transcripts is turned off, translation of stress-induced transcripts encoding heat shock proteins such as HSP70 and some transcription factors is maintained or enhanced (Anderson and Kedersha, 2002b; 2006; Kedersha and Anderson, 2002; Moore, 2005). mRNAs encoding constitutively expressed “housekeeping” proteins are redirected from polysomes to these discrete cytoplasmic foci, a process that is synchronous with stress-induced translational arrest (Anderson and Kedersha, 2002b; 2008; Kimball et al., 2003; Kedersha et al., 2005). SGs have been shown to contain the Argonaute proteins, microRNAs, a number of mRNA-editing enzymes, and proteins required for transposon activity (Anderson and Kedersha, 2009). “Germ granules” are cytoplasmic, nonmembrane-bound organelles unique to the germline. The term “germ (or germinal) granule” encompasses what are known as P granules in *Caenorhabditis elegans* and zebrafish, polar granules in *Drosophila melanogaster*, germinal granules in *Xenopus laevis*, and the perinuclear nuage in mammalian germ cells. Germ granules are thought to be a signature feature of germ cells in animals (Mahowald, 1968; al-Mukhtar and Webb, 1971; Eddy, 1974; 1975; Wilsch-Brauninger et al., 1997; Snee and Macdonald, 2004; Updike and Strome, 2010; Gao and Arkov, 2012). In some organisms (i.e., *Drosophila*, *Xenopus*, *Caenorhabditis elegans*, and zebrafish), germ granules are present continuously throughout development, with the exception of mature sperm. Germ granules share components with the P-bodies and SGs of somatic cells and often appear as compositional hybrids of SGs and P-bodies (Kotaja et

al., 2006; Gallo et al., 2008; Buchan and Parker, 2009; Lim et al., 2009; Voronina et al., 2011; Olszewska et al., 2012; Schisa, 2012). For instance, various isoforms of eukaryotic translation initiation factors are components of SGs and germ granules and are required for gametogenesis in *C. elegans*, *Drosophila*, mammals and plants (Amiri et al., 2001; Schisa, 2012; Sengupta and Boag, 2012). The relationship of stress and germ granules is reflected not only by their shared components but also by mechanisms of their formation. Like SGs (see above) germ granules require TIAR for their assembly (Beck et al., 1998). TIAR nullizygotes that survive to birth are sterile because of defective germ cell maturation (Beck et al., 1998). Germinal granules of germline cells in various animals, from sponges to vertebrates, were found to contain a protein product (RNA-helicase) of the *vasa* gene or related genes, a key determinant and a universal marker of germline cells in metazoans, which is necessary for the formation and maintenance of the structural organization of germ granules. In animals that reproduce only sexually, the expression of *vasa*-related genes is always exclusively confined to the germ cell line during the entire course of development, from early embryo up to gametogenesis (Ding and Lipshitz, 1993; Ikenishi, 1998; Castrillon et al., 2000; Raz, 2000; Matova and Cooley, 2001; Mochizuki et al., 2001; Extavour and Akam, 2003; Xu et al., 2005; Linder, 2006; Linder and Lasko, 2006; Seydoux and Braun, 2006; Sunanaga et al., 2006; Strome and Lehman, 2007; Ewen- Campen et al., 2010). Intriguingly, *Vasa* has a role in somatic stress responses of plants (Vashisht and Tuteja, 2006) and *Botryllus schlosseri*, a colonial urochordate (Rosner et al., 2009), organisms that form germline cells from a multipotent stem cell precursor. *Nanos* is an evolutionarily conserved RNA-binding protein essential for germ cell development and is a component of germ plasm in organisms, in which germ cells are specified by germ plasm-based 'preformation' (Wang and Lehmann, 1991; Subramaniam and Seydoux, 1999; Seydoux and Braun, 2006). Many proteins containing Tudor domains have been identified in stress and germ granules from different model organisms (Gao and Arkov, 2012). The Tudor domain is a small, 50–55 amino acid beta-barrel module that forms a pocket lined with aromatic amino acids (forming an aromatic cage) (Chen C et al., 2011; Pek et al., 2012a). The aromatic cage interacts with methylated amino acids, for example, lysines or arginines, of target proteins. In various model organisms, Tudor domain proteins play crucial roles in the assembly of stress granules (De Leeuw et al., 2007; Goulet, et al., 2008; Linder et al., 2008; Gao et al., 2010; Weissbach and Scadden,

2012) and germ granules (Boswell and Mahowald, 1985; Chuma et al., 2006; Strasser et al., 2008; Vasileva et al., 2009; Siomi et al., 2010; Pillai and Chuma, 2012). During most of germline development, germ granules appear as rounded fibrillar aggregates that cluster around nuclei (Voronina et al., 2011). This arrangement has been documented to persist from the stage of primordial germ cells (PGCs) of *Drosophila* (Mahowald, 1968; 1971), *C. elegans* (Strome and Wood 1982, 1983), *Xenopus* (Ikenishi et al., 1996), and zebrafish (Knaut et al., 2000). In mice, small granules surrounded by fibrillar matrix and mitochondria become apparent around the nuclei of PGCs two days after their formation at 9–9.5 days of gestation (Spiegelman and Bennett, 1973; Clark and Eddy; 1975). The germ granules are in intimate association with mitochondria (and are often described as "intermitochondrial cement or material/bar/cloud") and, taking into account the role of oxidative stress in SG assembly (Anderson and Kedersha, 2002b; Kedersha and Anderson, 2002; 2007; Gilks et al. 2004; Cohen et al., 2005; McEwen et al., 2005; Shenton et al., 2006; Kedersha and Anderson, 2007; Kedersha et al., 2008, Uniacke and Zerges, 2008), can be expected to be causally related to ROS, particularly H₂O₂ generation.

The putative function of germ granules in transgenerational epigenetic information transfer will be discussed in chapter 16.

7.2.8 DNA damage and repair

In contrast to other biomolecules DNA cannot be replaced, only repaired. Cells have acquired a variety of DNA repair mechanisms with broad, often overlapping substrate specificities to counteract the harmful effects of DNA injuries (Hoeijmakers, 2001; Friedberg et al., 2006). Increased formation of DSBs brings about a high demand for DNA damage response. Repair of DNA plays a large role in regulating mutant frequency (Klungland et al., 1999; Wang et al., 2006; Ikehata et al., 2007). A vast number of genes encoding proteins that take part in different DNA repair mechanisms show enhanced or specialized expression during spermatogenesis (Hirose et al., 1989; Menegazzi et al., 1991; Weeda et al., 1991; Alcivar et al., 1992; Engelward et al., 1993; Walter et al., 1994; 1996; Chen et al., 1995; Zhou and Walter, 1995; Li WH et al., 1996; van der Spek et al., 1996; Wilson et al., 1996; Mackey et al., 1997; Shannon et al., 1999; Kim et al., 2000; Baarends et al., 2001; Intano et al., 2001; Olsen et al., 2001; 2005; Hsia et al., 2003). For instance, nuclear extracts prepared from mixed germ cells exhibited a substantially higher uracil-DNA glycosylase-initiated

BER activity than other mitotically active cells/tissues, namely 5-fold higher than thymocytes and 6-fold higher than small intestine, a finding that cannot be explained simply by germ cell division rates (Intano et al., 2001). The removal of oxidized bases is performed predominantly by the BER pathway (Dianov et al., 2001; Mitra et al., 2001; Bohr et al., 2002) and it has been shown that induction of DNA repair enzymes occurs in response to oxidative stress (Samson and Cairns, 1977; Rusyn et al., 2000; Schärer and Jiricny, 2001; Wood et al., 2001; Barzilai and Yamamoto, 2004; Powell et al., 2005). The link is so close that changes in expression of BER genes have been proposed as sensitive *in vivo* biomarkers for oxidative DNA damage (Rusyn et al., 2004; Powell et al., 2005). There are a number of consequences of induction/deficiency in DNA repair that are important for the process of mutagenesis. Although induction would lead to enhanced repair, it has been suggested that this can be deleterious and promote mutagenesis (Cairns, 2000). If enzymes that act consecutively on different steps of repair are up-regulated unevenly, a state of imbalanced DNA repair might occur and lead to accumulation of both mutagenic and clastogenic lesions (Glassner et al., 1998; Posnick and Samson, 1999). Thus, at face value, the high levels of DNA repair proteins do an excellent job: spontaneous mutation frequencies are significantly lower for mixed germ cells compared to somatic tissues (Kohler et al., 1991; Dycaico et al., 1994; Walter et al., 1998; Murphey et al., 2013). (But importantly, what was measured in these studies was the small population of high-quality survivors of the germ cell quality-control carnage [e.g. Walter et al., 1998; see chapter 8]).

Given the key role of DNA repair for the faithful transmission of genetic information, DNA repair during mammal gametogenesis, particularly spermatogenesis, is far from optimal. In particular, the BER pathway plays a major role in regulating mutant frequency in the rodent male germline (Huamani et al., 2004; Allen et al., 2008). Importantly, there is no safety margin for BER in the germline: haploinsufficiency of DNA polymerase-beta that is required for the short-patch BER pathway results in reduced BER activity and elevated spontaneous mutagenesis in the mouse male germline but not in somatic tissues (Allen et al., 2008). BER by DNA glycosylases is the main pathway for repair of oxidative base lesions in DNA. In human, rat and mouse nuclear and mitochondrial extracts, the highest DNA glycosylase activities were in testis (Olsen et al., 2001; Karahalil et al., 2002), arguing for the highest oxidative stress in testes (regrettably ovaries were not included in the comparator tissues). The poor removal of oxidized purines (mainly repaired

by BER) and bulky DNA adducts (mainly repaired by NER) in human testicular cells are reflected in an accumulation of DNA damage such as 8-oxoG and benzo(a)pyrene adducts in human sperm (Sun et al., 1997; Zenzes et al., 1999; Irvine et al., 2000; Evenson et al., 2002; Olsen et al., 2005). DNA base lesions were preferentially removed from transcriptionally active genes compared to inactive regions (Bohr et al., 1985; Tu et al., 1996).

In vitro and *in vivo*, ROS exposure results in high frequencies of DNA single-strand breaks (SSBs) and double-strand breaks (DSBs) (Aitken et al., 1998a; Lopes et al., 1998; Kemal Duru et al., 2000; Karanjawala et al., 2002; Mills et al., 2003; Sawyer DE et al., 2003). DNA SSBs are frequent endogenous DNA lesions in human cells (Lindahl, 1993). In normal human cells, it is estimated that approximately 1% of DNA single-strand lesions are converted to approximately 50 endogenous DNA DSBs per cell per cell cycle (Vilenchik and Knudson, 2003). This number is similar to the estimate of the number of exogenous DSBs produced by 1.5–2.0 Gy of ionizing radiation (Vilenchik and Knudson, 2003). In various *E. coli* and yeast systems, repair of endogenous DSBs and break-induced replication were shown to be highly mutagenic with rates of mutation close to 10^{-5} per nt (Strathern et al., 1995; Rattray et al., 2002; Rattray and Strathern, 2003; Ponder et al., 2005; Galhardo et al., 2007; Yang et al., 2008; Hicks et al., 2010; Burch et al., 2011; Deem et al., 2011). DSBs are repaired in mammalian cells by two major pathways, namely non-homologous end joining (NHEJ) and homologous recombination (HR) using the sister chromatid as template (Critchlow and Jackson, 1998; Khanna and Jackson, 2001; Pastwa and Blasiak, 2003; Jeggo and Lobrich, 2005; Mao et al., 2008; Moynahan and Jasin, 2010; Brandsma and Gent, 2012). NHEJ and HR pathways are often described as “error-prone” and “error-free”, respectively, but this is an oversimplification (Shrivastav et al., 2008). While “error-prone” NHEJ functions equally well throughout the cell cycle, the “error-free” HR operates in S and G2 phases when sister chromatids become available (Mao et al., 2008). There are two different NHEJ pathways known to date that nevertheless display a similar potential to induce mutations. The canonical pathway, known as DNA-PKcs-dependent NHEJ uses DNA ligase IV, KU70, KU80 and XRCC4 to complete the DNA repair. NHEJ may proceed without some of the canonical factors using PARP1, DNA ligase III and XRCC1 as the alternative ‘back-up’ mechanism known as B-NHEJ (Iliakis, 2009).

Accumulating evidence indicates that DSBs trigger a

number of histone modifications around the DSB sites and these modifications may facilitate DSB repair (Lukas et al., 2011; Polo and Jackson, 2011). Oxidative stress induces H2AX phosphorylation in human spermatozoa (Li Z et al., 2006). Phosphorylation of the histone variant H2AX forms gamma-H2AX that marks DNA damage, particularly if the damage involves formation of DSBs (Rogakou et al., 1998; Sedelnikova et al., 2002). Yet, the deposition of H2AX itself may be a better indicator of endogenous DSB hotspots than H2AX phosphorylation (Seo et al., 2012). Within minutes of the induction of DNA DSBs in somatic cells, histone H2AX becomes phosphorylated at serine 139 and forms gamma-H2AX foci at the sites of damage (Rogakou et al., 1998; Cook et al., 2009; Xiao et al., 2009). These foci then play a role in recruiting DNA repair and damage-response factors and changing chromatin structure to accurately repair the damaged DNA (Rogakou et al., 1998; Paull et al., 2000; Hamer et al., 2003; Fernandez-Capetillo et al., 2004) but are also involved in genomic instability (Takahashi and Ohnishi, 2005). Studies of NHEJ efficiency in the nuclear extracts of primary cells from several myeloid malignancies that are associated with increased ROS production, demonstrate a significant increase in repair efficiency, compared to normal hematopoietic cells. However, this increased NHEJ activity was accompanied by a significant increase in the frequency of errors (misrepair) (Gaymes et al., 2002; Brady et al., 2003; Sallmyr et al., 2008). Moreover, abnormally stimulated HR may be leading to mutations (Nowicki et al., 2004).

HR repair activity is present at all stages of mouse male germ cell development, spermatocyte being the most proficient stage (Srivastava and Raman, 2007). In mouse testicular germ cell extracts, NHEJ activity was demonstrated (Sathees and Raman, 1999; Raghavan and Raman, 2004), and NHEJ is active in late spermatocytes (late pachytenes and early diplotenes). Probably there is an interplay between various DSB repair pathways (Goedecke et al., 1999; Lankenau, 2007; Ahmed et al., 2010a). In fact, in *Drosophila* each stage of germ cell differentiation might exhibit its own characteristic usage of different DNA repair pathways (Preston et al., 2006a; Lankenau, 2007). Moreover, this differential use appears to be modulated by age: HR increased linearly from less than 14% in young individuals to more than 60% in old ones (Preston et al., 2006b; Engels et al., 2007).

Undifferentiated spermatogonia are in the G0/G1 phase of the cell cycle, hence DSBs are expected to be processed predominantly by NHEJ (Rübe et al., 2011). In spermatogonial stem cells lacking compact

heterochromatin, histone-associated signaling components of the DNA repair machinery are completely absent and DSBs are rejoined predominantly by DNA-PK-independent pathways, suggesting the existence of alternative repair mechanisms. As a complimentary mechanism, the differentiating progeny, but not the spermatogonial stem cells themselves, promote apoptosis in response to low levels of DNA damage (Rübe et al., 2011). Phosphorylated histone H2AX was detected in a higher proportion of normal fetal gonocytes, and a wider range of adult spermatocyte differentiation stages (Bartkova et al., 2005b). gamma-H2AX occurs in all intermediate and B spermatogonia and in preleptotene to zygotene spermatocytes. Type A spermatogonia and round spermatids do not exhibit gamma-H2AX foci but show homogeneous nuclear gamma-H2AX staining, whereas in pachytene spermatocytes gamma-H2AX is only present in the sex vesicle (Hamer et al., 2003; Forand et al., 2004). DNA DSBs repair proteins differ for the various types of spermatogenic cells, no germ cell type possessing the complete set (Ahmed et al., 2007). The authors concluded that this likely leads to a compromised efficiency of DSB repair relative to somatic cell lines. In addition, the DNA damage response and efficiency of HR-based DNA repair can be expected to be downregulated (Song L et al., 2011) by the abundant expression of miR-18 in testicular germ cells (Björk et al., 2010) (see chapter 10.6.1). Oxidative stress can induce H2AX phosphorylation in human spermatozoa following DSB induction. However, the surveillance system involving gamma-H2AX, Rad50, and 53BP1 in human spermatozoa does not function effectively in DNA repair (Li Z et al., 2006). A significant number of DNA lesions may escape repair. During DNA replication these lesions may cause arrest of the replication fork, and/or the formation of replication gaps, which must be processed to complete replication and enable cell division (Livneh et al., 1993; Kreuzer, 2005; Lopes et al., 2006). One of the central mechanisms to overcome such lesions is translesion DNA synthesis (TLS), also termed translesion replication (TLR), or error-prone repair. The key components in this process are specialized DNA polymerases, characterized by a low fidelity and the ability to replicate across DNA lesions, even bulky ones. Because coding information of the modified bases is usually distorted, TLS is inherently an error-prone process, hence the term error-prone repair: the gap is repaired, but a mutation is produced (Livneh, 2001; 2006; Friedberg, 2005; Prakash et al., 2005; van der Laan et al., 2005; Waters et al., 2009). TLS polymerases are highly expressed in testicular germ

cells (McDonald et al., 1999; Yamada et al., 2000; Velasco-Miguel et al., 2003; van der Laan et al., 2005; Sun J et al., 2009a) and are intrinsically required for the long-term maintenance of spermatogenesis (Sun J et al., 2009a).

7.2.9 Mitochondrial ROS, uncoupling and aquaporin-8

Oxidative stress is a hallmark of gametogenesis and other sexual reproduction-related events (Riley and Behrman, 1991; Heininger, 2001; Agarwal et al., 2005; Nedelcu, 2005; Metcalfe and Alonso-Alvarez, 2010; Shkolnik et al., 2011). Oxidative stress regulates mitochondrial respiration (Richter, 1997) and mitochondrial respiration is required for gametogenesis (Treinin and Simchen, 1993; Jambhekar and Amon, 2008). The generation of RONS by sperm and oocyte mitochondria (Riley and Behrman, 1991; Liu L et al., 2000a; Vera et al., 2004; Liu Z et al., 2006; Koppers et al., 2008; Nabholz et al., 2008a; De Luliis et al., 2009; Ramalho-Santos et al., 2009) and by non-mitochondrial mechanisms (De Luliis et al., 2006; Sabeur and Ball, 2007) drive the process. In *Drosophila*, PINK1/Parkin that regulate mitochondrial function and oxidative stress and have a role in mitochondrial quality control, are required for male and female fertility and in particular for proper sperm maturation (Greene et al., 2003; Pesah et al., 2004; Clark et al., 2006).

Increased mtDNA rearrangements and deletions in human gametes (Brenner et al., 1998; Reynier et al., 1998; Barritt et al., 1999) witness this oxidative stress exposure. The mitochondrial mutation rate is orders of magnitude higher than the nuclear one (Brown et al., 1979; 1982; Ballard and Whitlock, 2004; Lynch et al., 2006). This hypermutability largely explains the high level of within-species mtDNA heterozygosity (Bazin et al., 2006) and the high amount of homoplasmy detected in animal mtDNA phylogenetic analyses (Springer et al., 2001; Delsuc et al., 2003; Galewski et al., 2006). The mtDNA neutral substitution rate varies by 2 orders of magnitude across mammalian species (Nabholz et al., 2008a). Mammal and bird species maximal longevity correlate with mitochondrial mutagenesis and evolutionary patterns of mitochondrial DNA diversity (Nabholz et al., 2008a; 2009), arguing for the fundamental role of a mitochondrial molecular clock in both the germline and soma and its role for phylogenetic and organismal dynamics and life history trajectories (Heininger, 2001; 2012). Mitochondria play a key role in steroidogenesis (Yacobi et al., 2007). The first and rate-limiting step in the biosynthesis of steroid hormones in the adrenals and gonads is the transfer of cholesterol across the

inner mitochondrial space from the outer mitochondrial membrane to the inner mitochondrial membrane, a process known to depend on the action of the steroidogenic acute regulatory protein (StAR) (Christenson et al., 2001; Stocco, 2001; Diemer et al., 2003a; Miller WL, 2007). Mitochondrial membrane potential, mitochondrial ATP synthesis, and mitochondrial pH are all required for acute steroid biosynthesis, suggesting that mitochondria must be energized, polarized, and actively respiring to support Leydig cell steroidogenesis (Allen JA et al., 2006). Steroidogenesis in Leydig cells produces ROS, largely from mitochondrial respiration and the catalytic reactions of the steroidogenic cytochrome P450 enzymes (Quinn and Payne, 1984; 1985; Peltola et al., 1996; Hales, 2002; Hanukoglu, 2006). Besides functioning as key enzymes in steroidogenesis, mitochondrial P450-type enzymes can function as a futile NADPH oxidase and leak electrons, thus producing superoxide and ROS (Hanukoglu, 2006). The primary source of ROS in sperm is the respiratory chain of the mitochondrion (Turrens et al., 1985; Gavella and Lipovac, 1992; Cadenas and Davies, 2000; Baker et al., 2005). The main ROS form in male germ cells is hydrogen peroxide (H_2O_2), the concentration of which in sperm has not been measured (Jones et al., 1979; Sharma and Agarwal, 1996; Aitken et al., 1998a). Both the perinuclear clustering of mitochondria in germline cells and long-range action of H_2O_2 are compatible with a potential role of H_2O_2 in the nuclear compartment during gametogenesis.

Mitochondrial ROS activate mitochondrial uncoupling proteins (Echtay et al., 2002a; b; Brand et al., 2004). Uncoupling proteins (UCPs) are phylogenetically conserved (Stuart et al., 1999; Vercesi, 2001; Czarna and Jarmuszkiewicz, 2005) mitochondrial inner membrane proteins that are important in regulating cellular fuel metabolism and as attenuators of ROS production through strong or mild uncoupling (Boss et al., 2000; Sluse et al., 2006; Azzu et al., 2010; Mailloux et al., 2011; Mailloux and Harper, 2011). UCPs uncouple proton flux through the inner mitochondrial membranes and ATP synthesis, providing a route for proton re-entry (Mattiasson and Sullivan, 2006), lowering the proton-motive force (Brand and Esteves, 2005). UCP2 and UCP3 diminish oxidative stress by lowering the mitochondrial membrane potential (Nègre-Salvayre et al., 1997; Gustafsson et al., 2004; Brand and Esteves, 2005). Acute increases in ROS production increase proton conductance through both UCP2 and UCP3, providing a negative feedback loop to limit further mitochondrial ROS formation (Echtay et al., 2002a; b). UCP2 was

detected in all germ cells under normal conditions, predominantly in elongate spermatids (Ricquier and Bouillaud, 2000; Zhang et al., 2007), possibly expressed in response to prooxidant TNF α (Lee FY et al., 1999). Germ cell UCP2 is upregulated by aging (Amaral et al., 2008), and hyperthermia (Zhang et al., 2007) and protected the cells from ROS-induced apoptosis (Zhang et al., 2007). Although the physiological role of UCP2/3 in a variety of tissues is still controversial (Pecqueur et al., 2001; Brand et al., 2004; Cannon et al., 2006; Echtay, 2007; Azzu et al., 2010; Mailloux and Harper, 2011; 2012; Shabalina and Nedergaard, 2011; Sluse, 2012), testicular UCP2 expression appears to be a marker of oxidative stress (Pecqueur et al., 2001; Brand et al., 2004; Echtay, 2007; Zhang et al., 2007; Amaral et al., 2008; Mailloux and Harper, 2011; 2012).

Mitochondrial aquaporins may facilitate the diffusion of H₂O₂ across biological membranes, modulating the outcome of cellular stress. Aquaporins (AQPs), are a family of small integral membrane proteins that primarily transport water across the plasma membrane (Agre and Kozono, 2003). There are 13 members (AQP0–12) in humans. They are divided into three subgroups based on the primary sequences: water selective AQPs (AQP0, 1, 2, 4, 5, 6, 8), aquaglyceroporins (AQP3, 7, 9, 10), and superaquaporins (AQP11, 12) (Ishibashi et al., 2009). The striking physicochemical similarity between water and H₂O₂ points to AQPs as likely candidates for H₂O₂ permeation in plants and animals (Henzler and Steudle, 2000; Bienert et al., 2007; Hooijmaijers et al., 2012). Experimental evidence suggests that certain AQPs act as peroxoporins and thus facilitate the diffusion of H₂O₂ across biological membranes (Henzler and Steudle, 2000; Bienert et al., 2007; Dynowski et al., 2008). AQPs are also involved in swelling of tissues under stress (Verkman, 2005; 2008). The AQP8 paralogue is characterized by an unusual primary structure, a location of the exon–intron boundaries in the gene different from those of other AQPs, suggesting that AQP8 has a separate phylogenetic origin from other AQPs (Zardoya and Villalba, 2001). AQP8 shares the highest sequence homology (38–40%) with the plant water channel AQP-TIP (Ishibashi et al., 1997; Ma et al., 1997; Koyama et al., 1998). AQP8 seems to be present in most metazoans (Zardoya and Villalba, 2001; Campbell et al., 2008; Tomkowiak and Pienkowska, 2010; Ishibashi et al., 2011). Membrane diffusion of H₂O₂ is facilitated by aquaporins AQP3 and AQP8 in mammals (Bienert et al., 2007; Miller et al., 2010) and TIP1;1 and PIP2;1 in plants (Bienert et al., 2007; Dynowski et al., 2008). Certain isoforms of

Arabidopsis thaliana AtPIPs, including AtPIP2;2, AtPIP2;4, AtPIP2;5, and AtPIP2;7, are also permeable for H₂O₂ (Hooijmaijers et al., 2012). AQP8 expression appears to be modulated by conditions involving oxidative stress (Yamamoto et al., 2001; Hardin et al., 2004; Yamamoto et al., 2007; te Velde et al., 2008; Yang M et al., 2009; Kortner et al., 2012). AQP8 is intracellular (Ishibashi, 2006), particularly localized at the inner mitochondrial membrane (Ferri et al., 2003; Calamita et al., 2005; 2007; Lee et al., 2005; La Porta et al., 2006; Lee and Thévenod, 2006; Gena et al., 2009) and endoplasmic reticulum (Ferri et al., 2003). Although AQP8 has been reported to transport water (Liu K et al., 2006), overall water or glycerol permeabilities of mitochondria isolated from AQP8 knockout were reported not to differ from those of mitochondria from wildtype mice (Yang et al., 2006). Moreover, the overall water permeability of brain mitochondria that lack AQP8 corresponds to that of liver and testis mitochondria with abundant AQP8 (Calamita et al., 2006) suggesting that water transport may not be the primary function of AQP8. Mitochondrial AQP8 may have a role in mitochondrial H₂O₂ release, mitochondrial permeability transition and cell death (Lee and Thévenod, 2006; Younts and Hughes, 2009; Marchissio et al., 2012). In fact, AQP8 upregulation may sensitize hepatocellular carcinoma cells to apoptotic insults (Jablonski et al., 2007; Younts and Hughes, 2009). Intriguingly, while gastrointestinal inflammation was found to downregulate AQP8 expression (Hardin et al., 2004; Yamamoto et al., 2007; te Velde et al., 2008; Kortner et al., 2012), neuronal ischemia and lactacystin (a proteasome inhibitor)-induced neuronal toxicity and apoptosis upregulated AQP8 expression (Chen et al., 2008; Yang M et al., 2009). Intriguingly, AQP8 is abundantly expressed by male and female gonadal tissues and germline cells (Ishibashi et al., 1997; Calamita et al., 2001a; b; Elkjær et al., 2001; Kageyama et al., 2001; McConnell et al., 2002; West-Farrell et al., 2009; Yeung, 2010). In the developing rat testis, AQP8 mRNA was first detected between 13 and 16 days post-partum, consistent with the reported first appearance of spermatocytes (13–14 days) and AQP8 protein was observed in adult rat spermatocytes (Kageyama et al., 2001). In the developing rat testis, transcripts of AQP7 became detectable between 23 and 25 days post-partum, when round spermatids have been reported to appear (Calamita et al., 2001b; Kageyama et al., 2001). However, genetic deletion of AQP7 and 8 in mice did not result in obvious abnormalities in sperm morphology and function (Yang B et al., 2005; Sohara et al., 2007; Yeung et al., 2009). However, AQP8-null mice had increased testicular

weight/size and a greater ratio of spermatogenic cells to Sertoli cells in seminiferous tubules but water content measured by wet-to-dry weight ratios showed no significant difference between AQP8-null and wild-type mice (Yang B et al., 2005). The latter findings may indicate a role of AQP8 in germline cell apoptosis. AQP8 is expressed in granulosa cells and upregulated by follicle stimulation hormone (McConnell et al., 2002; Mock et al., 2004; Su W et al., 2010) but is not expressed in oocytes (Edashige et al., 2000). AQP8 deficiency significantly lowered apoptosis rate in AQP8^{-/-} granulosa cells and increased corpus luteums in mature AQP8^{-/-} ovaries suggesting increased maturation and ovulation of follicles (Su W et al., 2010), thus increasing the fertility of female mice (Su W et al., 2010; Sha et al., 2011). During an 8 days' period of follicle growth in vitro, antrum formation and steroid production were monitored, and mRNA was isolated. Follicles that developed an antrum and had a steroidogenic profile similar to that of follicles in vivo had unchanging expression of AQP8 and HIF-1 α . Follicles that did not form an antrum or produce appropriate levels of estrogen and progesterone, however, demonstrated increasing levels of AQP8 and HIF-1 α , a pattern in gene expression resulting in decreased follicle differentiation and oocyte quality (West-Farrell et al., 2009).

7.2.10 Membrane lipid unsaturation

In naturally occurring polyunsaturated fatty acids (PUFAs), the hydrogen atoms (called bis-allylic hydrogens) attached to the single bonded –C– atom that separate the double-bonded carbon units (–C=C–) have the lowest C–H bond-energies of the fatty acid chain. This makes them the most susceptible to attack by ROS produced during aerobic metabolism (Halliwell and Gutteridge, 2007). The more polyunsaturated the fatty acid, the more bis-allylic hydrogens it has and consequently the more prone it is to oxidative attack by metabolism-produced free radicals. Docosahexaenoic acid (DHA; 22:6), which has six double bonds and consequently five bis-allylic hydrogens per chain, is 320-times more susceptible to ROS attack than the common monounsaturated oleic acid (18:1) which has no bis-allylic hydrogens in its chain (Hulbert, 2010). PUFAs increase membrane proton permeability and the activity of membrane-associated metabolically active proteins (Brand et al., 1994; Porter et al., 1996; Brookes et al., 1998; Wu et al., 2001; 2004; Else and Hulbert, 2003; Turner N et al., 2003; 2005a; b) and these observations have led to the development of the 'membrane pacemaker theory' of metabolism (Hulbert

and Else, 1999; 2000; 2004; 2005; Hulbert, 2003; 2007; 2008). It proposes that highly polyunsaturated acyl chains impart physical properties to membrane bilayers that enhance and speed up the molecular activity of membrane proteins and consequently the metabolic activity of cells and tissues (Hulbert, 2008). Vertebrate sperm are rich in PUFAs (Aitken et al., 1989a; b; Surai et al., 1998; Zalata et al., 1998; Lenzi et al., 2000; Bréque et al., 2003; Wathes et al., 2007) which renders their membranes particularly susceptible to free radical attack (Jones et al., 1979; Alvarez et al., 1987; Aitken et al., 1989a; b; Twigg et al., 1998; Lenzi et al., 2000). Unsaturated fatty acids not only are passive targets of oxidative stress. They may stimulate ROS generation and lipid peroxidation in spermatozoa and oocytes (Aitken et al., 2006; Wakefield et al., 2008; Koppers et al., 2010). A positive correlation was found between ROS production and lipid peroxidation (Rodrigues et al., 2010). Particularly, elevated PUFA levels enhance cellular ROS level in hypoxia, most likely by impairing the electron flux within the respiratory chain (Schönfeld et al., 2011). On the other hand, some PUFAs have a dual role in activating both UCP expression and uncoupling activity and have been shown to be the most potent UCP activators (Zackova et al., 2003; Beck et al., 2007; Rodrigues et al., 2010). Superoxide-induced lipid peroxidation leads to the production of reactive aldehydes, including 4-hydroxynonenal, the end-product of the lipoperoxidation cascade of omega-6 PUFAs (Echtay et al., 2003). These aldehydic lipid peroxidation products are in turn able to modify proteins such as mitochondrial uncoupling proteins and the adenine nucleotide translocase, converting them into active proton transporters. This activation induces mild uncoupling and so diminishes mitochondrial superoxide production (Echtay et al., 2005). Delta-6 desaturase-null mice (^{-/-}) are unable to synthesize PUFAs. The ^{-/-} males exhibit infertility and arrest of spermatogenesis at late spermiogenesis (Stoffel et al., 2008; Stroud et al., 2009). DHA supplementation was capable of restoring all observed impairment in male reproduction (Roqueta-Rivera et al., 2010). ELOVL2 is a member of the mammalian microsomal ELOVL fatty acid enzyme family, involved in the elongation of very long-chain fatty acids including PUFAs required for various cellular functions in mammals. The lack of Elov12 was associated with a complete arrest of spermatogenesis, with seminiferous tubules displaying only spermatogonia and primary spermatocytes without further germinal cells (Zadravec et al., 2011).

7.3 Male-driven mutagenesis

The testis has been appreciated as the engine of evolution (Agulnik et al., 1997; Short, 1997; Hales et al., 1999; Kleisner et al., 2010). In fish, birds and mammals, point mutations arise preferentially in the male gametes. Higher rates of mutation in the male germline, relative to the female germline, have been found in primates (Shimmin et al., 1993; Makova and Li, 2002), rodents (Chang et al., 1994), cats (Pecon Slattery and O'Brien, 1998), birds (Ellegren and Fridolfsson, 1997), fish (Ellegren and Fridolfsson, 2003), Arabidopsis (Whittle and Johnston, 2003) and gymnosperms (Whittle and Johnston, 2002). The male excess compared to mutations in female gametes has been estimated approximately five- to ten-fold in humans, six-fold in primates, two-fold in rodents, up to six-fold in birds (Shimmin et al., 1993; Chang et al., 1994; Redfield, 1994; Chang and Li, 1995; Crow, 1997b; 2000; Ellegren and Fridolfsson, 1997; 2003; Huang et al., 1997; Anagnostopoulos et al., 1999; Kahn and Quinn, 1999; Carmichael et al., 2000; Erlandsson et al., 2000; Fridolfsson and Ellegren, 2000; Li WH et al., 2002; Makova and Li, 2002; Bartosch-Härlid et al., 2003; Axelsson et al., 2004; Chimpanzee Sequencing and Analysis Consortium, 2005; Sandstedt and Tucker, 2005; Ellegren, 2007; Kong et al., 2012; Sun et al., 2012; Grégoire et al., 2013). These figures suggest that male bias may have accelerated along the mammal lineage. Data derived from studies in autosomal- and X-linked diseases, although variable, strongly support the notion of a male-driven mutagenesis (Risch et al., 1987; Bonaiti-Pellie et al., 1990; Rosendaal et al., 1990; Montandon et al., 1992; Oldenburg et al., 1993; Thompson and Chen, 1994; Tuchman et al., 1995; Becker et al., 1996; Thomas, 1996; Green et al., 1999; Ljung et al., 2001; Flodman and Hodge, 2003; Glaser and Jabs, 2004; Heron et al., 2010; O'Roak et al., 2012). Comparison of rates of evolution for X-linked and autosomal pseudogenes suggests that the human male mutation rate is 4 times the female mutation rate (Nachman and Crowell, 2000). However, there may be a substantial variance in human sex-specific mutation rates. In one study, 92% of germline de novo mutations were from the paternal germline, whereas, in contrast, in the other family, 64% of de novo mutations were from the maternal germline (Conrad et al., 2011). Recently, evidence for a male-to-female mutation rate of approximately 2 for the first invertebrate, *Drosophila*, has been presented, suggesting that DNA sequence evolution is male-driven in a wide variety of taxa (Bachtrog, 2008). Also, the ratio of partial to complete male compared to female sterility loads in *Drosophila* (0.5) is similar to that in the butterfly *Bicyclus anynana* (0.45) (Saccheri

et al., 2005). Moreover, in dioecious plants (species with independent sexes) there is also evidence for higher rate of mutation on the Y than the X chromosome (Filatov and Charlesworth, 2002; Whittle and Johnston, 2002; 2003) and a higher recombination rate in male gametes (Robertson, 1984; Zhuchenko et al., 1989; Busso et al., 1995).

Following Haldane's (1947) discovery that most mutations in human hemophilia are male-derived, point mutations leading to Lesch–Nyhan syndrome (Francke et al., 1976), hereditary retinoblastoma (Dryja et al., 1989; 1997; Zhu et al., 1989; Matsunaga et al., 1990; Kato MV et al., 1994; Munier et al., 1996), achondroplasia (Risch et al., 1987; Wilkin et al., 1998), Hutchinson–Gilford progeria syndrome (Eriksson et al., 2003; D'Apice et al., 2004), Muenke syndrome (craniosynostosis) (Rannan-Eliya et al., 2004), Noonan syndrome (multiple congenital anomaly syndrome) (Tartaglia et al., 2004), von Hippel-Lindau disease (familial cancer syndrome) (Richards et al., 1995), Rett syndrome (neurodevelopmental disorder) (Girard et al., 2001; Trappe et al., 2001; Zhu et al., 2010), multiple endocrine neoplasia Type B (Carlson et al., 1994; Schuffenecker et al., 1997), Apert syndrome (achrocephalosyndactyly) (Moloney et al., 1996), Crouzon syndrome and Pfeiffer syndrome (craniosynostotic disorders) (Glaser et al., 2000), Costello syndrome (mental retardation and predisposition to benign and malignant tumors) (Sol-Church et al., 2006), Townes–Brocks syndrome (malformation syndrome characterized by anal, renal, limb, and ear anomalies) (Böhm et al., 2006), Dravet syndrome (severe infantile epileptic encephalopathy) (Heron et al., 2010), and CHARGE syndrome (coloboma, heart defects, atresia of the choanae, retarded growth and development, genital hypoplasia, ear anomalies and deafness) (Pauli et al., 2012) were found to be either exclusively or largely paternal. Epidemiological data also suggest that paternally derived genetic damage may contribute significantly to the etiology of cancer in children and young adults (Aitken, 1999; Crow, 2000). Further evidence for the male mutation bias are findings that genes with detectable expression only in male reproductive tissues, evolve rapidly in many taxa, including *Drosophila* (Zhang Z et al., 2004a; Pröschel et al., 2006; Ellegren and Parsch, 2007; Haerty et al., 2007; Larracuenta et al., 2008; Assis et al., 2012) and mammals (Clark and Swanson, 2005; Ellegren and Parsch, 2007).

It has been conventional interpretation that this male excess is owing to a difference in the number of germline replications (Penrose, 1955; Miyata et al.,

1987; Crow, 1997a; Hurst and Ellegren 1998; Li WH et al., 2002; Ellegren, 2007). These differences have been accounted to the male-to-female ratio of the number of germ cell divisions per generation suggesting that errors in DNA replication are the primary source of mutations (Chang et al., 1994; Drost and Lee, 1995; Li WH et al., 1996; Hurst and Ellegren, 1998; Kahn and Quinn, 1999; Vogel and Motulsky, 2010). In the human male the number of cell divisions from zygote to a sperm is about 150 at age 20, 380 at age 30 and 610 at age 40, compared to only about 24 cell divisions from zygote to an ovum in human females (Vogel and Motulsky, 1997). More than 20 spontaneous congenital disorders have been reported to be associated with advanced paternal age (Jones et al., 1975; Glaser and Jabs, 2004; Arnheim and Calabrese, 2009; Sayres and Makova, 2011; Goriely and Wilkie, 2012; see also chapter 8.2.1) supporting the notion that the number of germ cell divisions is a key factor for the male mutation bias. Base substitutions are likely the most prominent type of male-biased mutations to arise from mitotic cell divisions because of the mis-incorporation of nucleotides by DNA polymerase (Johnson RE et al., 2000). Other types of mutations such as insertions and deletions were also found to be male biased from whole genome studies in rodents (Makova et al., 2004). Since insertions and deletions can occur from strand slippage during replication, this lent further support to the potential contribution of the higher number of cell divisions in the male mutation bias (Grégoire et al., 2013).

However, recent data indicate also a significant contribution of number of germline replication-independent mutagenic events in male germline cells (Agulnik et al., 1997; Crow, 1997b; Hurst and Ellegren, 1998; 2002; Huttley et al., 2000; Tiemann-Boege et al., 2002; Baker and Aitken, 2005; Blumenstiel, 2007; Pink et al., 2009; Yoon et al., 2009; Pink and Hurst, 2010; Grégoire et al., 2013). For instance, there was no age-dependent increase in the frequency (Kato et al., 2007) of a well-known de novo non-Robertsonian translocation, t(11;22)(q23;q11), of paternal origin (Ohye et al., 2010), suggesting that these translocations are independent of replication. Particularly, there is now substantial evidence that chromatin remodeling steps during post-meiotic events of spermatogenesis may not be genetically inert but could represent an evolutionary conserved, replication-independent, process that may act more specifically to introduce de novo mutations, insertions and deletions, or even chromosomal rearrangements such as translocations (Grégoire et al., 2013). An intriguing model presented by Blumenstiel (2007)

concluded that assuming a tradeoff between producing large numbers of sperm and expending energetic resources in maintaining a lower mutation rate, sperm competition would select for males that produce larger numbers of sperm despite a higher resulting mutation rate. There is male-biased mutation for classes of mutations that are likely independent of DNA replication numbers (Huttley et al., 2000; Blumenstiel, 2007; Pink et al., 2009). For example, a male bias has been observed in Arabidopsis for the transmission of mutations that arise from UV irradiation (Whittle and Johnston, 2003). By adjusting for the fact that over evolutionary time an autosome is equally likely to reside in a male or female germline cell whereas an X chromosome experiences a female cell environment 66% of the time (33% in a male environment), the sequence divergence between the X chromosomes of human and chimp can be compared to estimate the autosomal divergence (X/A ratio). Increased expression of several polymerases (pol kappa, pol lambda, and pol iota) that support mutagenic translesion DNA synthesis is observed in male meiotic mid-pachytene cells and in postmeiotic (round spermatid) cells (McDonald et al., 1999; Garcia-Diaz et al., 2000; Gerlach et al., 2000; Yamada et al., 2000; Velasco-Miguel et al., 2003; Bavoux et al., 2005; van der Laan, 2005). Conceivably, these specialized DNA polymerases generate genetic variability in the male germline (Friedberg et al., 2002). Moreover, cumulative evidence indicates that polymerases kappa, lambda, and iota may be involved in somatic hypermutation (Poltoratsky et al., 2001; Friedberg et al., 2002; Bavoux et al., 2005). A strong male mutation bias for neutral nucleotide substitutions was detected at non-CpG sites: alpha (the male-to-female mutation rate ratio) in the X-autosome comparison was ~6–7, which was similar to the male-to-female ratio in the number of germline cell divisions (Taylor et al., 2006). Male mutation bias was equally strong at CpG and non-CpG sites, suggesting the replication-dependent origin of these mutations (Taylor et al., 2006). In contrast, mutations at CpG sites, where mutations typically result from replication-independent deamination of methylated cytosines, exhibited weak male mutation bias: alpha in the X-autosome comparison was only ~2–3. The study also indicated weak male mutation bias for transversions at CpG sites, implying a spontaneous mechanism largely not associated with replication. Moreover, a weak male-biased mutation rate has also been found in *Drosophila*: mutagenic transposons are often transmitted paternally in an active state but maternally in a repressed state (Bingham et al., 1982; Bucheton et al., 1984; Yannopoulos et al., 1987;

Evgenev et al., 1997; Vieira et al., 1998). Computer simulations (Redfield, 1994) showed that the cost of excess male mutations can easily exceed the benefit of recombination, costs that would add to the various costs of sex listed in chapter 1.

In testes, a signalling role of hydrogen peroxide has been identified (Fujii and Tsunoda, 2011). Not all H_2O_2 produced within the mitochondrial matrix will survive to efflux from the mitochondria, owing to matrix peroxidases that consume H_2O_2 (Zoccarato et al., 2004; Andreyev et al., 2005; Rhee et al., 2005a; Murphy, 2009). These include peroxiredoxins (Rhee et al., 2001), catalase (Radi et al., 1991; Salvi et al., 2007) and glutathione peroxidases (Imai and Nakagawa, 2003). A striking feature of the rat germ cell antioxidant system is a very high SOD activity associated with low levels of glutathione peroxidase (GPx), glutathione S-transferase (GST), and glutathione reductase (GR) activity (Bauché et al., 1994), with GPx, GST and GR playing key roles in cellular defence against oxidative damage (Raes et al., 1987; Baker et al., 1988; Simmons and Jamall, 1988; Ketterer and Meyer, 1989; Mirault et al., 1991; Lavoie et al., 1992; Miller and Blakely, 1992). Moreover, no catalase activity that may be able to metabolize H_2O_2 was detected in testicular germ cells (Bauché et al., 1994). Intriguingly, the prooxidant actions of p53 appear to be dependent on its p53-inducible gene 3 (PIG3)-mediated downregulation of catalase activity (Kang MY et al., 2013, see chapter 8.2). A new family of antioxidative proteins, collectively referred to as peroxiredoxins (PRDX), have been identified (Rhee et al., 2005b). Six distinct gene products are known for the PRDX family in mammals. The most well-characterized function of Prx family members is the ability to modulate hydrogen peroxide signalling in response to various stimuli (Rhee et al., 2005b). PRDX2, the fastest regenerating redox protein (Chevallet et al., 2003), is more efficient in neutralizing H_2O_2 than catalase and GPx (Peskin et al., 2007) and is more effective in protecting cells from H_2O_2 damage than GPx (Berggren et al., 2001). PRDX2 transcripts and proteins occur in Leydig cells and Sertoli cells of mouse testis, while spermatogonia and spermatocytes apparently do not express them (Lee K et al., 2002), but spermatids and mature spermatozoa (Manandhar et al., 2009). PRDX4 plays a role in inhibition of NF-kappaB function as a cytosolic factor (Jin et al., 1997), but it also can activate NF-kappaB as an extracellular factor (Haridas et al., 1998). Based on observations in rat testes at puberty, a supportive function of the membrane-bound form of Prx4 in acrosome formation during spermiogenesis was proposed (Sasagawa et al., 2001a). PRDX4 knockout

results in elevated spermatogenic cell death via oxidative stress (Iuchi et al., 2009). As compared to the liver, whole rat testes express equivalent SOD activity but only 5% of the GPx liver levels and 2% of the liver catalase activity (Peltola et al., 1992). Testicular guinea pig SOD levels were found to be about twice as high as liver SOD in the same species, whereas GPx, GR and catalase were about 60, 5, and 300 times less, respectively (Kukucka and Misra, 1993). Intriguingly, catalase expression is downregulated by ROS via methylation of a CpG island in the Oct-1 promoter (Quan et al., 2011). In contrast to its role as an antioxidant, overexpression of SOD, unbalanced by enzymes that can metabolize H_2O_2 , has been shown to increase hydroxyl radical formation and to elevate steady-state hydrogen peroxide levels (Peled-Kamar et al., 1995; 1997). SOD has also been shown to catalyze the formation of hydroxyl radical from hydrogen peroxide (Yim et al., 1990; 1993). Increased MnSOD expression leads to increased H_2O_2 production (Rodriguez et al., 2000; Buettner et al., 2006; Sarsour et al., 2008). A number of reports indicate that either an increase or decrease in CuZnSOD/MnSOD activity may cause oxidative damage, apoptosis and cell cycle arrest (Oberley et al., 1981; Elroy-Stein et al., 1986; Avraham et al., 1988; 1991; Elroy-Stein and Groner, 1988; Norris and Hornsby, 1990; Amstad et al., 1991; Nelson SK et al., 1994; Rothstein et al., 1994; Troy and Shelanski, 1994; Kelner et al., 1995; Peled-Kamar et al., 1995; 1997; Bernard et al., 2001; Kim A et al., 2004; 2005; 2010; Sarsour et al., 2008). In accordance with these findings, transgenic male mice expressing higher levels of mitochondrial MnSOD have reduced fertility (Raineri et al., 2001). The copper-zinc superoxide dismutase (CuZnSOD) gene resides on chromosome 21 and is overexpressed in Down syndrome patients. Down syndrome patients show a multitude of abnormalities related to increased oxidative stress (Peled-Kamar et al., 1995; de Haan et al., 1997; Jovanovic et al., 1998; Iannello and Kola, 2001; Pallardó et al., 2006; Perluigi and Butterfield, 2011) caused by the imbalance in the SOD/Gpx ratio (de Haan et al., 1997; 2003). These findings indicate that mammal spermatogonia, pachytene spermatocytes and round spermatids are able to convert $O_2^{\cdot-}$ to H_2O_2 by SOD whereas they may encounter major difficulties to further metabolize hydrogen peroxide, as well as organic peroxides, to unreactive molecules. The difference between SOD and glutathione-dependent enzyme activity in germ cells may lead to saturation of the protective systems against peroxides. As a result, the H_2O_2 formed may be available for conversion into highly toxic hydroxyl radicals via Fenton-type reactions

(see chapter 4.1) (Bauché et al., 1994). As has been pointed out by Bauché et al. (1994), the consequences can be especially dramatic in the testis, with the risk of germ cell mutation and heritable mutation. Intriguingly, high levels of antioxidants had adverse effects on the progression of normal germ cell differentiation and male fertility (Ten et al., 1997; Shalini and Bansal, 2005; 2007; Brigelius-Flohe, 2006; Puglisi et al., 2007), arguing for the physiological role of a certain amount of oxidative stress in spermatogenesis.

The proteomic analysis of sperm differentiation reveals that male germ cells express a multitude of genes that are involved in stress responses including heat shock proteins, hypoxia-inducible factor, and DNA repair (Aguilar-Mahecha et al., 2001; Gupta, 2005; Martínez-Heredia et al., 2006). Circumstantial evidence indicates that at least part of the excess male germ cell mutation rate is due to, compared to female, a high level of male developmental oxidative stress: during spermatogenesis germ cells massively undergo apoptosis (Rodríguez I et al., 1997; Blanco-Rodríguez, 1998; Print and Loveland, 2000) induced by oxidative stress (Erkkilä et al., 1998; 1999). Metabolic shifts from mitochondria-produced ATP to glycolysis affecting ROS generation occur at several stages of male gametogenesis (Ramalho-Santos et al., 2009). In addition to mitochondrial sources, an enzymatic system for ROS generation located in the mammalian sperm plasma membrane that utilizes the reduced adenine dinucleotides (NAD(P)H) as a substrate via an NAD(P)H-dependent oxidase has been suggested as one mechanism for ROS-mediated signaling in spermatozoa (Aitken et al., 1992; 1995; 1997; Ball et al., 2001; Armstrong et al., 2002; Sabeur and Ball, 2006; 2007). NADPH oxidases are the only known enzyme family with the sole function to produce ROS (Altenhöfer et al., 2012). NADPH oxidase 5 (NOX5) is highly expressed in pachytene spermatocytes, round and elongating spermatids (Bánfi et al., 2001; Sabeur and Ball, 2007) indicating a role of this isoform in meiosis and sperm maturation.

Vertebrate sperm are rich in polyunsaturated fatty acids (Aitken et al., 1989a; b; Surai et al., 1998; Zalata et al., 1998; Lenzi et al., 2000; Bréque et al., 2003; Wathes et al., 2007) which renders plasma membranes particularly susceptible to free radical attack (Alvarez et al., 1987; Aitken et al., 1989a; b; Twigg et al., 1998; Lenzi et al., 2000). Moreover, the fact that germ cells are not well equipped to combat oxidative stress or xenobiotic-mediated injury probably explains the high sensitivity of these cells to oxidative stress (Gomes, 1970; Le Grande, 1970; David et al., 1971; 2005; Saini, 1997; Rockett et al., 2001; Sikka,

2001; Chakir et al., 2002; Saleh and Agarwal, 2002; Araripe et al., 2004; Rohmer et al., 2004; Vollmer et al., 2004; Jensen et al., 2006; Jørgensen et al., 2006; Gupta et al., 2007; Podrabsky et al., 2008; Sakata and Higashitani, 2008; Hansen, 2009; Crespo and Shivaprasad, 2010; Hales and Robaire, 2010; Prasad et al., 2011) and the extremely limited viability of isolated spermatogenic cells in culture (Chapin and Phelps, 1990). Several groups have demonstrated that, in contrast to spermatogonia, pachytene spermatocytes and round spermatids, elongated spermatids and spermatozoa have a reduced capability or are even unable to repair DNA damage (Ono and Okada, 1977; Van Loon et al., 1991). A variety of thioredoxins and glutathione peroxidases, oxidative stress-regulating systems, and Hsps are uniquely expressed in male spermatogenesis (Miranda-Vizuete et al., 2004; Gupta et al., 2007; Chabory et al., 2010). Particularly during meiotic synaptonemal complex formation when recombination occurs (Loidl, 1994; Egel, 1995; McKim et al., 1998), Hsps play an essential role (Allen et al., 1996; Dix et al., 1996; Dix, 1997; Iliopoulos et al., 1997; Berruti et al., 1998; Eddy, 1999; Son et al., 1999). Hsp70-2 knockout leads to failed meiosis, germ cell apoptosis and infertility in male but not female mice (Dix et al., 1996; Eddy, 1999) arguing for a specific spermatocyte vs. oocyte vulnerability. Although eleven per cent of proteins found in human spermatozoa are involved in protection against oxidative damage, apoptosis and cell cycling (Martinez-Heredia et al., 2006), they possess a limited arsenal of cytosolic antioxidant defences relative to somatic cells (Dowling and Simmons, 2009; Zini et al., 2009). Although, this shortfall seems to be counterbalanced by a high antioxidant capacity of the seminal fluid (Aitken, 1994; Smith R et al., 1996; Baker and Aitken, 2004), together with a range of seminal proteins (Menella and Jones, 1980; Jeulin et al., 1989; Nanogaki et al., 1992; Schöneck et al., 1996; Collins et al., 2004) that probably play a role in protecting spermatozoa.

In mice, a testes-specific form of cytochrome c is able to catalyse the reduction of H₂O₂ three times faster than its somatic counterpart, and a testes-specific form of cytochrome c is also more resistant to degradation by H₂O₂ than its somatic form (Liu Z et al., 2006). On the other hand, the apoptotic activity of testes-type cytochrome c is three to five times greater than the somatic type, thus playing a much more stringent role in apoptotic "quality control" (Liu Z et al., 2006). Testicular-type cytochrome c null mice are fertile but present with highly atrophied testes, with a reduced number of spermatocytes, spermatids and spermatozoa (Narisawa et al., 2002) possibly

indicating that testicular-type cytochrome c is required to detoxify the increased level of H_2O_2 and/or to enforce a stringent "quality control". The increased oxidative stress exposure of spermatozoa in comparison to oocytes is also epitomized by their defective maintenance of mtDNA (Reynier et al., 1998) which may underlie the almost exclusive maternal inheritance of mtDNA (Ohno, 1997a). 8-hydroxydeoxyguanosine (8-OHdG) is the most abundant oxidative DNA adduct and a key biomarker of oxidative DNA damage (Ames et al., 1993) and was found highest in 6-week-old male rat testes (Nakae et al., 2000), particularly in leptotene, zygotene, and early pachytene spermatocytes (Sakai et al., 2010).

The Fenton reaction (see chapter 4.1) may play a role in male germ cell mutagenesis (Wellejus et al., 2000). Cellular DNA damage under prooxidant conditions has been shown to be mediated by iron. Conversely, oxidative stress itself influences iron metabolism and iron proteins. Intracellular iron levels are increased in response to oxidative stress (Udipi et al., 2012). In fact, iron is an important element in the establishment of a prooxidant status in the cell (Meneghini, 1997; Kruszewski, 2003). Sertoli cells make transferrin which is an iron transport protein as part of a proposed shuttle system that effectively transports iron around the tight junction complexes to the developing germ cells (Sylvester and Griswold, 1994). Iron metabolism is compartmentalized and closely regulated to protect developing male germ cells from iron fluctuations (Leichtmann-Bardoogo et al., 2012). Seminal plasma transferrin levels have been proposed as a functional parameter of Sertoli cells (Barthelemy et al., 1988; Cek et al., 1992; Irisawa et al., 1993). In humans, many studies show that the transferrin level in the seminal plasma is correlated with sperm yield (Sueldo et al., 1984; Orlando et al., 1985; Barthelemy et al., 1988; Zalata et al., 1996). A low concentration of transferrin in the seminal plasma has been correlated with severity of oligospermia (Orlando et al., 1985; Zalata et al., 1996). On the other hand, iron was found to accumulate in the sperm and other testes cells (Hoyes et al., 1995; Lucesoli et al., 1999; Doreswamy and Muralidhara, 2005). Sperm-associated iron is constantly lost from the testicular iron pool; consequently there must be continuous transfer of iron from the general circulation to adluminal germ cells. In adult male rats, approximately 0.25% of injected 114m Indium, a transferrin-binding radionuclide, localised within the testis by 48 h postinjection and remained constant for up to 63 d. In neonates, 0.06% of the activity was in the testis by 48 h, and this declined such that by 63 d only 0.03% remained (Hoyes et al., 1995). Various models of iron overload, e.g.

beta-thalassemia, hemochromatosis (that is associated with increased risk of cancer), and a variety of animal models, predispose sperm to oxidative injury and impair fertility (Siemons and Mahler, 1987; Lucesoli et al., 1999; Perera et al., 2002; Lourdes de Pereira and Garcia e Costa, 2003; Doreswamy and Muralidhara, 2005; Aitken and Roman, 2008). Female patients with beta-thalassemia major and hypogonadotropic hypogonadism with diminished ovarian reserve responded favorably to gonadotrophins with 80% success rate while males responded less favorably than females (Bajoria and Chatterjee, 2011). The mitoferrin gene product and other iron metabolism proteins show enriched expression in the testes of mammals and insects, suggesting special roles for mitochondrial iron metabolism in spermatogenesis (Hales, 2010). Studies in vertebrates and yeast demonstrate a role for mitoferrin family members in import of iron from the cytosol into mitochondria (Zhang Y et al., 2006; Paradkar et al., 2009). Mutations in the *Drosophila* mitoferrin gene, resulted in male sterility, but did not display other gross abnormalities and no female sterility (Metzendorf and Lind, 2010). A role of the free iron pool in oxidative DNA damage and genetic instability has been suggested (Gackowski et al., 2002; Olinski et al., 2003). Iron metabolism is regulated in response to oxidative stress coordinated with oxidative stress defenses (Pantopoulos and Hentze, 1995; Hanson and Leibold, 1998; Zheng et al., 1999). Iron accumulation dependent on metabolic and oxidative stress (Romslo, 1975; Fujimoto et al., 1982; Ceccarelli et al., 1995; Wang et al., 1995) may sensitize cells to oxidative stress (Lipinski et al., 2000). Translocated to the nucleus, iron and other trace metals may replace zinc in zinc finger domains of transcription factors, generate free radicals and induce transcription-dependent mutations (Omichinski et al., 1993; Sarkar, 1995; Conte et al., 1996). Further regulatory influences may stem from the type of metal ion catalyzing the Fenton reaction, protection of DNA by histones and chromatin structure (Chiu et al., 1993; Oleinick et al., 1994). Epidemiological data also indicate that elevation of the body iron level may increase the risk of cancer (Nelson RL et al., 1994; Stevens et al., 1994; Huang, 2003).

In nature there is a striking inverse relationship between stress resistance and metabolic and proliferating activity. Well known examples are survival forms like spores, cysts and seeds, which display high stress resistance and virtually no metabolic activity. In yeast cells there is a clear inverse correlation between stress resistance and growth and metabolic activity (Schenberg-Frascino and Moustacchi, 1972; Plesset

et al., 1987; Van Dijck et al., 1995; Lu et al., 2009), indicating that there might be an incompatibility at the molecular level between high stress resistance and high metabolic activity (Van Dijck et al., 2000). In invertebrates, e.g. insects, the spermatogenic stress manifests by a, compared to females, higher susceptibility of male gametogenesis to temperature stress (David et al., 2005). The high level of germ cell proliferational and maturational stress may also explain the conspicuous susceptibility of mammalian male germ cells to additional stressors, e.g. heat and, for instance, their lower temperature threshold for Hsp activation (Precht et al., 1955; Sarge, 1995; Rockett et al., 2001; Banks et al., 2005; Setchell, 2006) and susceptibility to abdominal temperature in cryptorchidism that leads to infertility (Shikone et al., 1994; Yin et al., 1997; Lue et al., 1999). In the human scrotum the temperature is approximately five degrees lower than body temperature. The poor vascularization of the mammalian testes is requisite for the testicular lower temperature as can be inferred from varicocele, or dilation of the spermatic vein. Varicocele typically occurs on the left side only and is associated with an increase in male infertility (Fretz and Sandlow, 2002). Experimental left varicocele bilaterally increases testicular temperature in lab animals and causes a reduction in testicular sperm output (Turner, 2001). The unilateral lesion in humans also bilaterally increases testicular temperature (Goldstein and Eid, 1989) and establishes a trend toward increased blood flow (Ross et al., 1994). Pathogenesis of cryptorchidism infertility is mainly attributable to high testes temperature because in situ cooling of abdominal testes in pigs results in normal spermatogenesis (Frankenhuis and Wensing, 1979). Moreover, elevated lipid peroxidation has been demonstrated in a mouse model of experimentally induced cryptorchidism (Peltola et al., 1995). Oxidative stress is a major cause for thermal damage of mouse spermatogenic cells and leads to apoptosis and DNA strand breaks (Banks et al., 2005; Pérez-Crespo et al., 2008; Paul et al., 2008a; 2009). Thus, chronic heat stress such as in cryptorchidism (Ishii et al., 2005) causes ROS levels to rise beyond what can be managed by the antioxidative systems in the epididymis, resulting in spermatogenic cell death. Intuitively, it may be expected that testicular stress should upregulate sperm DNA repair mechanisms. However, following heat stress at 43° C, murine expression of a number of DNA repair genes such Ogg1 (involved in base excision repair), Xpg (involved in nucleotide excision repair) and Rad54 (involved in double-strand break repair) were all down-regulated (Rockett et al., 2001; Paul et al., 2008b). In response

to heat stress, decreased expression of polyADP-ribose polymerase (PARP) in the rat testis (Tramontano et al., 2000) was reported; PARP proteins are involved in detection of strand breaks and signalling in both the base excision repair and nucleotide excision repair pathways (Schreiber et al., 2002; Flohr et al., 2003). In addition, a decreased expression of oxidative stress-induced antioxidants (Rockett et al., 2001) may leave the germ cells more susceptible to oxidative damage during hyperthermia (Paul et al., 2008b). Heat stress induced by cryptorchidism appears to result in decreased expression of DNA polymerase beta and DNA ligase III both of which are involved in the final stages of DNA repair, for example, in both base and nucleotide excision repair (Tramontano et al., 2000). Intriguingly, Lupu et al. (2004) found a relationship between DNA repair efficiency and thermotolerance in isofemale lines of *Drosophila melanogaster* originating from 'Evolution Canyon' (Mt Carmel, Israel), with thermotolerant lines tending to repair DNA more efficiently than thermosensitive ones. Likewise, thermosensitivity of cancer cells is thought to be associated with their genetic instability (Wheldon, 1977).

Male spermatogenesis in a wide variety of taxa is highly temperature-sensitive (Precht et al., 1955; Cowles, 1965). Paul et al. (2008a) reported that in vitro fertilization with sperm recovered from male mice in which the scrotum was heated to 42°C resulted in embryos with reduced ability to complete development. Females mated to males exposed to scrotal heating had conceptuses with smaller fetal and placental weights compared with controls (Jannes et al., 1998; Paul et al., 2008a). In modern mammals, the most sensitive steps with regard to temperature appear to be the maintenance of spermatogonial stem cells and the survival of gametes through meiosis and spermatid differentiation (Setchell, 1998; Ivell, 2007). Most mammals need 2 to 10°C below core body temperatures for viable sperm production and maturation (Moore, 1926; Cowles, 1958; 1965; VanDemark and Free, 1970; Waites, 1970; Bedford, 1977; Carrick and Setchell, 1977; Knobil and Neill, 1995). For spermatogenesis to proceed, a lower temperature achieved by the migration of the testes into the scrotum, is necessary. In addition, the pampiniform plexus is a highly efficient countercurrent heat exchanger in which the arterial blood is precooled before it reaches the testis, while venous blood is warmed to body temperature before it returns to the abdomen (Rommel et al., 1998; Brackett, 2004).

Part of the high reproductive success of mammals has

been attributed to the fact that their immature offspring are protected inside the mother's womb. On the other hand, there is no adaptive interpretation for the phenomenon of mammalian testicular descent (David et al., 2005). Indeed, an external location of the testes makes them prone to a diversity of wounds or accidents and may expose them to ionizing, mutagenic radiation (Oakberg, 1959; Ash, 1980; Ojala et al., 2004; Kleisner et al., 2010; Wright, 2010; Merrifield, 2011), and it is easy to argue that internal protection should be favored by natural selection (David et al., 2005). It has been speculated that evolution of the scrotum occurred because of the need for low temperatures either for spermatogenesis, sperm storage or to minimize mutations in gamete DNA (Moore, 1926; Short, 1997; Werdelin and Nilsson, 1999; Bedford, 2004). In agreement with this idea, in several mammalian species testes and epididymides remain in the body cavity and descend to the scrotum, i.e. to a lower temperature, only for the duration of the breeding season (Precht et al., 1955). Such seasonal testicular migrations are seen in chiropterans (Kruttsch, 1955; Marshall and Corbet, 1959; Kruttsch and Crichton, 1987; Jolly and Blackshaw, 1988), insectivores (Marshall, 1911), rodents (Rasmussen, 1917; Moore et al., 1934), carnivores (Koudele, 1986) and primates (Ramakrishna and Prasad, 1967). In some species, such as dogs, the scrotum can become hairless and acquire a dark coloration to aid heat radiation, emphasizing again the physiological importance of a cool scrotum (Ivell, 2007). Rhinos and tapirs have subcutaneous testes which lie in a scrotal-like sac external to the abdominal wall (Ottow, 1955). Importantly, subterranean mammals underwent a convergent loss of scrotum (Burda, 2003; Nevo, 1999). Mammals that inhabit an aquatic environment (cetacean, hippos, seals and walruses) lack a scrotum (Kleisner et al., 2010). Since spermatogenesis is just as threatened by testicular cooling as it is by testicular heating (Zhang Z et al., 2004b), aquatic mammals need to have intra-abdominal testes in order to keep them warm at all times. Dolphins, seals and Florida manatees possess a vascular countercurrent or anastomotic heat exchanger that functions to cool their intra- or para-abdominal testes (Rommel et al. 1992; 1995; 2001; Pabst et al., 1995). Elephants have abdominal testes, considered as a primitive trait (Kleisner et al., 2010). There is palaeontological, anatomic and genetic evidence suggesting that they may have had an aquatic origin in the distant past (de Jong, 1998; Gaeth et al., 1999; Inuzuka, 2000; Glickman et al., 2005). The elephant's ancestors probably had intra-abdominal testes for a long time

since there is no vestige of the countercurrent heat exchange mechanism – the pampiniform plexus – found in all scrotal mammals and no evidence of testicular migration or descent into a scrotum (Short et al., 1967; Gaeth et al., 1999). This is in marked contrast to the situation in cetaceans (whales and dolphins), which are thought to have evolved from a terrestrial (presumably scrotal) artiodactyl ancestor about 60 M years ago, and, although they have retracted their testes back into the abdomen, they have retained a well-developed pampiniform plexus (Glickman et al., 2005). In female mammals temperature gradients between mature Graafian follicles and ovarian stroma for human, rabbit, pig, and cow generally fell in the range of 1.3–1.7°C: follicles were always cooler than stroma. Temperature gradients are maintained locally by counter-current heat exchange mechanisms (Hunter et al., 2006).

Birds, for aerodynamic streamlining possess intra-abdominal testes. Cooling of the testes occurs via the adjacent air-sacs (into which inspired air is first drawn) (Cowles, 1965). However, the thoracic air sacs do not appear to be required for normal spermatogenesis (Williams, 1958; Herin et al., 1960). In breeding males of some species of birds, particularly passerine birds, the caudal sperm-storage region of the vas deferens is expanded into a cloacal protuberance which contains the convoluted portion of the vas deferens outside the abdomen (Salt, 1954; Wolfson, 1954). In sparrows and juncos the seminal vesicles protrude, during the sexual season, into the cloaca where the temperature is about 4°C lower than that of the body cavity (Wolfson, 1954; Hafez, 1964). Only sperm obtained from these evaginated vesicles are motile. There is also evidence that avian spermatogenesis may proceed mainly at night when body temperature is lowest and periods of hyperthermia are not likely to be experienced (Riley, 1937; 1940; Miller, 1938; Murton et al., 1970a; b; Greenwood and Wheeler, 1985). The domestic fowl, however, may have a unique system of heat shock tolerance mediated by both the amount and polyadenylation of Hsp70 and ubiquitin transcripts (Mezquita et al., 1998) that allows spermatogenesis at temperatures deleterious e.g. to mammals (Beaupré et al., 1997). Development of spermatogenesis in young fowl appears to be speeded up at temperatures lower than the abdominal temperature, but the process does not seem to be favored by very low temperatures (Williams, 1958). Species that need a high aerobic capacity, such as flighted birds could not get airborne at all if they did not have an aerobic capacity several-fold higher than even fast runners like the cheetah. In birds, the apoptotic threshold is low: they

are sensitive to ROS leak from mosaic respiratory chains and quickly trigger apoptosis, translating into infertility and low fecundity (Lane, 2011a). Compared to mammals, the mitochondrial ROS leak of birds is nearly 10-fold lower (Barja, 2007). Taking into account that mitochondrial ROS generation is temperature-dependent (Zar and Lancaster, 2000; Abele et al., 2002; Heise et al., 2003; 2006; Mujahid et al., 2005; 2007), these features may explain the higher temperature tolerance of avian spermatogenesis.

Lizards kept in warm temperatures quickly exhibit testicular collapse (Cowles and Burlison, 1945). In male lizards, the range of temperatures preferred by each species appears to be critically adjusted to a level compatible with the maximum tolerable temperature for the testes, for 3 weeks 10 hr/day exposure to temperatures 1-2 °C higher resulting in marked spermatogenic damage (Licht, 1965).

Intriguingly, poikilotherm fishes display a male lower-temperature comfort zone. Male guppies prefer a significantly lower temperature (24.5°C) than females (28.2°C) or juveniles (28.1°C). Treatment of juveniles and females with testosterone lowers their preferred temperature to that of males (Johansen and Cross, 1980). This gender-differential temperature preference, at least during the reproductive period, has been observed in other fish species as well (Hagen, 1964; Baker et al., 1970; Swain and Morgan, 2001; Hernández-Rodríguez et al., 2002; Podrabsky et al., 2008). In rainbow trout, the maximal heat shock response of male germ cells, that are located in the same body compartment like the other organs, occurs at a significantly lower temperature (22°C) than for somatic cells (28°C) (Le Goff and Michel, 1999). These findings strongly suggest the existence of a particular mode of heat shock susceptibility of male germ cells that is not restricted to homeotherms (Le Goff and Michel, 1999).

Taken together, there is a clear trend from lower to higher taxa for an increasing male gametogenic stress that renders male gametogenesis susceptible to additional stressors, e.g. temperature stress (see chapter 14.1).

7.3.1 Chromatin remodeling in elongating spermatids

In this chapter, I will largely adhere to the excellent review of Grégoire et al. (2013). During spermiogenesis, the round haploid spermatids undergo a major morphological differentiation program characterized by one of the most dramatic changes in chromatin structure known to the eukaryotic world. Most of the histones are replaced by protamines

providing both mechanical and chemical stability to the mature sperm chromatin (Ward, 2011). The molecular mechanism leading to such a striking nuclear transition is yet poorly understood but relies on histone variants, key post-translational modifications and general degradation of histones (Laberge and Boissonneault, 2005; Govin et al., 2006, 2007; Awe and Renkawitz-Pohl, 2010; Grégoire et al., 2011). The chromatin remodeling steps are specifically associated with transient, endogenous DNA strand breaks that are detected in the whole population of both mouse and human spermatids (Sakkas et al., 1995; Marcon and Boissonneault, 2004; Leduc et al., 2011a). Comet assays (Collins, 2004) in neutral conditions showed a clear accumulation of DSBs specifically in the nuclear DNA of spermatids throughout elongation. The origin of these DSBs is not clear but they may be created by several, mutually non-exclusive, possibly synergistic, mechanisms: enzymatically, for instance by type II topoisomerases (McPherson and Longo, 1993; Laberge and Boissonneault, 2005; Meyer-Ficca et al., 2011), from the activity of ROS (Muratori et al., 2006; Sakkas and Alvarez, 2010), or simply from the mechanical stress induced by the change in chromatin structure (Boissonneault, 2002; Muratori et al., 2006; Sakkas and Alvarez, 2010). Topoisomerase II appears as the unique enzyme responsible for the transient double-stranded breaks in elongating spermatids but depends on histone hyperacetylation for its activity (Laberge and Boissonneault, 2005). Chromatin remodeling in spermatids involves massive withdrawal and degradation of histones that should leave transient free DNA supercoils (Boissonneault, 2002). Such a high degree of free superhelical density is likely to generate non B-DNA structures which can be responsible for breakpoint hotspots and chromosomal rearrangements (Wang G et al., 2008). For instance, Z-DNA, characterized by a left-handed instead of a typical right-handed double helical structure, is generated within regions of high negative supercoiling and may serve as a recognition signal for DSB formation (Kha et al., 2010). High density of free supercoils independent of replication can produce cruciform extrusion that may also act to signal breakpoints involved in translocations (Inagaki et al., 2009). Transient DSBs were observed in spermatids of both human, rat and mouse (Marcon and Boissonneault, 2004; Meyer-Ficca et al., 2005; Leduc et al., 2008), but evidence of transient DSBs in spermatids was also reported in fruit flies (*Drosophila melanogaster*) (Rathke et al., 2007), in grasshopper (*Eyprepocnemis plorans*) (Cabrero et al., 2007) as well as in algae (*Chara vulgaris*) (Wojtczak et al., 2008). Taken together, these observations point to an

evolutionarily conserved, physiological mechanism. These physiological DSBs trigger a repair response, based on the detection of the phosphorylated H2AX histone variant (gammaH2AX) and in situ detection of DNA polymerase activity in elongating spermatids (Leduc et al., 2008, 2011b). The presence of DSBs in this haploid context would necessarily prevent homologous recombination to be used as a reliable, template DNA repair mechanism that depends on sister chromatids as this is the case during the S phase in somatic cells (Grégoire et al., 2013). NHEJ processes must therefore be used in order to repair DSBs in spermatids but, based on studies in somatic cells, these mechanisms are associated with limited insertions or deletions at the repair site which alter the DNA sequence, although the structural integrity of the DNA is restored. Even from a homogeneous set of starting DNA ends as substrate, NHEJ creates important variations in the non-templated addition at the two DNA ends (Lieber, 2010). There are two different NHEJ pathways known to date that nevertheless display a similar potential to induce mutations. The canonical pathway, known as DNA-PKcs-dependent NHEJ uses DNA ligase IV, KU70, KU80 and XRCC4 to complete the DNA repair. NHEJ may proceed without some of the canonical factors using PARP1, DNA ligase III and XRCC1 as the alternative 'back-up' mechanism known as B-NHEJ (Iliakis, 2009). PARP1 is involved in oxidative-stress response pathways (Virág, 2005). In round spermatids both NHEJ pathways are active (Ahmed et al., 2008; 2010b; Rube et al., 2011; Grégoire et al., 2013). In addition to having to rely on error-prone DNA repair systems, the chromatin remodeling context is likely to create an impediment to the repair process and the overall DNA repair capacity was found to decrease as spermatids progress through their differentiation program (Olsen et al., 2005; Marchetti and Wyrobek, 2008; Ahmed et al., 2010b). The spermatids that are formed after meiotic division II are increasingly transcriptionally and translationally silenced during the condensation of the chromatin. Thus these post-meiotic spermatids have a minimal capacity for DNA repair (Sega, 1974; 1979; Sotomayor et al., 1978, 1979; Tanaka and Katoh, 1979; Zbinden, 1980; Sega and Sotomayor, 1982; Working and Butterworth, 1984; Sotomayor and Sega, 2000) and therefore their DNA could be damaged in a cumulative manner, as the sperm cannot respond by inducing either apoptosis or DNA repair, as they are transcriptionally silent.

7.3.2 The gametogenesis-cancerogenesis connection

Gamete formation has been likened to a benign, slowly advancing but in the end lethal sort of cancer that is fought against by the soma (De Loof, 2011). Germline cell differentiation is controlled by a specific set of genes whose expression is tightly locked into the repressed state in somatic cells. Large-scale epigenome alterations, now evidenced in nearly all cancers, lead to aberrant activation of these normally silenced genes, as attested by the many reports describing the expression of testis-specific factors, known as cancer/testis (CT) genes, in various cancer cells. In normal adult testis, expression of CT antigens is present in spermatogonia and, to a variable degree, in later stages of sperm cell maturation (Takahashi et al., 1995; Jungbluth et al., 2000a; b; 2001a; 2002; Gjerstorff et al., 2006). In fetal ovary, immature germ cells (oogonia/primary oocytes) express CT antigens, whereas oocytes in the resting primordial follicles do not (Jungbluth et al., 2001b; Nelson et al., 2007). CT genes comprise more than 240 members from 70 families, and can be subdivided into two broad categories based on chromosomal localization on the X chromosome and on autosomes. The observation of shared characteristics between germline cells and tumor cells has led to the concept that recapitulation of portions of the germline gene-expression programme might contribute characteristic features to the neoplastic phenotype, including immortality, invasiveness, hypomethylation and DNA instability (Old, 2001; Zendman et al., 2003; Kalejs and Erenpreisa, 2005; Simpson et al., 2005). One of the distinguishing and near-universal hallmarks of cancer growth is hypoxia. Unregulated cellular proliferation leads to formation of cellular masses that extend beyond the resting vasculature, resulting in oxygen and nutrient deprivation. The resulting hypoxia triggers a number of critical adaptations that enable cancer cell survival, including apoptosis suppression, altered glucose metabolism, and an angiogenic phenotype. Oxygen depletion stimulates mitochondria to elaborate increased ROS, with subsequent activation of signaling pathways, such as HIF1alpha, that promote cancer cell survival and tumor growth (Fruehauf and Meyskens, 2007). Elevated rates of ROS have been detected in almost all cancers, where they promote many aspects of tumor development and progression (Dreher and Junod, 1996; Klaunig et al., 2010; Liou and Storz, 2010; Sosa et al., 2013).

Off-context activity of some of the testis-specific epigenome regulators can reprogram the somatic cell epigenome toward a malignant state by favoring self-renewal and sustaining cell proliferation under stressful conditions, thereby constituting a major oncogenic mechanism (Cheng et al., 2011; Wang J et

al., 2011). Intriguingly, the expression of CT genes in a variety of cancers correlates with and may be causally involved in the DNA instability of cancers and thus contribute to tumor progression (Bodey, 2002; Iwata et al., 2005). Moreover, CT gene expression is associated with hypomethylation and transcriptional activation (De Smet et al., 1999; Rosty et al., 2002; Sato et al., 2004; Lee YM et al., 2006; Ye et al., 2005; Ehrlich, 2009), hypoxic response activation (Aprelikova et al., 2009; Kuphal et al., 2010), microsatellite instability, defective DNA mismatch repair (Iwata et al., 2005; Okada et al., 2005) and anti-apoptosis (Cilensek et al., 2002; Monte et al., 2006). A link between DNA hypomethylation, genomic instability and carcinogenesis has been established (Chen et al., 1998; Saito et al., 2002; Fan et al., 2003; Kanai, 2010). Ectopic expression of germline-specific genes can drive tumor growth in *Drosophila* (Janic et al., 2010) and *Hydractinia* (Millane et al., 2011). It was proposed that the aberrant expression of these genes by cancer cells confers a range of phenotypic traits that are essential for the survival and function of gametes and their descendents. These gamete-specific products would be deleterious for the orderly requirements of normal somatic cells, but highly advantageous for the cancer cell (Simpson et al., 2005).

8. Sex:...and selection of the "pearls among the pebbles"

One is left with the feeling that some essential feature of the situation is being overlooked.

J. Maynard Smith, 1976a

Summary

The competitive advantage of organisms depends on their stress resilience and acquisition of limited resources. The selection principles that work at the level of individuals are also pervasively deployed at the cellular level during development, immune surveillance and cancerogenesis. Cell competition, modulated by redox balance, is an efficient mechanism for selecting cell quality and thereby ensuring that the requisite cellular tasks will be done by the most efficient and competitive cells. Population genetic calculations have predicted that germ cell competition-based selection, if existent, would act as a sieve eliminating deleterious mutations and increasing the frequency of beneficial ones, reducing the genetic load imposed on the population by several

orders of magnitude. A general pattern emerges: sperm that are less costly and subjected to a harsher (epi-)mutagenic process also are subjected to a more stringent selection program. Overall, selection regimes can be distinguished at more or less discrete levels: germ cells, gametes, fertilization, embryos/offspring, nonrandom mating. Their high developmental stress damages sperm mitochondria and they are eliminated subsequently. In oocytes, mitochondria pass through a selective bottleneck that maintains mitonuclear coadaptation and rewinds Muller's ratchet.

If, as outlined in chapter 10, sexual reproduction introduces (epi)genetic variation by a plethora of (epi)mutations, the evolution of sex had to resolve a major dilemma: (epi)mutagenesis not only creates potential beneficial mutations but carries the much higher hazard of detrimental effects (Morgan, 1903; Sturtevant, 1937; Kibota and Lynch, 1996; Thatcher et al., 1998; Boe et al., 2000; Imhoff and Schlotterer, 2001) on the viability of germline cells. For its evolutionary success, sexual reproduction had to remove the excess genetic load. In microbial colonies with their billion-fold individuals (of which each can be viewed as a germ cell) chances are good that by the stochastic mutagenic process single organisms may have acquired beneficial mutation(s) that favor their survival in the selective environment of their harsh habitat. With the advent of multicellular organisms and the segregation of a germline, evolution "faced" the fundamental problem of evolvability. Kirschner and Gerhart (1998) defined evolvability as "the capacity to generate **nonlethal** phenotypic variation" (my bold type). In the light of the stochasticity of mutagenesis the key issue is the viability of the mutants. Importantly, no evidence suggests so far that sexually or asexually reproducing organisms have the capacity to direct or choose which genetic variants will arise (Sniegowski and Lenski, 1995) (but see the concept of interpretive mutations as advanced by Jablonka and Lamb, 2005). The ecological conditions decide whether a specific genetic change is beneficial or detrimental. Reproductive organs have no sensors and feedback control (but see chapter 12) to sense the environmental conditions and to control the fit of the mutation to these environmental conditions. To create large numbers of mutants and let natural selection decide over their viability is the unicellular strategy. In multicellular organisms this would mean a large investment into possibly poorly viable and reproductively less fit organisms. In resource-limited environments (see chapter 3) this wouldn't have been an optimal strategy (and would hardly have

established the evolutionary success of sexual reproduction). A targeted approach would be to invest as little as possible into small, mutated, organisms and have them selected by natural selection or select them internally for their quality. In fact, the former approach is realized by external fertilizations of a variety of marine organisms and plants (Serrão et al. 1996; Yund, 2000) while the latter approach is realized by internal fertilizations in a multitude of terrestrial and aquatic organisms. The censor to differentiate between beneficial and deleterious mutations and the gametes carrying them is cellular function and thus eventual survival. Cell survival is regulated by redox signaling (Heininger, 2001; Trachootham et al., 2008; Groeger et al., 2009; Fulda et al., 2010). Thus, oxidative and nitrosative stress serves the dual purpose to effect gametogenetic mutagenesis and gamete quality assurance. And exposing the gametes to a stressful environment introduces a selective bottleneck selecting the most stress resistant and resilient of them. In contrast to asexual reproduction with its direct reproductive lineage, sex evolution had to introduce an additional selection process which subjects particularly the sperm to a rigid 'quality control' (a feature which has received little attention in all sex evolution theories) (Sutovsky et al., 2001; Sutovsky, 2003). In fact, spontaneous death of germ cells is a widespread phenomenon in the testes of many metazoan species (Roosen-Runge, 1973; Sasso-Cerri et al., 2006; Riesgo et al., 2008). The degree and the modes of the cell elimination are species-specific, but in general the abnormalities appear to originate during gametic mitosis and meiosis (Roosen-Runge, 1973). To exert a rigid quality control sexual reproduction "relies" on five levels of selection: germ cell-, gamete-, fertilization-, embryo/offspring- and sexual-selection.

8.1 Selection: the pervasive phenomenon in evolution

In a system like the immune system, moulded by cellular selection, precision of the end product is made possible by introducing the highest possible degree of randomness at the earliest stages.

Michaelson, 1987

Populations have the potential to grow exponentially, but this is confronted with the limited nature of resources (Heininger, 2012). That populations outgrow the available resources is the central idea of Malthus's *An Essay on the Principle of Population* (1798). The study of this work led Darwin to the conclusion that the pressure exerted by limited resources is a natural form of selection, analogous to breeder's artificial selection (Ruse, 2009). On all levels of biological organization,

competition for scarce resources is a pervasive driver of evolution (Loreau, 1998; Fisher and Hoekstra, 2010; Heininger, 2012). Natural selection subsequently rewards those individuals who compete best for the scarce resources and can use them most economically (Grover, 1997). Thus, natural selection is an outcome of this competition (Fisher 1930; Endler, 1986; Bock, 2003; 2010).

Gamete overproduction requires a gamete bottleneck: a stochastic bottleneck inevitably would drive Muller's ratchet and result in mutational meltdown; only a selection-associated bottleneck ensures long-term viability of populations. Competition is pervasive at every level of life—in ecology, economics, between countries and states, and in families—and helps to determine order, status, and survival (Johnston, 2009). The possibility that cells of multicellular organisms may also compete with one another has been postulated several times over the past two centuries (Díaz and Moreno, 2005). In 1881, Wilhelm Roux proposed the idea of a cellular struggle for survival during development (Roux, 1881; Heams, 2012). Wilhelm Roux transferred Charles Darwin's theory of the struggle for existence to the fight among cells and "parts" of the organism in the process of ontogenesis. As evidence for the conflict between cell types, he referred to pathological processes in which cells of one tissue start to invade another (Roux, 1881). His idea received no acclaim, since cells within multicellular organisms were thought to display conflict mediation/repression between, and cooperation of, the different cell types because cooperation increases the fitness of the group (Michod, 1996; 2005; Frank, 2003b). A common hypothesis is that the unicellular bottleneck of the germ cell acts as a conflict mediator, by increasing the kinship among cells in the organism, thereby aligning the interests of cells with the interests of the organism (Bell and Koufopanou, 1991; Maynard Smith and Szathmáry, 1995; Grosberg and Strathmann, 1998). Repression of competition within social groups has been suggested as a key mechanism driving the evolution of cooperation and the major evolutionary transitions (Leigh, 1977; Alexander, 1979; 1987; Buss, 1987; Maynard Smith, 1988; Maynard Smith and Szathmáry, 1995; Szathmáry and Maynard Smith, 1995; Frank, 1995; 2003; 2009; Ratnieks et al., 2006; Gardner and Grafen, 2009). As shown in bacterial communities, repression of competition *per se*, as opposed to increased relatedness, is driving the observed increase in cooperation (Kümmerli et al., 2010). In bacteria, hypermutability accelerates the breakdown of cooperation due to increased sampling of genotypic space, allowing mutator lineages to generate

non-cooperative genotypes (Harrison and Buckling, 2005; 2011), and cheat on the others (Vulic and Kolter, 2001), a phenomenon that also may underlie cancerogenesis (Heininger, 2001). However, competition is also a strong coevolutionary force resulting in selection of fitter individuals (Zambrano et al., 1993; Heininger, 2012)

Tilman (1982) defined competition as ‘an interaction between individuals brought about by a shared requirement for a resource in limited supply leading to a reduction in the survivorship, growth, and/or reproduction rates of the competing individuals concerned’. According to Welden and Slauson (1986) “competition is the induction of strain in one organism as a direct result of the use of resource items by another organism”. Darwin imagined, in his last paragraph of the *Origin of Species*, a tangled bank of competing organisms, and it now seems that we can stretch his analogy to the dynamic interactions of cells that populate niches during development and repair (Green, 2010). Thus, Darwinian principles of variation and selection can be extended to sub-organismal entities, e.g. organelles, cells and the germ-soma competition (Edelman, 1987; Stoner et al., 1999; Heininger, 2001; 2012; Weiss, 2006). There are several established criteria accepted as evidence of competition among populations (McLean et al., 1997; Gaudin et al., 2004). For example: (i) The presence of competitors should modify the equilibrium size of a population. (ii) The presence of competitors should alter the dynamics of a population, e.g. the life expectancy of the individuals of the population. (iii) It should be possible to modify the equilibrium dynamics of two competing populations through the manipulation of the available resources.

Cell competition was discovered in the imaginal discs of *D. melanogaster* almost 40 years ago (Morata and Ripoll, 1975). It initially described a situation in which slowly dividing cells were eliminated by apoptosis from a population of more rapidly dividing cells (Morata and Ripoll, 1975; Simpson, 1979; Simpson and Morata, 1981; Moreno et al., 2002; Lolo et al., 2012), despite the fact that they would have been viable on their own (Morata and Ripoll, 1975; Simpson, 1979; Simpson and Morata, 1981; Moreno et al., 2002; de la Cova et al., 2004; Li and Baker, 2007; Moreno, 2008). Thus, competition is context-dependent—cells acquire “winner” or “loser” identity only when in confrontation; each is viable in a homotypic environment (Johnston, 2009; Baker, 2011; Lolo et al., 2012). Cellular competition also occurs in *Drosophila* tracheal branching morphogenesis (Ghabrial and Krasnow, 2006) and in postmitotic epithelial tissue repair

(Tamori and Deng, 2013). It seems unlikely that such an effective mechanism to select for cell fitness should be confined to flies (Díaz and Moreno, 2005). In fact, cell competition has now been firmly established in a variety of taxa, including mammals (Oliver et al., 2004; Oertel et al., 2006; Sansom et al., 2007; Bondar and Medzhitov, 2010; Marusyk et al., 2010; Tamori et al., 2010; Baker, 2011; Kim et al., 2011; Krueger et al., 2011; Merlo et al., 2011; Petrova et al., 2011; de Beco et al., 2012; Norman et al., 2012). In vitro findings suggest that cell competition outcome is modulated by redox balance (Merlo et al., 2011) and activation of the Jun N-terminal kinase (JNK) stress-response pathway (Moreno et al., 2002; de la Cova et al., 2004; Moreno and Basler, 2004). Consistent with the role of these signaling pathways, competition intensity increases in high-intensity competitive environments (Chesson and Huntly, 1997; Violle et al., 2010; Miller et al., 2011). Competition among cells provides an efficient mechanism for selecting cell quality and thereby ensuring that the requisite cellular tasks will be done by the most efficient cells (Abrams, 2002; Díaz and Moreno, 2005; Khare and Shaulsky, 2006; Morata and Martin, 2007; Johnston, 2009; Green, 2010; Baker, 2011; de Beco et al., 2012; Vivarelli et al., 2012). Like in the ecological context, competition for limited resources underlies the cellular selection regime (McLean et al., 1997; De Boer et al., 2001; Gaudin et al., 2004). Soluble, growth-inhibitory factors, possibly including miRNA (Kosaka et al., 2012), mediate the competitive interactions between stressed cells (Komarova et al., 1998; Yu X et al., 2006; Senoo-Matsuda and Johnston, 2007; Kosaka et al., 2012). Here, it is proposed that these secreted factors are the cellular arms of competitive wars that cause the bystander effects observed in multiple cellular stress models (Sowa Resat and Morgan, 2004; Yu X et al., 2006; Di et al., 2008; Asur et al., 2009; 2010; Illynskyy and Kovalchuk, 2011).

Caporale (2009) posited that “selection must act on the mechanisms that generate variation, much as it does on beaks and bones”. On the other hand, it is variation that gives selection the raw material to work on. Variation can be caused both by genetic, epigenetic or stochastic processes. Stochasticity in gene expression gives rise to cell-to-cell variability in protein concentrations and individual cells differ widely in responsiveness to uniform physiological stimuli (see Heininger, 2012). Cellular oxidative stress-dependent responses, although undoubtedly programmed, are also highly variable (Heininger, 2012), at least in part based on the stochasticity of mitochondrial bioenergetic/oxidative events (Hüser et al., 1998; Genova et al., 2003; Passos et al., 2007; Wang W et

al., 2008). Cells employ a variety of quality surveillance and assurance systems including molecular chaperones (Esser et al., 2004; McClellan et al., 2005; Bukau et al., 2006; Buchberger et al., 2010; Arias and Cuervo, 2011), the ubiquitin/proteasome pathway (Sutovsky et al., 2001; 2002; Kostova and Wolf, 2003; Sutovsky, 2003; Thompson et al., 2003; Kwon et al., 2005; Taylor and Rutter, 2011), autophagy (Jin and White, 2007; Yorimitsu and Klionsky, 2007; Lee JY et al., 2010; Lee and Yao, 2010; Arias and Cuervo, 2011; Murrow and Debnath, 2013), mitochondrial turnover (Tatsuta and Langer, 2008; Twig et al., 2008; Dagda and Chu, 2009; Luce et al., 2010), the endoplasmic reticulum (Ellgaard and Helenius, 2003; Jørgensen et al., 2003; Kostova and Wolf, 2003; Kleizen and Braakman, 2004; Groenendyk and Michalak, 2005; Buchberger et al., 2010), and apoptosis (Yin et al., 1998; 2002; Meier et al., 2000; Groenendyk and Michalak, 2005; Jin and White, 2007; Igaki, 2009). Quality control implies that it selects for performance in cellular functions and eliminates inferior units. Cellular selection is the ultimate consequence when repair systems fail or are overwhelmed. Cellular selection within multicellular organisms does not only occur within the immune system and between cancer cells (Nowell, 1976; Kisielow and von Boehmer, 1995; McLean et al., 1997; Breivik and Gaudernack, 1999; von Boehmer et al., 2003; Vineis, 2003; Frank and Nowak, 2004; Merlo et al., 2006; Moreno, 2008; Vermeulen et al., 2008; Kim et al., 2011; Tamori and Deng, 2011; Thomas et al., 2013) but, as predicted by Roux (1881), is ubiquitous during development (Purves, 1980; Kupiec, 1986; 1996; 1997; Edelman, 1987; Michaelson, 1987; 1993; Otto and Orive, 1995; Møller and Pagel, 1998; Otto and Hastings, 1998; Deppmann et al., 2008; Tamori and Deng, 2011; de Beco et al., 2012). At least two major theories are based on selectionism, even if at different levels. The clonal selection theory that was elaborated by Jerne (1955) and Burnet (1957), and later confirmed by Tonegawa (1976; 1983), states that the diversity of the antibody repertoire in dedicated immune cells is achieved by random gene recombination events, leading to a huge number of small cellular lineages (Heams, 2012). Another major selectionist theory is the 'selective stabilization of synapses' (Changeux et al., 1973; Changeux and Danchin, 1976), later confirmed and even explicitly named 'neural Darwinism' (Edelman and Mountcastle, 1978; Edelman, 1987).

Male-biased mutagenesis requires that genetic variation created by this bias undergoes stronger selective scrutiny. Male-biased genes are evolving more rapidly than female-biased genes (Zhang Z et

al., 2004a; Davis JC et al., 2005; Hambuch and Parsch, 2005; Eads et al., 2007), providing evidence that males experience stronger positive selection than females (Ranz et al., 2003; Connallon and Knowles, 2005; Eads et al., 2007; Ellegren and Parsch, 2007; Mallet and Chippindale, 2011).

An early and massive wave of apoptosis in the testis occurs among germinal cells during the first round of spermatogenesis (Russell, 1977; Huckins, 1978; Kerr, 1992; Blottner et al., 1995; Rodríguez I et al., 1997; Matsui, 1998; Kimura et al., 2003; Strbenc et al., 2003; Dadhich et al., 2010; Aitken et al., 2011). Massive apoptotic death occurs at multiple sites within the testes (Russell, 1977; Kerr, 1992; Baum et al., 2005; Kwon et al., 2005; Zheng et al., 2006; Codelia et al., 2008; Vergara et al., 2011). Mammalian germ cell apoptosis during normal spermatogenesis has been estimated to result in the loss of up to 75% of the potential numbers of mature sperm cells in the adult testis (Oakland, 1956; Huckins, 1978; De Rooij and Lok, 1987; Bartke, 1995; Dunkel et al., 1997). Recent evidence indicates that the extent of gamete apoptosis may even have been underestimated (Mitchell et al., 2011).

In mammals, oogenesis begins with the formation of primordial germ cells and encompasses a series of cellular differentiation events, from primordial germ cells to oogonia, from oogonia to oocytes, and from oocytes to eggs. Extensive degeneration of germ cells has been described during embryonic, fetal, and early postnatal stages of oogenesis before follicle formation. In the mouse embryo, early morphological studies have shown that cell death may occur in primordial germ cells or oogonia (12–13 days post coitum, dpc), but mainly in oocytes at the zygotene/pachytene stage of meiotic prophase I (MPI; from 16.5 dpc through birth; Bakken and McClanahan, 1978).

Following such episodes, the number of oocytes decreases from w20,000 at 13.5 dpc to about 6000–10,000 after 6 days, at birth (Burgoyne and Baker, 1981; Tam and Snow, 1981). More recently, McClellan et al. (2003) performed a careful study of the number of oocytes throughout MPI in the embryonic mouse ovaries and reached the conclusion that the decrease of oocyte population during this period (about 65% loss) is a continuous process without apparent peaks of degeneration.

A variety of theories were put forward to explain the "waste" (Tilly, 2001): death by neglect, death by defect and death by self-sacrifice. Before discussing these theories, I would like to recall a couple of fundamental evolutionary principles.

In a world of limited resources (Heininger, 2012) metabolic efficiency and economic utilization of resources are fitness traits under directional selection (Fitter, 1986; Zotin, 1990; Boggs, 1992; Parsons, 1997; 2005; 2007; Stelling et al., 2002; Hunt et al., 2004; Demetrius, 2005; MacLean, 2008; Frank, 2010; Heininger, 2012). For instance, if two amino acids at a given position on the protein can do the same job, then selection might favor the retention of the one for which synthesis requires less energy. The amino-acid compositions in the proteomes of *Escherichia coli* and *Bacillus subtilis* reflect the action of such selection pressure (Akashi and Gojobori, 2002). The amino acid sequences of highly abundant proteins in *E. coli*, *Saccharomyces cerevisiae*, and *Schizosaccharomyces pombe* have to compromise between optimization for their biological functions and reducing the consumption of limiting resources for their synthesis. By contrast, the amino acid sequences of weakly expressed proteins are more likely to be optimized for their biological functions (Li N et al., 2009). In a wide range of taxa, highly and broadly expressed genes, such as housekeeping genes, are shorter in both their intronic and coding sequences than genes expressed at low level or in a few tissues (Hurst et al., 1996; Castillo-Davis et al., 2002; Urrutia and Hurst, 2003; Eisenberg and Levanon, 2003; Vinogradov, 2004; De Ferrari and Aitken, 2006; Tu et al., 2006; Rao et al., 2010). Because transcription and translation are energetically costly, this shortness has been interpreted as a result of selection for economy (Castillo-Davis et al., 2002; Urrutia and Hurst, 2003; Eisenberg and Levanon, 2003; Seoighe et al., 2005; Rao et al., 2010). According to MacArthur and Wilson (1967, p. 149): "Evolution ... favours efficiency of conversion of food into offspring". In a similar ecological context, an energetic definition of fitness was put forward. According to the concept of Brown et al. (1993; 2004), reproductive power is composed of two component processes: acquisition (acquiring resources and storing them in reproductive biomass) and conversion (converting reproductive biomass into offspring) (Loreau, 1998; Allen C et al., 2006). In a world of limited resources, waste production should be strongly selected against. In fact, a significant proportion of the transcriptome that has been regarded as 'junk' and 'transcriptional noise' (Brosius, 2003; 2005; Volf, 2006; Kapranov et al., 2007; Ponjavic et al., 2007; Struhl, 2007) appears increasingly to be functional and selected for (Muotri et al., 2007; Ponjavic et al., 2007; Nordström et al., 2009; Ponting et al., 2009; Khachane and Harrison, 2010; Lebenthal and Unger, 2010; Managadze et al., 2011; Atkinson et al., 2012; Barry and Mattick, 2012; Hu et al., 2012; Lee,

2012; Rinn and Chang, 2012). Thus, it makes little evolutionary sense that organisms that exert such economy with regard to other energetically costly functions should senselessly engage in immense waste production related to their most fundamental biological function of reproduction. In a world of limited resources, such organisms should be easily outcompeted by organisms that exert a higher efficiency when converting resources into offspring (MacArthur and Wilson, 1967; Brown et al., 1993; 2004).

Outlining the traditional theories, about the rationale behind the gamete overproduction, I use the arguments brought forward by Tilly (2001).

Death by neglect. Death by neglect is used to conceptualize developmental cell death such as the high loss of neurons during the formation of the central nervous system (Giehl, 2001). The competition between cells for a limiting amount of growth ('survival') factors has been proposed as a key component of organogenesis (Jacobson et al., 1997). Cells that receive insufficient trophic support from their environment simply wither and die. Evidence for 'death by neglect' in the developing female germline comes mainly from studies of gametogenic failure in mutant female mice that lack germ-cell survival factors, such as stem-cell factor (Mintz and Russell, 1957) or interleukin-1 α/β (Morita et al., 2001). Furthermore, in vitro culture of fetal mouse ovaries in the absence of serum or cytokines leads to a rapid induction of germ-cell apoptosis, and germline death in this artificial situation of acute neglect can be prevented by adding exogenous survival factors (Morita et al., 1999). In addition, fetal ovarian germ-cell death both in vivo and ex vivo is attenuated in female mice by deletion of either a key stress sensor (ceramide) (Morita et al., 2000) or a downstream executioner of apoptosis (caspase-2) (Bergeron et al., 1998). In fact, the increased numbers of oocytes that are lost from the ovaries of mice that are deficient in germ cell survival factors can be rescued from death by the inactivation of the caspase-2 gene (Morita et al., 2001). Likewise, withdrawal of hormonal support enhances apoptosis in male germ cells (Sinha Hikim et al., 1995; 1997; Tesarik et al., 1998; 2002; Woolveridge et al., 1999).

Death by defect. A second theory for why so many germ cells are lost during fetal ovarian development is that apoptosis eliminates oocytes with meiotic pairing or recombination anomalies. The idea is that a surveillance (or quality-control) mechanism detects and removes defective oocytes and retains meiotically competent oocytes for the formation of primordial

follicles. Evidence for 'death by defect' comes mainly from studies of impaired germline development in mice with genetic mutations that cause abnormalities in either chromosomal recombination or pairing during meiosis. For example, inactivation of the ataxia telangiectasia-mutated (*Atm*) gene causes massive germ-cell apoptosis in both sexes at, or shortly after, prophase I of the first meiotic division. As a consequence, *Atm*-deficient female mice are born with ovaries that lack oocytes (Barlow et al., 1998). Various testicular injuries, all of them known to induce DNA damage, including heat (Lue et al., 1999) and toxicant exposure (Ku et al., 1995; Li LH et al., 1996), radiation (Meistrich, 1993), freezing and thawing (Tesarik et al., 2000) have been shown to enhance the apoptotic process as compared with the physiological condition. In the human testis, apoptosis appears to be the final result of various testicular and systemic pathologies (Gandini et al., 2000).

Interestingly, this model of death by defect is unaffected by the simultaneous inactivation of the gene that encodes either caspase-2 or its upstream activator Bax (Morita et al., 2001). This indicates that fetal oocyte apoptosis occurs by more than one pathway, and that death by defect might not be amenable to control by experimental manipulation or therapeutic intervention. Mutant mice with X-chromosome defects have also been used to support the death by defect hypothesis. Female mice that lack a second X chromosome (XO) or that harbour a large X-chromosome inversion (InX/X) show gametogenic failure (Burgoyne and Baker, 1985), presumably due to failed chromosome pairing, which leads to increased germline death during the development of the fetal ovaries. A similar situation occurs in Ullrich–Turner (XO) syndrome in humans (Zinn and Ross, 1998). Mutant mice with X-chromosome defects have also been used to support the death by defect hypothesis. Unfortunately, cytogenetic evidence from investigations of oocyte attrition in human fetal ovaries has not clearly shown whether meiotic defects are a cause or a consequence of germline apoptosis (Speed, 1988; Mittwoch and Mahadevaiah, 1992).

Therefore, the jury is still out on the contribution, if any, of death by defect to the overall number of oocytes that are eliminated by apoptosis before birth under normal physiological conditions.

It should be noted that both "Death by neglect" and "Death by defect" that are treated here as independent factors, in my theory constitute interdependent factors of the gamete quality control system by competition for trophic factors.

I will not dwell on the third theory discussed by Tilly (2001): "**Death by self-sacrifice**". I have shown (Heininger, 2001; 2012) that "altruistic suicide" is evolutionary no man's land. How could a cell that "decides" voluntarily to commit suicide possibly transmit to its progeny the genes that program cell death? This evolutionary nonsense is still thoughtlessly reiterated in textbooks and scientific publications and certainly warrants another evolutionary blow (in preparation).

There is good evidence for both separate and synergistic roles for both testosterone and follicle-stimulating hormone (FSH) in achieving quantitatively normal spermatogenesis. Based on withdrawal and replacement studies, FSH has key roles in the progression of type A to B spermatogonia and, in synergy with testosterone, in regulating germ cell viability. Testosterone is an absolute requirement for spermatogenesis. In rats, it has been shown to promote the adhesion of round spermatids to Sertoli cells, without which they are sloughed from the epithelium and spermatid elongation fails (McLachlan et al., 2002). Withdrawal of trophic support results in a potentially stressful environment (Sinha Hikim and Swerdloff, 1999). Programmed cell death (apoptosis) is required for normal spermatogenesis in mammals (Knudson et al., 1995; Furuchi et al., 1996; Rodríguez I et al., 1997; Tres and Kierszenbaum, 1999). In some transgenic mice in which spermatogonial apoptosis was inhibited, there was an accumulation of spermatogonia and early spermatocytes that eventually all entered apoptosis (Knudson et al., 1995; Furuchi et al., 1996; Rodríguez I et al., 1997). Currently, it is thought that germ cell death serves to ensure cellular homeostasis and the fine balance between germ cells and Sertoli cells (Blanco-Rodríguez, 1998; de Rooij and Russell, 2000; Kierszenbaum, 2001). Huckins (1978) suggested that degeneration might be a mechanism to limit germ cells to that number which can be sustained by the Sertoli cell population, referred to as "density-dependent regulation" (de Rooij and Russell, 2000), which has become very popular (Kierszenbaum, 2001). In fact, the elongate spermatid/Sertoli cell ratio (a measure of the workload of the Sertoli cell and a prime factor determining their efficiency) in various mammalian species is approximately 10:1 (Russell and Peterson, 1984; Russell and Griswold, 1993), but significantly lower in primates (Johnson et al., 1984b; Russell and Peterson, 1984; Russell and Griswold, 1993; Johnson et al., 2008). Yet, meta-analyses demonstrated that the efficiency of spermatogenesis in several nonhuman primate species is comparable to that of rodents which are considered as species with highly

efficient germ cell production. Comparative data from various primates revealed that Sertoli cell work load is species-specific but has no impact on germ cell numbers and on the efficiency of spermatogenesis (Luetjens et al., 2005). The relative inefficiency of human spermatogenesis has been well documented, with the human testis producing comparatively low numbers of sperm cells per unit weight of testis compared to various animal species (Brinkworth et al., 1997). However, the germ cell/Sertoli cell ratio has been taken as given and the question for the adaptive role of this ratio, particularly the “understaffing” of Sertoli cells, has not been asked. Cell kinetic and radiobiological data indicate that Sertoli cells more resemble arrested proliferating cells than the classic postmitotic and terminally differentiated somatic cells that they have always been assumed to be (Ahmed et al., 2009; Tarulli et al., 2012). For instance, unlike terminally differentiated cells, Sertoli cells express a puzzling mixture of proliferation inducers and inhibitors (Ahmed et al., 2009). Sertoli cells proliferate in seasonal breeders, in which season-dependent variations in Sertoli cell numbers per testis occur (Hochereau-de Reviers and Lincoln, 1978; de Reviers et al., 1980; Johnson and Thompson, 1983; Johnson and Nguyen, 1986; Hötzel et al., 1998; Sinha Hikim et al., 1988; Johnson et al., 1991; Tarulli et al., 2006). The regulation of testicular development and proliferation of adult Sertoli cells is influenced by follicle-stimulating hormone (Orth et al., 1988; Singh and Handelsman, 1996; McLachlan et al., 2002; Johnston et al., 2004), testosterone (McLachlan et al., 2002; De Gendt et al., 2004; Johnston et al., 2004), estrogen (Fisher et al., 1998; Shetty et al., 1998; Pentikäinen et al., 2000; Kula et al., 2001; Oliveira et al., 2001) and thyroid hormone (Jannini et al., 1993; Van Haaster et al., 1993; Cooke et al., 1994; Holsberger and Cooke, 2005). Reducing estrogen synthesis in developing boars by inhibition of aromatase resulted in delayed lumen formation, lower testicular weight, fewer detergent-resistant spermatids, and fewer Sertoli cells, but by 7 to 8 months, these boars had recovered and had larger testes, more detergent-resistant spermatids per testis, and more Sertoli cells (At-Taras et al., 2006). It can be concluded that a delay in testicular maturation/puberty allows for a longer window for the proliferation of Sertoli cells and maturation of Leydig cells, leading to larger testes and higher spermatid production (Kula et al., 2001; At-Taras et al., 2006). In adult mice deficient for inducible nitric oxide synthase, testis weights were approx. 31% higher and testicular sperm count was 65% higher than in control animals (Lue et al., 2003). Associated with a reduced incidence of spontaneous

germ cell apoptosis and unchanged rate of germ cell proliferation, mutant mice had a ~40% increase in the number of pachytene spermatocytes and ~34% in round spermatids, with no apparent changes in the number of preleptotene spermatocytes and spermatogonia (Lue et al., 2003). Neonatal hypothyroidism also lengthens the period of Sertoli cell proliferation, with consecutive increases in Sertoli cell number, testis weight, and daily sperm production when euthyroidism is re-established (Cooke et al., 1991; Cooke and Meisami, 1991; Hess et al., 1993; De França et al., 1995; Matta et al., 2002; Holsberger and Cooke, 2005). Meachem et al. (1996) extended the normal period of Sertoli cell proliferation, resulting in increased Sertoli cell numbers that persisted into adulthood; the number of Sertoli cells per testis was 118% and 149% greater in 90-day-old rats that had been treated with follicle-stimulating hormone during the first 10 or 15 days of life, respectively. In vertebrates, number of Sertoli cells and amount of smooth endoplasmic reticulum of Leydig cells (but not Leydig cell number) are related to relative testis mass and efficiency of spermatogenesis (De França et al., 1995; Johnson, 1995; Matta et al., 2002; Sharpe et al., 2003; Atanassova et al., 2005; Ford et al., 2006; Petersen and Söder, 2006). Testis mass and sperm output are increased in diverse taxa under the co-evolutionary pressure of sperm competition risk (Harcourt et al., 1981; Billard, 1986; Møller 1988a; b; 1989; 1991; Jennions and Passmore, 1993; Gage, 1994; Møller and Briskie, 1995; Hosken, 1997; Stockley et al., 1997; Hosken and Ward, 2001; Hosken et al., 2001; Garamszegi et al., 2005). Thus, there are physiological processes that could augment Sertoli cell numbers but there seem to exist adaptive reasons that keep Sertoli cell numbers relatively low. A clue to these adaptive reasons is provided by the finding that, compared with normospermic counterparts, teratospermic cats have a higher sperm output achieved by more sperm-producing tissue, more germ cells per Sertoli cell, and reduced germ cell loss during spermatogenesis. However, gains in sperm quantity are produced at the expense of sperm quality (Neubauer et al., 2004). The germ cell quality signal, TNFalpha (Pentikäinen et al., 2001), mediates a negative feedback loop to Leydig cells that have been shown to respond to TNFalpha by decreasing their biosynthesis of testosterone (Li et al., 1995; Mauduit et al., 1998; Budnik et al., 1999). In rodent testis, the demise of spermatogonia (Allan et al., 1992), spermatocytes, and spermatids (Billig et al., 1995; Henriksen et al., 1995; Sinha Hikim et al., 1995) occurs through an apoptotic mechanism regulated by gonadotropins and androgens. Intriguingly,

testosterone has been shown to both inhibit (Tapanainen et al., 1993; Henriksen et al., 1995; Erkkilä et al., 1997) and induce (Henriksen et al., 1995; Lue et al., 2006; Jia et al., 2007; Wang et al., 2007) germ cell apoptosis in a stage-specific manner.

Reproduction biology failed to outline an evolutionary rationale for the waste production of gametes. Taking into account the legendary “twofold cost of sex” (Maynard Smith, 1978a), the millionfold “costs of waste gamete production”, if having no adaptive function, should definitely deter any organism from investing into sexual reproduction. The fitness function $w(x)$ describes how resources affect individual survival and reproductive success and its value is the expected number of offspring born to individuals with x units of resource (Rogers, 1992). According to MacArthur and Wilson (1967, p. 149): “Evolution ... favours efficiency of conversion of food into offspring”. In this regard, sexual reproduction should be highly uneconomic. Yet “..unnecessary but costly structures or activities should be lost in evolution.” (Michod, 1999a). Organisms have to bear heavy costs of reproduction (Dewsbury, 1982; Nakatsuru and Kramer, 1982; Heininger, 2012) that are paid in terms of reduced growth, immunocompetence, stress resistance and survival (Richner et al., 1995; Møller et al., 1998; 1999; Siva-Jothy et al., 1998; Brown et al., 2000; Rigby and Jokela, 2000; Hosken, 2001; Heininger, 2012). Organisms that would have been able to economize these costs, e.g. by minimizing the huge “waste” gamete production, would have a substantial competitive advantage. An adaptive explanation of these counterintuitive features is urgently warranted. It is often argued that further improvements in replication fidelity and DNA repair become too costly (André and Godelle, 2006), reflecting the combined metabolic and temporal costs of perfection in replication and transcription fidelity (Kimura, 1967; Sniegowski et al., 2000). But wouldn't it be much more resource-efficient and resource-saving to invest into the perfection of replication and transcription fidelity than to produce millions and billions of “waste/poor-quality” gametes? Particularly, since the huge energetic investment into this “waste” production results in gonadal functional hypoxia (at least in mammals), and is associated with increased metabolic/oxidative stress and genetic instability that further deteriorates gamete quality. In fact, improving genome replication fidelity is feasible in General Purpose Genotypes, as has been shown e.g. in asexual *Darwinula stevensoni* (Rossi et al., 1998; 2004; Schön et al., 1998; 2000, 2003; 2009; Gandolfi et al., 2001) and an invasive grass weed (Le Roux et al., 2007). Although evolutionarily highly successful, these organisms rather appear to be evolutionary

dead-ends. That evolution did not reward this economized, but non-innovative, conversion of reproductive biomass into offspring (Brown et al., 1993; 2004) but rather favored the increase of this “waste” investment along the phylogenetic axis from invertebrates to mammals clearly emphasizes the adaptive role of this gamete overproduction. In fact, theoretical models show that mate and gamete selection are more efficient in the use of biomass, energy and time, than natural selection at the level of organisms, helping to make sexual reproduction an evolutionary success (Jaffe, 2004).

The disposable soma theory (DST) predicts that aging occurs due to the accumulation of damage during life and that failures of defensive or repair mechanisms contribute to aging (Kirkwood, 1977; Kirkwood and Holliday, 1979; Kirkwood and Austad, 2000). It postulated a special class of gene mutations with antagonistic pleiotropic effects in which hypothetical mutations save energy for reproduction (positive effect) by partially disabling molecular proofreading and other accuracy promoting devices in somatic cells (negative effect). In other words, given finite resources, the more resources an animal spends on bodily maintenance, the less it can expend on reproduction, and vice versa. This theory has a variety of implausibilities (see Heininger, 2012). According to the DST, any resources not used for reproduction should benefit the somatic maintenance and repair and delay aging. Therefore waste of resources during reproduction should be selected against.

Importantly, the adaptive explanation integrates both the arguments of the death by neglect and death by defect theories into a coherent concept. I will present compelling evidence that there are several levels of selection that unfold during sexual reproduction. I would have preferred to call these levels summarily as “sexual selection”. However, a narrow use of the term “sexual selection” in the sense of pre-mating and postmating selection is currently deeply entrenched in the scientific literature. The future will show whether a broad use of the term can prevail. But for the time being, I will use the term “sexual selection” in its narrow sense and use the term “sexual mutagenesis-selection-cascade” (SMSC) for the entire sexual reproduction-related bet-hedging strategy.

8.1.1 Cell competition and Myc

Myc family transcription factors are phylogenetically conserved and arose before the divergence of the choanoflagellate and metazoan lineages (Walker et al., 1992; Atchley and Fitch, 1995; Gallant, 2006; Hartl et al., 2010; Young et al., 2011). The Myc target gene network is estimated to comprise about 15% of all

genes from flies to humans. Both genomic and functional analyses of c-Myc targets suggest that while c-Myc behaves as a global regulator of transcription, groups of genes involved in cell cycle regulation, metabolism, ribosome biogenesis, protein synthesis, and mitochondrial function are over-represented in the c-Myc target gene network (Dang et al., 2006). Thus expression of Myc family transcription factors is closely tied to cell growth and proliferation as well as inhibition of terminal differentiation and induction of apoptosis (Grandori et al., 2000; Zhou and Hurlin, 2001; Pelengaris et al., 2002; de la Cova and Johnston, 2006). c-Myc also affects the stability of the whole genome and triggers the initiation of a complex network of genomic instability via the induction of ROS (Kuttler and Mai, 2006; Prochownik and Li, 2007). On the other hand, Myc facilitates replication under stress (Herold et al., 2009) and regulates both proliferation and apoptosis (Evan et al., 1994; Secombe et al., 2004; Montero et al., 2008). MYC is a potent oncogene that can promote tumorigenesis in a wide range of tissues (Verbeek et al., 1991; Felsher and Bishop, 1999; Pelengaris et al., 1999; Jain et al., 2002; Flores et al., 2004; Soucek et al., 2008; Sodir et al., 2011). The ability of Myc-overexpressing cells to abrogate apoptosis and maintain proliferation in a cell autonomous manner is an important step in tumor progression (Evan and Vousden, 2001). MYC is the most frequently amplified oncogene and the elevated expression of its gene product, the transcription factor c-Myc, correlates with tumor aggression and poor clinical outcome (Nesbit et al., 1999; Beroukhi et al., 2010; Lin et al., 2012). Elevated expression of c-Myc occurs through multiple mechanisms in tumor cells, including gene amplification, chromosomal translocation, single nucleotide polymorphism in regulatory regions, mutation of upstream signaling pathways, and mutations that enhance the stability of the protein (Eilers and Eisenman, 2008; Meyer and Penn, 2008; Pomerantz et al., 2009; Wright et al., 2010). Rather than binding and regulating a new set of genes, c-Myc amplifies the output of the existing gene expression program (Lin et al., 2012; Littlewood et al., 2012; Nie et al., 2012). The relative level of Myc between cells is a marker of competitiveness. Cells that express more Myc become "supercompetitors" that outcompete even wild-type cells (Abrams, 2002; de la Cova et al., 2004; Moreno and Basler, 2004; Secombe et al., 2004; Rhiner et al., 2009). Loss of completely normal, wild-type cells in the presence of triplo-myc or tetraplo-myc 'supercompetitor' cells reinforces the conclusion that competition does not reflect any intrinsic defect in the outcompeted population but is a response to relative

competitiveness (Baker, 2011). In addition to MYC, cell competition is regulated by a variety of signaling pathways (Moreno et al., 2002; Bondar and Medzhitov, 2010; Marusyk et al., 2010; Rhiner et al., 2010; Tamori et al., 2010; Baker, 2011; Vincent et al., 2011; Chen CL et al., 2012; Norman et al., 2012; Rodrigues et al., 2012; Verghese et al., 2012; Vivarelli et al., 2012), including p53 (Bondar and Medzhitov, 2010; Green, 2010; de Beco et al., 2012).

Secreted protein acidic, rich in cysteine (SPARC)/osteonectin is a secreted multifunctional glycoprotein and belongs to the family of matricellular proteins, which modulate cell-cell and cell-matrix interactions and are induced during morphogenesis, development, tissue injury, and tissue remodeling (Lane and Sage, 1994; Clark and Sage, 2008). Mammalian SPARC is known to bind several extracellular matrix (ECM) proteins and modulate the activity of various growth factors/chemokines (TGF-beta, VEGF, etc.). It has been mainly found to function in de-adhesion, anti-proliferation and regulation of ECM production (Framson and Sage, 2004). In *Drosophila* development, SPARC is transcriptionally upregulated in loser cells during cell competition that provides a transient self-protective signal by inhibiting caspase activation in outcompeted cells (Portela et al., 2010). As a self-protecting signal, SPARC has also been implicated in cancerogenesis (Brekken et al., 2003; Framson and Sage, 2004; Clark and Sage, 2008; Arnold and Brekken, 2009; Petrova et al., 2011). The expression of SPARC in human tumors is also consistent with its role during cell competition (Petrova et al., 2011). SPARC is expressed in mouse spermatogonia, pachytene spermatocytes and less in round spermatids (Pang et al., 2006). During fetal testis development, SPARC is internalized in Sertoli, Leydig, and germ cells suggesting an intracellular regulatory role in these cell types (Wilson MJ et al., 2006). Non-transformed cells are anchorage dependent for the execution of the mitotic program (Chiarugi and Fiaschi, 2007). Hence, survival and development of germ cells depends on their continuous and close contact to Sertoli cells (McLachlan et al., 2002; Schulz et al., 2010). In this context, SPARC-mediated de-adhesion (Murphy-Ullrich et al., 1995; Greenwood and Murphy-Ullrich, 1998; Framson and Sage, 2004; Sweetwyne et al., 2004; Liu A et al., 2009) may be a mechanism mediating the fate of germ cells during cell competition.

8.1.2 Germ cell competition

Germ cell selection occurs when cells that differ genetically (because of mutation, crossing over, or

gene conversion) also differ in their propensity to proliferate or survive during development (Hastings, 1989; Otto and Hastings, 1998). Although, the possibility of germline selection as a mechanism contributing to natural selection and organismal evolution was raised as early as in the 1930s (Shapiro, 1936; Haldane, 1937), selection among cells during the development of an individual has played only a cameo role in population genetics theory (Otto and Hastings, 1998). Population genetic calculations have predicted that such selection, if existent (it was held that conflict between cells are a potent threat to the integrity of multicellular individuals and needed to be reduced), would have significant effects on the frequencies and types of mutations and alleles in a population (Hastings, 1989; Otto and Orive, 1995; Otto and Hastings, 1998). Because selection within the individual acts as a sieve eliminating deleterious mutations and increasing the frequency of beneficial ones, mutations observed among progeny are pre-selected, hindering the spread of deleterious mutations, and reducing the genetic load imposed on the population by several orders of magnitude (Otto and Orive, 1995; Otto and Hastings, 1998). These effects increase with the number of cells within the germline and with the number of cell divisions (Otto and Hastings, 1998).

Mutations at the dominant white-spotting (*W*) locus of the mouse are one of the heritable disorders causing sterility and have pleiotropic effects on growth and differentiation of germ cells, erythrocytes, melanocytes, and mast cells. The *W* locus has been determined to be allelic with the *c-kit* proto-oncogene (Chabot et al., 1988; Geissler et al., 1988; Tan et al., 1990). The *c-kit* gene plays a fundamental role during the establishment, the maintenance and the function of germ cells. In the embryonal gonad the *c-kit* tyrosine kinase receptor and its ligand Stem Cell Factor (SCF) are required for the migration, survival and proliferation of primordial germ cells. In the postnatal animal, *c-kit*/SCF are required for the production of the mature gametes in response to gonadotropic hormones. *c-kit* is required for the survival and/or proliferation of the differentiating type A spermatogonia and for the growth and maturation of oocytes, but the primitive (undifferentiated) type A spermatogonia or spermatogenic stem cells are independent from *c-kit* (Yoshinaga et al., 1991; Manova et al., 1993; Mauduit et al., 1999; Sette et al., 2000). Mice homozygous or double-dominant heterozygous for some, but not all, *W* mutant alleles, such as *W*/*W*^v, *W*^v/*W*^v, and *W*⁴⁴/*W*⁴⁴ mice, are known to have postnatal viability but to be impaired in their fertility, an impairment almost always due to lack of

germ cells in the gonads (Coulombre and Russell, 1954; Geissler et al., 1981). In homozygotes for mutant alleles, the germ cells fail to increase after 9 days of gestation, a consequence of a deficiency in proliferative capacity of the PGC during migration from the hindgut region to the genital ridges (Mintz, 1957; Mintz and Russell, 1957). Heterozygotes for several severely impaired alleles, such as *W*³⁵, *W*³⁸, *W*⁴⁰, *W*⁴², and *W*⁴³ have smaller testes; and *W*³⁹/*W*³⁹ mice, which are viable and have limited fertility, showed reduced spermatogenic activity (Geissler et al., 1981). The *W*^{sh} and *W*^f mutant alleles have rather weak effect on proliferation and/or differentiation of germ cells (Guenet et al., 1979; Lyon et al., 1984); the homozygotes and the heterozygotes between them are fertile. However, regenerative differentiation after surgical reversal of cryptorchidism was impaired in *W* mutants, suggesting a functional significance of the *W* (*c-kit*) gene in postnatal gametogenesis in males (Koshimizu et al., 1991). Nakayama et al. (1990) used chimeras between *W* embryos and *+/+* embryos to investigate germ cell competition. Cleavage-stage embryos from the mating between *W*^{sh}/*W*^f males and *W*^{sh}/*W*^f females were aggregated with *+/+* embryos to produce chimeras. Three male (*XY*↔*XY*) and three female (*XX*↔*XX*) chimeras were mated with *+/+* partners. Two male chimeras made only *+/+* progenies. In the remaining one male, the proportion of *+/+* progeny was larger than that of *W*^f/*+* progeny, whereas the contribution of *+/+* cells was considerably smaller in the fibroblast population. In contrast, such an apparent predominance of *+/+* progenies was not observed in the three female chimeras examined (Nakayama et al., 1990). The results suggest a selective survival of *+/+* germ cells in the male but not the female gonads arguing for a more stringent germ cell competition and quality control in males. The authors speculated that using *W* mutants with more severely impaired germ cell proliferative potential, may have allowed to demonstrate germ cell competition and selective progeny generation also in females (Nakayama et al., 1990).

In the *Drosophila* ovary, germ stem cells have a competitive relationship for niche occupancy, which may serve as a quality control mechanism to ensure that accidentally differentiated stem cells are rapidly removed from the niche and replaced by functional ones (Jin et al., 2008). *dmyc*, the homolog of the human *c-myc* oncogene, is known to be required for endoreplication of the *Drosophila* differentiating cysts (Maines et al., 2004) and its higher expression gives a competitive advantage to germline stem cells (Rhiner et al., 2009). *c-myc* expression is modulated by growth

regulators and is correlated with the establishment and maintenance of the 'growing state' in somatic cells (Kelly et al., 1983; Armelin et al., 1984; Campisi et al., 1984). Intriguingly, however, in non-dividing *Xenopus* oocytes c-myc mRNA is present at a steady-state level 10^4 fold the myc content of proliferative somatic cells. This very high level of c-myc transcript was reached early in oogenesis and remained constant in cell cycle-arrested vitellogenic oocytes, suggesting a posttranscriptional control and that the function of the c-myc gene in oocytes may not be implicated directly in sustaining DNA synthesis or mitosis (Godeau et al., 1986; Taylor et al., 1986; Méchali et al., 1988). C-MYC is also expressed in growing and fully grown mouse oocytes (Suzuki T et al., 2009). Yet, it appears that in oogenesis of a variety of higher vertebrate taxa p53, as a sensor of cellular fitness (de Beco et al., 2012), rather than Myc took over the role of cell competition censor (Ghafari et al., 2009; Belyi et al., 2010; Levine et al., 2011). A possible reason for this switch in higher taxa may be that p53 is a tumor suppressor while MYC is an oncogene that is routinely downregulated in differentiating cells (Reitsma et al., 1983; Campisi et al., 1984; Dotto et al., 1986; Resnitzky et al., 1986) as a barrier to oncogenesis. Although physiological HIF1 responses can inhibit the activity of normal MYC, paradoxically, the deregulated expression of oncogenic MYC collaborates with HIF to confer the tumor metabolic phenotype that is described as the Warburg effect, or aerobic glycolysis (Dang, 2007; Dang et al., 2008).

In response to a Sertoli cell-derived growth factor, glial cell line derived neurotrophic factor, mouse spermatogonial stem cells proliferate and up-regulate N-myc expression (Braydich-Stolle et al., 2007). In various invertebrate and vertebrate seasonal breeders, c-myc is seasonally expressed in testicular tissue indicating peak expression during active spermatogenesis (Walker et al., 1992; Chieffi et al., 1995; 1997). c-Myc is specifically highly expressed in rodent spermatogonia and spermatocytes (Koji et al., 1988; Wolfes et al., 1989; Uetani et al., 1994; Teng and Vilagrasa, 1998) and in human sperm cells (Kumar et al., 1993). In erythroleukemia cells, in primary keratinocytes, in teratocarcinoma, in myeloid M cells, and in human promyelocytic cells, c-Myc protein down-regulation is required to reach the state of differentiation (Reitsma et al., 1983; Campisi et al., 1984; Dotto et al., 1986; Resnitzky et al., 1986). Likewise, a stage of c-Myc gene down-regulation during meiosis has been hypothesized to be necessary for triggering spermatogenic cells to differentiate (Stewart et al., 1984). Spermatocyte apoptosis induced by gossypol, an uncoupling agent

to oxidative phosphorylation, is correlated with biphasic c-Myc protein expression (Teng and Vilagrasa, 1998). Within 0.5 to 2 h of the addition of gossypol to spermatocytes, levels of c-Myc proteins fall dramatically and remain at a low level for the next several hours. Between 3 and 5 h after exposure to gossypol, the c-Myc protein content returns to preexposure (or higher) levels, another 1.5–4 h before the apoptotic death of germ cells (Teng and Vilagrasa, 1998). The fall of c-Myc protein levels is consistent with the loss of competitive potential of metabolically stressed spermatocytes. Likewise, a rapid and constant induction of HL-60 cell apoptosis depends on a combination of down- and up-regulation of the c-Myc gene (Kimura et al., 1995). In mice (Suzuki et al., 1996) and rats (Kodaira et al., 1996), overexpression of a c-myc transgene in testis caused arrest of spermatogenesis during meiosis, massive apoptosis of primary spermatocytes and subsequent sterility.

8.2 Germ cell selection

As pointed out by Hastings (1991), individual genes in **sexual** organisms pass through numerous **asexual** mitotic cell divisions in the germline prior to meiosis and sexual recombination. The processes of mitotic recombination, mitotic crossing over, and mitotic gene conversion may create genotypic diversity between diploid cells in the germline (John and Miklos, 1988; Lankenau, 2007) and have been demonstrated in yeast (Malone and Esposito, 1980; Rudin and Haber, 1988; Lichten and Haber, 1989; Yuan and Keil, 1990; McGill et al., 1993), plants (Puchta et al., 1993), flies (Kennison and Ripoll, 1981; Gethmann, 1988; Lankenau, 2007) and mammals (Panthier et al., 1990; Rouet et al., 1994; Choulika et al., 1995; Sargent et al., 1997; Liang et al., 1998; Johnson and Jasin, 2001; Helleday, 2003; Moynahan and Jasin, 2010). The rate of mitotic crossing-over has been estimated to be within the range of 10^{-4} to 10^{-2} per individual generation in *Drosophila* (Gethmann, 1988), 10^{-5} to 10^{-4} per individual generation in plants (Evans and Paddock, 1979), and 10^{-7} to 10^{-5} per cell generation in yeast (Lichten and Haber, 1989; Yuan and Keil, 1990). Recombination repair is often referred to as an error-free repair pathway and advantageous to the cell. However, recombination is a double-edged sword and may also result in loss of heterozygosity (Sengstag, 1994; Tischfield, 1997). Particularly, copying of a donor sequence associated with gene conversion may be mutagenic (Pâques et al., 1998; 2001; Hicks et al., 2010), due to inefficient mismatch repair during gene conversion (McGill et al., 1998; Hicks et al., 2010).

It has been shown in vivo that at least two-thirds of rodent type A spermatogonia undergo programmed

cell death (Oakberg, 1956; Clermont, 1962; Huckins and Oakberg, 1978; Allan et al., 1992; Dym, 1994). The extrinsic pathway of apoptosis that is characterized by the oligomerization of death receptors such as FAS or tumor necrosis factor followed by the activation of caspase-8 and caspase-3, plays an important role in germ cell apoptosis throughout the first wave of spermatogenesis in the rat under physiological conditions (Jahnukainen et al., 2004; Moreno et al., 2006; Zheng et al., 2006; Lizama et al., 2007; Codelia et al., 2008; Tripathi et al., 2009; Vergara et al., 2011). Particularly, spermatogonia and midpachytene spermatocytes are eliminated (Krishnamurthy et al., 1998; Oldereid et al., 2001; Weinbauer et al., 2001; Francavilla et al., 2002; Jahnukainen et al., 2004; Royere et al., 2004). Apoptosis both with and without caspase activation invariably requires oxidative stress (Smith R et al., 2006; Lysiak et al., 2007; Kalia and Bansal, 2009; Maheshwari et al., 2009). Intriguingly, spermatogonia have been thought to have a high tolerance to oxidative stress that is due to high levels of Zn and Cu/Zn superoxide dismutase (Celino et al., 2011). However, high levels of SODs, if unbalanced by enzymes that can metabolize H_2O_2 , may have detrimental effects on cellular redox homeostasis as discussed in chapter 7.3.

Primitive type A (collected from 6-day-old mice) and type A spermatogonia (collected from 8-day-old mice) have the highest spontaneous mutant frequencies, followed by type B spermatogonia, preleptotene spermatocytes, leptotene and zygotene spermatocytes, pachytene spermatocytes, round spermatids, and epididymal spermatozoa, all of which display a similarly low mutant frequency (Walter et al., 1998). Ionizing radiation (IR) induces an increased mutant frequency, the amount of which declines as cells progress through spermatogenesis (Xu et al., 2008). Shapiro (1936) and Abrahamson et al. (1966) showed that premeiotic male germ cells undergo selection against X-linked lethals. These studies revealed mechanisms that exist to eliminate premeiotic cells with elevated mutation frequencies during spermatogenesis (Walter et al., 1998; Xu et al., 2008; 2010). In fact, apoptosis functions in male germ cells to mediate a decline in mutant frequency during spermatogenesis by removing cells with a high mutant frequency (Walter et al., 1998; Xu et al., 2008; 2010). Thus, apoptosis occurs extensively in the first wave of spermatogenesis in rodents and is critical as quality control tool eliminating less competitive germ cells (see chapter 8.1).

Genes expressed in the germline whose products

affect cell viability (such as many “housekeeping” enzymes) may be subjected to selection acting on their variability resulting in a non-Mendelian output of gametes (Massicotte et al., 2006). Such genes will be governed by the population genetics of the sexual/asexual life cycle rather than the conventional sexual/Mendelian life cycle (Hastings, 1991). Importantly, many housekeeping genes are in general highly expressed (Vinogradov, 2004; Zhu et al., 2008) and are involved in cellular metabolism, energy, stress responses, cell adhesion, signal transduction, cytoplasmic and nuclear functions, such as protein and intracellular transport (Dix, 1997; Lequarré et al., 1997; Rose-Hellekant et al., 1998; Krisher and Bavister, 1999; Khurana and Niemann, 2000; Neuer et al., 2000; Aguilar-Mahecha et al., 2001; Rockett et al., 2001; Dalbiès-Tran and Mermillod, 2003; Muramoto et al., 2003; Yu et al., 2003; International Chicken Genome Sequencing Consortium, 2004; Krisher, 2004; Urner and Sakkas, 2005; Lowe et al., 2007), arguing for a role of these genes, and the cellular processes regulated by them, in the germline cell selection process. On the basis of publicly available expressed sequence tag data, a large fraction (40%) of currently-annotated human genes are universally expressed (Zhu et al., 2008). There is a hierarchy of purifying selection that is reflected by the pattern of molecular evolution. Comparisons of pufferfish (*Takifugu rubripes*), chicken and human genomes reveal around 7,000 genes that have 1:1 orthologs in all three species, suggesting a ‘core’ of genes that may have an essential role in all vertebrates (International Chicken Genome Sequencing Consortium, 2004; Furlong, 2005). The sequences in this core tend to be more conserved than other orthologs, indicating that strong purifying selection is acting upon them, stressing their functional importance. When cells were subjected to hypoxia, HIF-1 preferentially bound to loci that were already transcriptionally active under normal growth conditions characterized by the presence of histone H3 lysine 4 methylation, the presence of RNA polymerase II, and basal production of mRNA. Cell type-specific differences in HIF-1 binding were largely attributable to differences in the basal gene expression patterns in the cells (Xia and Kung, 2009). Thus, the expression level is one of the major determinants of protein evolution (Sharp, 1991; Green et al., 1993; Duret and Mouchiroud, 2000; Pál et al., 2001; 2006; Krylov et al., 2003; Rocha and Danchin, 2004; Zhang and Li, 2004; Agrafioti et al., 2005; Drummond et al., 2005; 2006; Koonin and Wolf, 2006; Rocha, 2006; Drummond and Wilke, 2008; Wolf et al., 2008). Conserved patterns of simple covariation between sequence evolution, codon

usage, and mRNA level in *E. coli*, yeast, worm, fly, mouse, and human suggest that selection against toxicity of misfolded proteins generated by ribosome errors suffices to create all of the observed covariation (Drummond and Wilke, 2008). Studies on the yeast *Saccharomyces cerevisiae* indicate that the strongest predictor of evolutionary rate is expression level of a protein that explains 30–50% of the variation in the rate of protein evolution (Pál et al., 2001; Drummond et al., 2005; 2006), much more than any other known variable. Furthermore, many amino-acid changes seem to be due to positive selection, often reflecting arms races or compensatory mutations rather than adaptation to changed environments (Pál et al., 2006). Broadly expressed proteins in mammals (Duret and Mouchiroud, 2000; Subramanian and Kumar, 2004), insects (Subramanian and Kumar, 2004) and plants (Wright et al., 2004), that can be expected to be expressed in germ cells evolve more slowly than tissue-specific proteins that can be expected to be not expressed in germ cells (Duret and Mouchiroud, 2000; Subramanian and Kumar, 2004; Zhang and Li, 2004; Liao and Zhang, 2006). Proteins functioning during different stages of development may be predisposed to having mutations of different selective effects. Thus, proteins expressed early in development and particularly during mid–late embryonic development evolve unusually slowly (Davis JC et al., 2005). Housekeeping genes evolve more slowly in protein sequence than tissue-specific genes (Hughes and Hughes, 1995; Hastings, 1996; Duret and Mouchiroud, 2000; Hirsh and Fraser, 2001; Jordan et al., 2002; Zhang and Li, 2004). Similarly, protein dispensability affects evolutionary rate (Hurst and Smith, 1999; Hirsh and Fraser, 2001; Jordan et al., 2002; Wall et al., 2005; Zhang and He, 2005; Liao et al., 2006; Larracuente et al., 2008). Genes expressed early in spermatogenesis had rates of divergence similar to the genome median, while genes expressed after the onset of meiosis were found to evolve much more quickly. Rates of protein evolution were fastest for genes expressed during the dramatic morphogenesis of round spermatids into spermatozoa. Late-expressed genes were also more likely to be specific to the male germline (Good and Nachman, 2005). Tissue expression tends to evolve rapidly for genes that are expressed in only a limited number of tissues, whereas tissue expression can be conserved for a long time for genes expressed in a large number of tissues (Duret and Mouchiroud, 2000; Zhang and Li, 2004; Yang J et al., 2005; Liao et al., 2006; Parmley et al., 2007; Park and Choi, 2010). A similar relationship can be seen when exons of a given gene are considered: alternatively spliced exons (which are generally also tissue specific) evolve at

higher rates than constitutively spliced exons (Xing and Lee, 2005). However, there appears to be no reduction of mutation rates in genes expressed specifically in the germline (Duret and Mouchiroud, 2000). Expression pattern is an essential factor in determining the selective pressure on functional sites in both coding and noncoding regions. Conversely, silent substitution rates do not vary with expression pattern, even in ubiquitously expressed genes. This latter result thus suggests that synonymous codon usage is not constrained by selection in mammals (Duret and Mouchiroud, 2000). In addition to this high gene expression, high-evolutionary-rate, hotspots, another class of mutagenesis hotspots was identified in the genome characterized by reduced repair in hypermethylated lowly-transcribed genes (Zhao and Epstein, 2008; Tang and Epstein, 2010). These processes result in regional mutation-rate variation within genomes (Wolfe et al., 1989; Ellegren et al., 2003).

To compensate for the stochastic nature of the (epi)mutation and recombination process, sexual reproduction relies on sperm and oocyte quality control. The cytokine TNF α appears to be a paracrine factor that signals germ cell quality (Pentikäinen et al., 2001). TNF α is known to be secreted by testicular germ cells (De et al., 1993). TNF α effectively and dose-dependently plays an anti-apoptotic role via the activation of NF- κ B (Barkett and Gilmore, 1999; Pentikäinen et al., 2001; Suominen et al., 2004). Various studies have shown that NF- κ B has both anti- and pro-apoptotic effects within cells (Kaltschmidt et al., 2000; Pentikäinen et al., 2002; Mathur et al., 2011). The expression of the TNF receptor protein in the seminiferous epithelium was predominantly found in Sertoli cells (De et al., 1993; Mauduit et al., 1996; 1998; De Cesaris et al., 1999; Pentikäinen et al., 2001). In Sertoli cells, TNF α regulates the production of germ cell trophic factors, e.g. lactate (Nehar et al., 1997; Boussouar et al., 1999; Erkkilä et al., 2002), transferrin (Sigillo et al., 1999; Lécureuil et al., 2004), glutathione (Meroni et al., 2000; Rahman, 2000; Yang H et al., 2005; Reuter et al., 2009), and IGF-binding protein (Besset et al., 1996). TNF- α stimulated NF- κ B binding to the androgen receptor promoter, induced androgen receptor promoter activity, and increased endogenous androgen receptor expression in primary cultures of Sertoli cells (Delfino et al., 2003). In addition, cultured Leydig cells have been shown to respond to TNF α by decreasing their biosynthesis of testosterone (Li et al., 1995; Mauduit et al., 1998; Budnik et al., 1999), possibly a negative feedback loop that tightens the

supply of the trophic factor, securing the maintenance of the quality assurance system.

Studies of mouse, rat, and human testicular apoptosis have shown that the Fas-Fas ligand system (Nagata and Golstein, 1995; Nagata, 1997) is a powerful mediator of male germ cell death (Lee J et al., 1997; 1999b; Boekelheide et al., 1998; Pentikäinen et al., 1999; Yin et al., 2002) and possibly involved in the quality control mechanism of the produced gametes (Braun, 1998; Ross et al., 1998; Odorisio et al., 1998; Francavilla et al., 2000; Neubauer et al., 2004). The Fas system is a mechanism through which cells expressing Fas ligand (FasL) induce apoptosis of Fas expressing cells. The testis is the only organ that constitutively expresses abundant amounts of FasL mRNA (D'Alessio et al., 2001). p53 has been reported to target the Fas gene for transcription (Owen-Schaub et al., 1995; Schilling et al., 2009), and up-regulation of Fas appears to be p53-dependent (Müller et al., 1997; Yin et al., 2002). FasL and Fas, expressed by Sertoli cells and germ cells, respectively, respond to environmental conditions and initiate germ cell death. In the rat seminiferous tubules, Sertoli cells express FasL (Suda et al., 1993; French et al., 1996; Richburg et al., 2000; D'Abrazio et al., 2004). FasL associates with the Fas receptor, which is a type I transmembrane receptor, located on testicular germ cells (Lee J et al., 1997; 1999b; Boekelheide et al., 1998; Pentikäinen et al., 1999). Up-regulation of Fas is a common and critical step for initiating germ cell death in vivo. Moreover, if Sertoli cells are injured, they up-regulate FasL to eliminate Fas-positive germ cells (Lee et al., 1997; 1999). In cultured mouse Sertoli cells, TNF α regulates the expression and function of the Fas system, suggesting a role for TNF in testicular apoptosis (Barkett and Gilmore, 1999; Riccioli et al., 2000). Germ cell-derived TNF α appears to down-regulate the level of the Fas ligand and thereby reduce physiological germ cell apoptosis (Pentikäinen et al., 2001; Suominen et al., 2004). Another study reported that FasL mRNA is strongly expressed in differentiating germ cells and that the protein is thereafter displayed on the surface only when the gamete is fully mature and, as spermatozoon, leaves the testis (D'Alessio et al., 2001). The authors proposed that FasL protein displayed on the surface of mature spermatozoa may represent a self-defense mechanism against lymphocytes present in the female genital tract (Riccioli et al., 2003).

Spermatogonia bearing relatively higher mutation frequencies are more likely to be included among the apoptotic cells than are those with low mutation

frequencies (Walter et al., 1998). Cell competition (see chapter 8.1) that selects for the least damaged cells is controlled by p53 (Bondar and Medzhitov, 2010; Green, 2010; Marusyk et al., 2010), possibly via p53 C-terminal regulatory domain signaling (Wang YV et al., 2011). In invertebrates and vertebrates, p53 family proteins are activated by oxidative stress (Jayaraman et al., 1997; Xie et al., 2001; Martindale and Holbrook, 2002; Chen K et al., 2003; Vousden and Lane, 2007; Kotinas et al., 2012; Gambino et al., 2013), monitor the genomic quality of germ cells, protect them against stress and, in an ambivalent role, eliminate inferior ones (Norimura et al., 1996; Ollmann et al., 2000; Derry et al., 2001; Suh et al., 2006; Yamada et al., 2008; Gonfloni et al., 2009; Hu, 2009; Belyi et al., 2010; Levine et al., 2011). With regard to its protective role, p53 appears to play a central role in repressing ROS-induced stresses by upregulating antioxidant genes (Tan et al., 1999; Budanov et al., 2004; Sablina et al., 2005; Bensaad et al., 2006; Matoba et al., 2006; Tomko et al., 2006; Meiller et al., 2007; Cano et al., 2009; Chen et al., 2009; Olovnikov et al., 2009; Hu W et al., 2010; Pallepati and Averill-Bates, 2010; Popowich et al., 2010; Budanov, 2011; Nam and Sabapathy, 2011; Nii et al., 2012; Vurusaner et al., 2012; Kang MY et al., 2013). p53 couples energy metabolism and ROS formation by modulating the transcription of target genes that control the fluxes through mitochondrial respiration, glycolysis, or the pentose phosphate shunt (Liu B et al., 2008). On the other hand, high p53 expression appears to be a marker of "losers" in cell competition (Bondar and Medzhitov, 2010; Marusyk et al., 2010) that increases ROS production and activates apoptosis pathways (Johnson et al., 1996; Polyak et al., 1997; Donald et al., 2001; Liu and Chen, 2002; Martindale and Holbrook, 2002; Macip et al., 2003; Hussain et al., 2004; Sablina et al., 2005; Valko et al., 2007; Mai et al., 2010; Pani and Galeotti, 2011; Vurusaner et al., 2012; Kang MY et al., 2013). One of the cell fate decisions mediated by p53 may be via the repression of Hsp70 expression (Agoff et al., 1993). Intriguingly, both the antioxidant and prooxidant actions of p53 may be mediated by its concentration-dependent effects on catalase activity (Kang MY et al., 2013). The p53-inducible gene 3 (PIG3)-mediated downregulation of catalase activity (Kang MY et al., 2013) may explain the low level of catalase activity in rat testicular germ cells (Bauché et al., 1994). Throughout metazoan phylogenesis, p53 and its homologues mediate spontaneous germ cell apoptosis and failure to remove defective germ cells by this mechanism results in increased percentages of abnormal gametes and reduced fertility (Beumer et al., 1998; Yin et al., 1998;

Sinha Hikim and Swerdloff, 1999; Gartner et al., 2000; Schumacher et al., 2001; Lettre et al., 2004; Baum et al., 2005; Kwon et al., 2005; McKee et al., 2006; Pankow and Bamberger, 2007; Codelia et al., 2010; Xu et al., 2010). Many invertebrates, such as *C. elegans* and *Drosophila melanogaster*, have only one p53 family member, which resembles more closely p63 and p73 than p53 with regard to both structural and functional aspects. The p53 members from *C. elegans*, CEP-1 (Derry et al., 2001; Ross et al., 2011), and from *D. melanogaster*, Dmp53 (Ollmann et al., 2000), are both exclusively required for germline fidelity. Unique isoforms of the p53 homolog p63, the most ancient member of the p53 gene family, are highly and specifically expressed in human testicular germ cells (Amelio et al., 2012). Phylogenetically, this expression was supported by insertion of an endogenous retrovirus with its requisite LTR with strong promoter activity that occurred 10 to 15 million years ago during primate evolution at the branching point to long-lived Hominidae. Upon DNA damage, the resulting germ cell-associated, transcriptionally active p63 suppresses proliferation and induces apoptosis in mice (Beyer et al., 2011) like in the sea anemone *Nematostella vectensis* (Pankow and Bamberger, 2007) selecting against germ cells that evolved genomic instability.

Human females are provided with approximately $1-2 \times 10^6$ oocytes at birth, a starting reserve that is further decimated by apoptosis to fewer than 4×10^5 at puberty (Baker, 1963). Although definitive proof has been lacking, the purge of oocytes that takes place before and after birth is widely suspected of being a mechanism of ridding the germline of genetically inferior eggs (Jansen, 2000; Jansen and Burton, 2004). Routinely in the range of 35-45 years there is a well-known decrease in oocyte number (to ~ 25000; Faddy et al., 1992) and reproductive competence (Serhal and Craft, 1989; Jansen, 1995; Faber et al., 1997) Thereafter, there can be an exponential acceleration in numeric decline (Faddy et al., 1992) to fewer than 1000 in the years immediately preceding ovarian senescence (on average, around age 50) (Richardson et al., 1987; Faddy et al., 1992; Wise et al., 1996). In the span of 4 weeks (every ovarian cycle during the reproductive years), tens or hundreds of follicles start their growth from the resting primordial state. Yet in most circumstances just one follicle each month presents its oocyte to be fertilized. The observer could reasonably suspect that he or she is witnessing a competition: waves of folliculogenesis and waves of atresia, with a very small number of winners (Medvedev, 1981; Krakauer and Mira, 1999; Jansen, 2000; Jansen and Burton, 2004). In fact,

oocyte selection, at least in part, is due to competition of follicles for trophic factors such as growth hormone, IGFs, basic fibroblast growth factor and VEGF that ensure proper vascularization and provision of nutrients (Neeman et al., 1997; Schams et al., 1999; Berisha et al., 2000; Silva et al., 2009). The VEGF signaling pathway also operates as evolutionarily conserved selective agent in cellular competition during angiogenic sprouting (Jakobsson et al., 2010; Krueger et al., 2011; Blanco and Gerhardt, 2013). Bidirectional communication between oocytes and granulosa and cumulus cells is responsible for nurturing oocyte growth, the gradual acquisition of oocyte developmental competence and oocyte selection (Gilchrist et al., 2008). p63 is constitutively expressed in female germ cells during meiotic arrest and, monitoring the integrity of the female germline, is essential in a process of DNA damage-induced oocyte death (Suh et al., 2006; Gonfloni et al., 2009; Deutsch et al., 2011a; b; Amelio et al., 2012). Together with its control of recombination (Stürzbecher et al., 1996; Lu et al., 2010), p53 family members are involved in the complete cascade of gametogenic events, assessing and assuring quality and stress resilience of germ cells (Amelio et al., 2012).

The ubiquitin-proteasome system is a universal cellular quality control system (Hershko and Ciechanover, 1998; Taylor and Rutter, 2011). In spermatogenesis, the ubiquitin-proteasome system is required for the degradation of numerous proteins throughout the mitotic, meiotic, and postmeiotic developmental phases (Wilkinson, 1997; Baarends et al., 1999; 2000). Ubiquitin C-terminal hydrolase (UCH) L1 is expressed at high levels in both testis and epididymis and may play an important role in the regulation of spermatogenesis (Martin R et al., 1995; Fraile et al., 1996; Kon et al., 1999; Kwon et al., 2003). Furthermore, it has been suggested that UCHL1 also functions as a regulator of apoptosis (Harada et al., 2004b). UCHL1-deficient testes of gad mice have reduced ubiquitin levels and are resistant to cryptorchid injury-mediated germ cell apoptosis (Kwon et al., 2004). Testicular germ cells in the immature testes of gad mice are resistant to the early apoptotic wave that occurs during the first round of spermatogenesis. In adult gad mice, cauda epididymidis weight, sperm number in the epididymis, and sperm motility were reduced. Moreover, the number of defective spermatozoa is significantly increased; however, complete infertility was not detected. These data indicated that UCHL1 is required for normal spermatogenesis and sperm quality control and demonstrated the importance of UCHL1-dependent apoptosis in spermatogonial cell

and sperm maturation (Kwon et al., 2005).

The heat shock transcription factor (HSF) family regulates expression of heat shock genes via a heat shock element. HSF1 is also involved in quality-control mechanisms, eliminating injured male mouse germ cells when these cells are exposed to stress (Nakai et al., 2000; Izu et al., 2004; Widlak et al., 2007). Male mice deficient in both HSF1 and HSF2 are sterile with severe defects in spermatogenesis (Wang G et al., 2004) while female mice deficient in HSF1 are infertile as well (Xiao et al., 1999). In *Drosophila*, a single HSF is necessary for oogenesis (Jedlicka et al., 1997).

In *Hydra*, oocyte determination involves a mechanism that establishes a subset of precursor interstitial cells competent to differentiate into oocytes. The oocyte is singled out from this subset and the competence of the remaining cells to become oocytes dramatically decreases as they adopt the alternative nurse cell fate. Nurse cells differentiate and enter an unusual apoptosis program where they are phagocytosed by the oocyte (Miller et al., 2000). Spermatogenesis in *Hydra* is associated with apoptosis of pre-meiotic spermatocytes (Kuznetsov et al., 2001). Significant apoptosis occurs premeiotically during normal spermatogenesis in teleost and cartilaginous fishes (Billard, 1969; Callard et al., 1995; 1998; Cinquetti and Dramis, 2003; Prisco et al., 2003; McClusky, 2005; 2011; Corriero et al., 2007; 2009; Leal et al., 2009; McClusky et al., 2009), amphibians (Yazawa T et al., 1999, 2000, 2003; Ricote et al. 2002; Sasso-Cerri et al., 2006) and reptiles (Comitato et al., 2006; Zhang L et al., 2008). However, spermatogonia loss may also be as low as 5% as in cod (Almeida et al., 2008).

Programmed cell death is implemented during germline, mid- and late-oogenesis of a variety of Diptera and is absolutely required for the normal maturation of the developing egg chambers (Nezis et al., 2000; 2001; 2002; 2003; 2006a; b; c; McCall, 2004; Baum et al., 2005). Each *Drosophila* ovary is composed of approximately fifteen ovarioles, chains of developing egg chambers. Egg chambers are sixteen-cell germline cysts surrounded by up to a thousand somatic follicle cells (King, 1970; Spradling, 1993; Wu et al., 2008). In *Drosophila* oogenesis, three waves of apoptosis occur (Pritchett et al., 2009): PGC cell death (Coffman, 2003), mid-oogenesis cell death (McCall, 2004) and nurse cell death (Velentzas et al., 2007). In addition to germline cell death, cell death occurs in the somatic follicle cells (Pritchett et al., 2009). Approximately 50% of initially formed PGCs successfully migrate and are incorporated into the gonads. The remaining PGCs do not transdifferentiate but are eliminated (Sonnenblick, 1950; Underwood et

al., 1980; Technau and Campos-Ortega, 1986). Removal of a phospholipid survival factor seems to be responsible for guiding PGC away from the midline and to eliminate those PGCs unable to follow (Zhang N et al., 1996; 1997; Starz-Gaiano et al., 2001; Hanyu-Nakamura et al., 2004; Renault et al., 2004; Boldajipour and Raz, 2007). Extavour and García-Bellido (2001) investigated whether mutations in heterozygosis are subject to premeiotic selection in the germline and showed that cell selection that precedes and conditions subsequent zygotic selection takes place in mosaic germ-line populations. This apoptosis is mediated by *Drosophila* p53 pathways in which signaling between p53 and cellular metabolism are integrated to regulate programmed cell death decisions (Yamada et al., 2008). In *Drosophila* oogenesis, somatic follicle cells surround the egg chamber providing the proper environment for the development of the 16 germline cells that are derived from a single germline precursor cell by four mitotic divisions to generate interconnected 16-cell groups known as germline cysts. During these cell divisions, the cysts elaborate a cytoskeletal polarity that ultimately causes one cell to develop as an oocyte, while the others become nurse cells (Spradling, 1993; Johnstone and Lasko, 2001; Reichmann and Ephrussi, 2001). The nurse cells support the development of the oocyte providing organelles, proteins and maternal RNAs to the oocyte through the ring canals (Trogakos and Margaritis, 2002). The development of each mature egg is always accompanied by the apoptosis of its 15 sister nurse cells at the end of oogenesis (McCall and Steller, 1998; Buszczak and Cooley, 2000; McCall, 2004; Velentzas et al., 2007; Pritchett et al., 2009).

Like in *Drosophila*, a quality control system with downregulation of a survival factor seems to be responsible for guiding mouse PGCs away from the midline towards the genital ridges and to eliminate those PGCs unable to follow (Mahakali Zama et al., 2005; Runyan et al., 2006; Boldajipour and Raz, 2007).

Interestingly, in the developing *Xenopus* ovary containing oogonia and stage I oocytes, the apoptosis seems to be limited to the somatic cells, and there is no indication of apoptosis in the germ cells (Kloc et al., 2004b). In *Xenopus* oocytes, pentose phosphate pathway generation of NADPH is critical for oocyte survival. Pentose phosphate pathway-mediated inhibition of cell death resulted from the inhibitory phosphorylation of caspase 2 (Nutt et al., 2005). p53 regulates the blockade of glycolysis, directing the pathway into the pentose phosphate shunt to produce

NADPH (Bensaad et al., 2006; Green and Chipuk, 2006), increasing glutathione levels which promotes the scavenging of RONS.

It has been estimated that roughly one half of all female germ cells die in the adult *C. elegans* hermaphrodite gonad (Gumienny et al., 1999; Gartner et al., 2000; 2008; Navarro et al., 2001; Jaramillo-Lambert et al., 2007). More recent estimates of germ cell proliferation rates indicate that approximately 20 germ cells are produced every hour, while only ~3 oocytes are laid (Fox et al., 2011; Bailly and Gartner, 2013). Apoptosis only occurs in the female and not in the male germline and is thus only present in hermaphrodites (Gumienny et al., 1999; Gartner et al., 2000; Jaramillo-Lambert et al., 2010). The core cell death machinery is expressed in female and male germlines; however, CED-3 caspase is not activated in the male germline. Intriguingly, recombination checkpoint functions in male germ cells to promote repair of meiotic recombination intermediates, thereby improving the fidelity of chromosome transmission in the absence of apoptosis (Jaramillo-Lambert et al., 2010). Oocyte cell death occurs exclusively during the adult stage and primarily in the loop region containing pachytene stage meiotic germ cells.

8.2.1 Case study: paternal age effect disorders

Advanced paternal age has been associated with an increased risk for spontaneous congenital disorders, including Apert syndrome (caused by FGFR2 mutations), achondroplasia, and thanatophoric dysplasia (FGFR3), and Costello syndrome (HRAS), that were collectively termed “paternal age effect” (PAE) disorders (Arnheim and Calabrese, 2009; Goriely and Wilkie, 2012). All are caused by a small number of dominantly-acting point mutations in key developmental regulators, which cluster within the growth factor receptor-RAS signaling pathway; moreover, the causative point mutations originate almost exclusively from the unaffected fathers, indicating that the original mutational events are taking place during spermatogenesis. Extensive analyses of the birth incidence of achondroplasia showed that unaffected fathers in their fifties are 10-fold more likely to have offspring with a de novo achondroplasia mutation compared with unaffected fathers in their twenties (Risch et al., 1987). Individuals born with Apert syndrome exhibit prematurely fused cranial sutures and fused fingers and toes. Two nucleotide substitutions in the human FGFR2 gene (C755G or C758G) are responsible for virtually all sporadic cases of Apert syndrome. The birth frequency of individuals with new mutations at either of these two nucleotide

sites suggests that the mutation frequency at either site is 100- to 1,000-fold greater than expected based on what is known about transversion mutations since humans and chimpanzees last had a common ancestor (Nachman and Crowell, 2000) and mutation data at many human disease loci (Kondrashov, 2003). (Qin et al., 2007; Choi et al., 2008). In one case (Tiemann-Boege et al., 2002), the magnitude of the sex bias for the C755G Apert syndrome was at least 99-fold greater in the male germline than in the female germline (Wilkin et al., 1998; Glaser et al., 2000), whereas estimates of male bias (male-driven evolution) using data on neutral mutations at many different sites would indicate only an approx. five- to ten-fold male bias (see chapter 7.3).

The hotspot model, the idea that the nucleotide has a higher-than average chance of undergoing a base substitutions at both sites (C755G and C758G) has been ruled out (Qin et al., 2007; Choi et al., 2008). Various mutations associated with PAEs in testes of unaffected men were not uniformly distributed across each testis as would be expected for a mutation hotspot but were highly clustered and showed an age-dependent germline mosaicism (Qin et al., 2007; Choi et al., 2008; 2012; Shinde et al., 2013; Yoon et al., 2013). An alternate hypothesis to explain the high mutation frequencies argues that diploid premeiotic cells carrying the mutations have a selective advantage over wild-type cells (Tiemann-Boege et al., 2002; Goriely et al., 2003; 2005; Crow, 2006; Qin et al., 2007; Choi et al., 2008; 2012; Shinde et al., 2013; Yoon et al., 2013). This selection takes place on self-renewing Ap spermatogonial stem cells (SrAp) carrying the mutations that arise at approximately the frequency expected from the existing data on neutral mutations (Nachman and Crowell, 2000; Kondrashov, 2003). The selection model proposes that mutant adult SrAp occasionally divide symmetrically (inferred rate 1 out of 100 divisions on average, or approximately once every 4 y), whereas wildtype SrAp always undergo asymmetric self-renewal divisions. Rare patients with multiple mutations in the FGFR2 gene that leads to Apert syndrome were also cited as support for a germline selection model (Goriely et al., 2005). In another study (Goriely et al., 2003), the authors exploited a nearby single nucleotide polymorphism (SNP) to argue that selection acted on the C755G mutation.

In other PAE disorders, there is evidence for positive selection of mutant premeiotic spermatogonia. First, 97–99% of the de novo mutations leading to achondroplasia (the most common form of dwarfism) result from a G-to-A transition mutation at base pair

1138 (G1138A) in exon 10 of fibroblast growth factor receptor 3 (FGFR3) (Shiang et al., 1994; Rousseau et al., 1996). The cytosine at base pair 1138 is part of a CpG dinucleotide and, if methylated, is highly susceptible to mutation caused by spontaneous deamination (see chapter 10.3.1.1). Direct measurement of the G1138A mutation frequency in sperm suggested that the high frequency may be explained by selection (Tiemann-Boege et al., 2002; Crow, 2006). The observed G1138A mutation distribution in human testes fits a model, where mutant spermatogonial stem cells have a proliferative advantage over unmutated cells (Dakouane Giudicelli et al., 2008; Shinde et al., 2013).

The Noonan syndrome (NS), whose features include characteristic craniofacial abnormalities, short stature, heart defects, intellectual disability and delay, and a variety of other anomalies, as well as a predisposition to certain cancers, is among the most common Mendelian genetic diseases (~1/2,000 live births) (Tartaglia and Gelb, 2005; Allanson and Roberts, 2011). Most cases (50%–84%) are sporadic, and new mutations are virtually always paternally derived (Tartaglia et al., 2004). More than 47 different sites of NS de novo missense mutations are known in the PTPN11 gene that codes for the protein tyrosine phosphatase SHP-2. Surprisingly, many of these mutations are recurrent with nucleotide substitution rates substantially greater than the genome average; the most common mutation, A922G, exceeds the genome average A>G mutation frequency by more than 2,400 fold (Yoon et al., 2013). Data of the spatial distribution of the A922G mutation in testes from unaffected men were inconsistent with hypermutation, but consistent with germline selection: mutated spermatogonial stem cells gained an advantage that allowed them to increase in frequency (Yoon et al., 2013).

Multiple endocrine neoplasia type 2 (MEN2) is characterized by thyroid cancer, variable penetrance of tumors or hyperplasia in other endocrine organs. Half of all new cases result from sporadic mutations, the vast majority (>95%) of which arise in the male germline (Carlson et al., 1994; Kitamura et al., 1995). The average age of the males who transmit a new mutation to their children is greater than that of the average age of all fathers (Carlson et al., 1994). Since almost all sporadic cases are caused by the same nucleotide substitution in the RET proto-oncogene, the calculated disease incidence is 100–200 times greater than would be expected based on the genome average mutation frequency. The spatial distribution of the mutation in testes of unaffected men suggested

that the MEN2B mutation provides an advantage for spermatogonial clonal expansion by altering signaling pathways (Choi et al., 2012).

I offer an alternative interpretation: All published work missed the fact that spermatogonia undergo a massive wave of apoptosis that selects against low-quality germ cells (see chapter 8.2). Thus the observed birth frequency may not only be due to positive selection of mutated gametes but may simply reflect the lack of negative selection. Although, a variety of PAE-mutations occur in proto-oncogenes (Choi et al., 2012; Yoon et al., 2013) that may confer a competitive advantage to the gametes carrying them (see chapter 8.1.1). Compared to putatively neutral mutations, the mutation rate per cell division was found not elevated at the nucleotides under study in the Apert and the heritable cancer syndromes (Qin et al., 2007; Choi et al., 2008; 2012). Moreover, the C755G mutations arise at approximately the frequency expected from the existing data on neutral mutations (Nachman and Crowell, 2000; Kondrashov, 2003) that per definition cannot be selected against during the germ cell selection process because they are not “seen” by evolution. Both the clonal expansion of mutated spermatogonia and the lack of negative selection may jointly contribute to the observed PAE. The fibroblast growth factor receptor 3 (FGFR3) gene does not appear to be a housekeeping gene since it is highly methylated both in mature sperm and oocytes (El-Maarri et al., 1998). This finding does not preclude that the gene is expressed during gametogenesis. However, it is thought that only housekeeping genes that are expressed during gametogenesis should give rise to a selective advantage or disadvantage. At any rate, the evidence from PAEs supports the notion of a germ cell selection process.

8.3 Selective mitochondrial bottleneck

Another selective process during sexual reproduction unfolds in cell organelles. Here, only the selection of mitochondria is considered, but it can be expected that a similar process of organelle competition occurs between varieties of chloroplasts (Eberhard, 1980). Mitochondrial functionality is dependent on a harmonious and concerted interplay of approximately 1,000 genes with the vast majority encoded in the nuclear genome, and usually only 37 encoded by mitochondrial DNA (mtDNA) (Mootha et al., 2003; Sickmann et al., 2003; Gregersen et al., 2012). Localization of fundamental components of mitochondrial respiration in two different compartments of the cell requires extensive anterograde (nucleus to organelle) and retrograde (organelle to nucleus) signaling to maintain respiratory

efficiency (Woodson and Chory, 2008; Chacinska et al., 2009). A complex signaling network regulates the replication and transcription of mtDNA, with ATP balance and oxidative phosphorylation activity of individual mitochondria serving as potential signals (Allen, 1993). The proximity of mtDNA to the sites of oxidative phosphorylation and ROS production, the fact that mtDNA is not associated with histones, an error-prone polymerase and limited DNA repair are primary explanations for high mutation pressure on mtDNA (Shigenaga et al., 1994; Bogenhagen, 1999; de Grey, 1999). Increased mtDNA rearrangements and deletions in human gametes (Brenner et al., 1998; Reynier et al., 1998; Barritt et al., 1999) witness the high mutation rate. The mitochondrial mutation rate is much higher than the nuclear one (Brown et al., 1979; 1982; Ingman et al. 2000; Mishmar et al. 2003; Ballard and Whitlock, 2004; Kivisild et al. 2006; Lynch et al., 2006). On the other hand, ROS have been implicated in stimulating mtDNA replication in mammalian and yeast cells (Moreno-Loshuertos et al., 2006; Hori et al., 2009).

With few exceptions, mtDNA is maternally inherited (Birky, 1995; White et al., 2008). As many as 100,000 copies are passed on in mammalian oocytes. Taking into account the high developmental oxidative stress to which sperm mitochondrial DNA is exposed, it should have inferior quality, compared to oocyte mitochondrial DNA, and its elimination should be an evolutionary necessity. Various theories have been proposed to explain the uniparental inheritance of mitochondrial DNA (Birky, 1995). In *Caenorhabditis elegans*, the paternal mitochondria are eliminated after fertilization (Rawi et al., 2011; Sato and Sato, 2011). In *Drosophila*, mitochondrial DNA is removed from developing spermatids in a process requiring the mitochondrial nuclease, Endonuclease G (DeLuca and O'Farrell, 2012). In the Japanese medaka fish, paternal mtDNA vanishes within sperm mitochondria after fertilization, and in bovine embryos, paternal mitochondria are eliminated during the first two zygotic cell divisions (Nishimura et al., 2006; Sutovsky et al., 1996). Before fertilization, sperm mitochondria commonly harbor multiple DNA deletions (Reynier et al., 1998). Poorly motile sperm have higher numbers of mtDNA per cell than progressively motile sperm do. Such specimens also have a higher abundance of mtDNA species with deletions (Kao et al., 1995). In a man with the mtDNA A3243G mutation, decreasing sperm motility correlated with an increase in mutant mtDNA from 42 to 64% (Spiropoulos et al., 2002) implying that mitochondrial defects accentuate the degree of mtDNA damage that is commonly acquired during spermatogenesis and epididymal transit

(Jansen and Burton, 2004). In contrast to the situation in which competing spermatozoa find themselves, the egg has for the entire time been in a relatively anaerobic and metabolically quiet environment, one suited for shielding the egg's genomes from DNA damage and mutation (Jansen and Burton, 2004).

Here, I reproduce for the most part the excellent review of Nick Lane (2011a): "If large complex cells are not possible at all without tiny mtDNA genomes, then there is a necessary interaction between mtDNA and the nuclear genes encoding mitochondrial proteins. In other words, mosaic respiratory chains, whose protein subunits are encoded by two separate genomes, are a strictly necessary feature of eukaryotic cells; eukaryotes could not exist with any other arrangement. The trouble is that the proteins encoded by the two genomes must interact with nanoscopic precision, or electron flow down respiratory chains will be blocked. Any blockage of electron flow in an aerobic world leads to a high rate of ROS leak, a collapse in energy charge (which is to say, an irreversible fall in ATP levels), the oxidation of membrane lipids such as cardiolipin, and the release of cytochrome c. The surprising involvement of cytochrome c in apoptosis (Blackstone and Green, 1999), emerges as an explicit prediction of the hypothesis that eukaryotic cells must undergo functional selection for the compatibility of mtDNA and nuclear genes encoding adjoining respiratory chain subunits (Lane, 2011b). The speed of electron transfer down respiratory chains depends on the distance between redox centres, and slows down by about an order of magnitude per Ångström additional distance, for reasons that relate to the probability of transfer by quantum tunnelling (Moser et al., 2006). A likely consequence of even single nucleotide mutations or polymorphisms in mtDNA would be small misalignments in subunit juxtaposition, slowing electron transfer. Slower electron transfer increases the reduction state of respiratory complexes, making them more reactive with oxygen and therefore increasing ROS leak and susceptibility to apoptosis. Thus, any mismatch between mtDNA and nuclear genes encoding respiratory-chain subunits should increase the risk of apoptosis. Selection for mitonuclear coadaptation necessarily involves oxidative stress (Lane, 2011a; b). It has been argued that selection for mitonuclear coadaptation cannot take place during oocyte development, because at this time the new nuclear background is not known. Selection for mitonuclear coadaptation must therefore take place after fertilization, during development or after birth (Lane, 2011a). A variable apoptotic threshold has profound implications for fertility, fecundity, adaptability,

fitness, aging and age-related disease. The reason is simple. Setting the apoptotic threshold high – meaning a high tolerance of ROS-leak before apoptosis is triggered – enables high fertility and fecundity. Poor mitonuclear match is overlooked, and embryos that would fail to develop in more discerning animals develop full term. Some degree of heteroplasmy (the presence of two or more mtDNA haplotypes in the same individual) is tolerated and indeed can be beneficial, as a range of mtDNA enables greater adaptability to changing environments. However, the offspring are less fit, and more likely to suffer from mitochondrial diseases. They will have lower aerobic capacity. Worst of all, they will leak ROS from their mitochondria at a faster rate, without triggering apoptosis. The outcome is a shorter lifespan, and a greater tendency to oxidative stress and chronic inflammatory conditions linked with aging, such as diabetes, cardiovascular disease and cancer. In short, there is a trade-off between fertility, fecundity and adaptability, on the one hand, and aerobic capacity, life-span and susceptibility to age-related disease on the other (Lane, 2009). The trade-off is mediated by sensitivity to oxidative stress.” (Lane, 2011a)

In mouse, the process in which many mtDNA molecules are discarded and only a few are transmitted to PGCs was thought to be random (Jenuth et al., 1996). However, the study of fitness effects of distinct mtDNA haplotypes (MacRae and Anderson, 1988; Clark and Lyckegaard, 1988; Nigro and Prout, 1990; Fos et al., 1990; Kambhampati et al., 1992; Hutter and Rand, 1995; Kilpatrick and Rand, 1995; García-Martínez et al., 1998; Rand et al., 2001) and statistical tests of neutral models of molecular evolution (Whittam et al., 1986; Excoffier, 1990; Ballard and Kreitman, 1994; Ballard, 2000a; b; Nachman et al., 1994; 1996; Nachman, 1998; Quesada et al., 1999; Rand et al., 1994; 2000; Rand and Kann, 1996; 1998; Templeton, 1996; Wise et al., 1998; Weinreich and Rand, 2000; Blouin, 2000) have identified multi-level selection of mtDNA (Birky, 1995; Bergstrom and Pritchard, 1998; Jacobs et al., 2000; Rand, 2001). The selection of mtDNA variants is likely to depend on the complex interplay of the fusion and fission apparatus, mitophagy regulation, ROS production and antioxidant defences (Skulachev, 1996b; Kanki et al., 2009; Malena et al., 2009; Zhou et al., 2010). Mitochondria from different strains and species of *Drosophila* have been transplanted in various combinations to construct experimental heteroplasmic lines, revealing clear evidence for selection in the cytoplasm (Matsuura et al., 1989; 1991; de Stordeur et al., 1989; de Stordeur, 1997). However, various nuclear backgrounds can have considerable

effects on the selection coefficients of mtDNAs in heteroplasmic cells and germlines (Kilpatrick and Rand, 1995; Doi et al., 1999). It is evident that the mitochondrial genome is subject to strong selective pressure and to assure survival it had to develop strategies to slow down or halt the ratchet. Muller (1964) proposed that asexual genomes (like organellar genomes) will inevitably accumulate deleterious mutations, resulting in an increase of the mutational load, an inexorable, ratchet-like, loss of the least mutated class and extinction. At least two processes are thought to operate to rewind Muller's ratchet in mtDNA (Saccone et al., 2002):

(i) the homoplasmy of mitochondrial DNA molecules during oocyte maturation (Bergstrom and Pritchard, 1998). In metazoans a severe bottleneck, restricting the number of mtDNA molecules passing through the germline, is taking place. This mechanism is essential in maintaining both mitochondrial genetic quality and mitonuclear match (Lane, 2011a; b) over evolutionary time, as it is able to restore genetic homoplasmy among descendants; moreover, the bottleneck improves mitochondrial performance and, over a longer time scale, acts to slow the progression of the ratchet.

(ii) female germ cell atresia (Krakauer and Mira, 1999). Another mechanism related to the mt genetic bottleneck is the female germ cell atresia, which reduces the population of female germ cells to a small fraction of that present in early fetal life; recent studies demonstrated that this process not only assures the selection of high-quality mitochondria, necessary for descendants, but it is also able to retard Muller's ratchet. Indeed, there is a significant positive correlation between the number of offspring and the number of mitochondria in germline cells and a negative correlation between the number of mitochondria in oocytes and the fraction of follicles undergoing atresia. Species with small litters need to have high-quality mitochondria in the oocytes to be sure that descendants are fit for survival; for this reason the mitochondrial bottleneck needs to be more severe. Indeed, this mechanism decreases the number of mitochondria to a level that highlights the difference in functionality among cells: only cells with healthy mitochondria will be able to escape the apoptotic process occurring during atresia.

8.3.1 Mitochondrial homoplasmy

Again Nick Lane (2011a): “Mitonuclear mismatch is unavoidable. The only question is how much can or ‘should’ be tolerated. The basic problem is that the tempo and mode of evolution of the two genomes are quite distinct (see above). Species that need a high

aerobic capacity, such as flighted birds or bats, could not get airborne at all if they did not have an aerobic capacity several-fold higher than even fast runners like the cheetah. On the other hand, rats do not require a high aerobic capacity, and so could presumably tolerate a poorer mitonuclear match. Put another way, there must be an adjustable threshold, above which ROS leak stimulates apoptosis and developmental failure, and below which ROS leak is tolerated, or might even be beneficial as a redox signal (Lane, 2009). In birds, the apoptotic threshold is low: they are sensitive to ROS leak from mosaic respiratory chains and quickly trigger apoptosis. A poor mitonuclear match leads to slow electron flow, high ROS leak and swift apoptosis, translating into infertility and low fecundity. An intolerance of heteroplasmy means a low incidence of mitochondrial disease but also a low adaptability to changing conditions. On the positive side, birds have a high aerobic capacity, a long lifespan and low susceptibility to the chronic inflammatory conditions characteristic of old age in mammals. The difference is not trivial. Pigeons and rats have a similar body size and similar metabolic rate, even a similar foraging lifestyle, to the point that pigeons are often dismissed as flying rats. Far from it. Rats live for 3 – 4 years, pigeons for 35, ten times longer. Their mitochondrial ROS leak is nearly 10-fold lower (Barja, 2007). While this difference makes no sense in terms of the efficiency of respiration (the proportion of ROS leak as a fraction of total oxygen consumption is too small) it makes a big difference in terms of functional selection for mitonuclear match, and it makes a big difference in terms of lifespan and healthspan." (Lane, 2009; 2011a)

In the absence of external factors, heteroplasmy should, theoretically, be the default state for mtDNA under a simple mutation-drift scenario. The high mutation rate coupled with the large population size of mtDNA in mature oocytes would make a state of homoplasmy in any cell, tissue or individual surprising under a simple neutral drift model, in the absence of mechanisms that effectively remove genetic diversity from the mtDNA population (White et al., 2008). A state of heteroplasmy is also reached if paternal mtDNA enters the egg cytoplasm at fertilization, referred to as paternal leakage. In this case, a heteroplasmic state has been achieved in the fertilized oocyte, not via mutation, but due to the coexistence of mitochondria from two unique ancestral lineages. Until recently, paternal leakage was thought impossible as it was widely held that paternal mtDNA did not reach the egg cytoplasm (Ankel-Simons and Cummins, 1996). However, interspecific paternal leakage has been revealed in silkmoths, fruit flies, periodical cicadas and

salmonids (Arunkumar et al., 2006; Sherengul et al., 2006; Ciborowski et al., 2007; Fontaine et al., 2007) and cases of intraspecific paternal leakage include scorpions, fruit flies, and lizards (Gantenbein et al., 2005; Sherengul et al., 2006; Ujvari et al., 2007). However, despite the high mtDNA polymorphism in populations, most individuals appear to be homoplasmic with respect to their mtDNA, i.e. a human individual's mtDNA population is ca. 99.9% identical (Monnat and Loeb, 1985; Lutz et al., 2000). Mice harbouring heteroplasmy showed a significant reduction in metabolic rate, reduced activity and feeding, hyperexcitability and a decreased capacity to learn and remember, even when the two mtDNA types appear to function equally well against the same nuclear background (Jones, 2012; Lane, 2012; Sharpley et al., 2012). Mathematical modelling suggests that uncontrolled heteroplasmy can indeed lower fitness significantly, with approximately 90% of homoplasmic populations achieving 95% fitness, compared with barely 50% of heteroplasmic populations (Lane, 2011b). The existence of two sexes helps to optimize mitonuclear match by generally promoting homoplasmy (Lane, 2011b).

There are reports about individuals that are heteroplasmic with regard to mtDNA (Greenberg et al., 1983; Howell et al., 1992; 1996; Bendall and Sykes, 1995; Comas et al., 1995; Bendall et al., 1996; 1997; Jazin et al., 1996; Marchington et al., 1997; Parsons et al., 1997; Hühne et al., 1998; Lutz et al., 2000; Klütsch et al., 2011). Individuals affected by mtDNA diseases are usually heteroplasmic: most of their tissues and cells have a mixture of both normal and mutant mtDNAs (Poulton et al., 2010). There is also a threshold effect (tissues function normally unless the proportion of mutant mtDNA rises above a particular level) in most diseases. The level of this threshold varies with both tissue and mutation type, usually in the range 50 to 100% mutant mtDNA, but occasionally as low as 10% (Sacconi et al., 2008). Heteroplasmy is conceivable at three levels. These are: (i) The cell: a single cell contains only mitochondria that are homoplasmic, but different cells carry variants. (ii) The mitochondrion: one cell carries different mtDNA haplotypes, but each single mitochondrion is homoplasmic. (iii) The nucleic acid: an individual mitochondrion carries different mtDNA types (Lutz et al., 2000). Pedigree analyses of heteroplasmic individuals in cattle, mice and humans revealed that mtDNA genotypes shift rapidly among offspring and return to homoplasmy in some progeny within a few generations (Hauswirth and Laipis, 1982; Olivo et al., 1983; Ashley et al., 1989; Laipis et al., 1988; Gyllensten et al., 1991; Koehler et al., 1991; Larsson

et al., 1992; Blok et al., 1997; Meirelles and Smith, 1997; Brown et al., 2001; Sharpley et al., 2012), suggesting that a mtDNA bottleneck accounts for the rapid segregation. However, other work suggests that mtDNA heteroplasmy may be stably maintained for multiple generations (Gemmell et al., 1996; Ivanov et al., 1996; Howell and Smejkal, 2000; Taylor and Breden, 2002). A rapid switch from heteroplasmy to homoplasmy, which is occasionally observed in animals, indicates that the mtDNA copy number in the primary oocyte (the size of the inheritance unit) may be as low as one or a few molecules (Koehler et al., 1991; Bendall et al., 1997). To determine the fate of mtDNA mutations, Fan et al. (2008) introduced mtDNAs containing two mutations that affect oxidative phosphorylation into the female mouse germline. The severe ND6 mutation was selectively eliminated during oogenesis within four generations, whereas the milder mutation was retained throughout multiple generations even though the offspring consistently developed mitochondrial myopathy and cardiomyopathy (Fan et al., 2008). On the other hand, in insects it may take 500 generations to return to homoplasmy (Solignac et al., 1984; Harrison et al., 1985; Rand and Harrison, 1986), suggesting the mtDNA bottleneck is considerably less strong in insects compared to mammals (White et al., 2008). The switch to homoplasmy seems to be common only in animals while in plants it usually results in a different level of heteroplasmy (Kmiec et al., 2006).

Different authors proposed that the bottleneck exists at different sites and works through different mechanisms. The assumed stages include the earliest PGCs where the germ cell number is small and there is a low number of mitochondria in each PGC (Jansen and de Boer, 1998; Krakauer and Mira, 1999; Cree et al., 2008; Wai et al., 2008); during expansion of the oogonial population (Jenuith et al., 1996); during postnatal folliculogenesis, during which a clone of mtDNA replicates fast and populates the developing oocyte, diluting out preexisting mtDNA (Wai et al., 2008); during oocyte maturation, during which there is about a 100-fold increase of mtDNA, the amplification may use a limited number of template mtDNA molecules and yield one predominating genotype in the mature oocyte (Hauswirth and Laipis, 1982; Marchington et al., 1998); or during early embryonic development, cells that form the embryonic inner cell mass rather than extraembryonic tissues may receive very different ratios of heteroplasmic mtDNAs (Laipis et al., 1988; White et al., 2008). Most of the blastocyst forms extra-embryonic tissues; thus, only a subset of all cells (the inner cell mass, ICM) will contribute to the developing embryo (Hogan et al., 1986; Fleming et al.,

1992). The apportionment of mitochondria to the ICM constitutes a numerical bottleneck, during which rare mtDNA haplotypes are prone to loss (Bergstrom and Pritchard, 1998). Wai et al. (2008) reported that PGCs possessed a mean of ~280 mtDNA copies and showed by directly tracking the evolution of mtDNA genotypic variance during oogenesis that a genetic bottleneck for the transmission of mtDNA occurs during postnatal oocyte maturation through replication of a subpopulation of genomes. However, another group presented evidence that the mitochondrial bottleneck occurs without reduction of mtDNA content in female mouse PGCs (Cao et al., 2007; 2009). Whether the bottleneck occurs during oogenesis (i.e. during the development of mature oocytes from PGCs), embryogenesis (i.e. in the cleaving embryo from the zygote to the establishment of the germ layers including the PGCs), or both remains uncertain (Jenuith et al., 1996; Smith et al., 2002; Cao et al., 2007; 2009; Cree et al., 2008; Wai et al., 2008). Wolff et al. (2011) measured the genetic variance in mtDNA heteroplasmy at three developmental stages (female, ova and fry) in chinook salmon. A mathematical model estimated the number of segregating units (N_e) of the mitochondrial bottleneck. Values for mtDNA N_e were 88.3 for oogenesis, and 80.3 for embryogenesis. The results suggest that the mechanism underlying the mtDNA bottleneck is conserved between fish and mammals, and showed that segregation of mtDNA variation is effectively complete by the end of oogenesis (Wolff et al., 2011).

The Balbiani body, or mitochondrial cloud, is a transient structure, containing mitochondria, Golgi, endoplasmic reticulum (ER) and RNA, that forms in the young (previtellogenic) oocytes of insects and vertebrates (Guraya, 1979; Cox and Spradling, 2003; Kloc et al., 2004a; Wilk et al., 2005; Pepling et al., 2007; Zhou et al., 2010; Voronina et al., 2011). It has been proposed that in the Balbiani body the best mitochondria for incorporation in the germline are selected (Guraya, 1979; Cox and Spradling, 2003; Kloc et al., 2004a; Pepling et al., 2007; Zhang YZ et al., 2008; Zhou RR et al., 2010; Castellana et al., 2011). Zhou RR et al. (2010) believe that a selective bottleneck occurs in the maturation of oocytes. Based on estimates of the mitochondrial inner membrane potential of mature zebra fish oocytes, they showed that the most efficient mitochondria with high-inner membrane potential tend to be recruited preferentially into the mitochondrial cloud (Zhang YZ et al., 2008; Zhou RR et al., 2010). Different distribution patterns of low- and high-inner membrane potential mitochondria in human and animal oocytes have been reported (Sun et al. 2001; Van Blerkom et al. 2003; Van

Blerkom 2008; Zhang YZ et al., 2008).

8.3.2 Follicle atresia

For mitochondria, the processes of oogenesis, follicle formation and loss constitute a restriction/amplification/constraint event of the kind predicted by L. Chao (1997) for purification and refinement of a haploid genome. Maintaining the integrity of mitochondrial inheritance is such a strong evolutionary imperative that at least some features of ovarian follicular formation, function and loss can be expected to be primarily adapted to this specific purpose (Jansen and de Boer, 1998). In this vein of thought, cumulative evidence indicates that the removal of pathogenic mtDNA mutations occurs during female germline development by purifying selection (Nielsen and Weinreich, 1999; Nielsen, 2001; Fan et al., 2008; Stewart et al., 2008a; b; Poulton et al., 2010; Castellana et al., 2011; Pereira et al., 2011). Krakauer and Mira (1999) considered cellular atresia as a possible response to Muller's ratchet, particularly in birds and mammals. In their view, only a very small number of all primordial follicles (and the primary oocytes inside them) reach maturation during the first stages of fetal life; the others undergo apoptosis. In this way, germ cells carrying "less functional" mitochondrial genomes are removed. In particular, species which produce small numbers of offspring tend to undergo a more severe bottleneck event, in order to guarantee the survival and viability of the (few) members of the future generation. Tracking mtDNA mutations between generations in the murine model, it has been shown that most deleterious mtDNA mutations are removed during germline development, while less detrimental mtDNA mutations are more likely to pass through the female germline and are transmitted to the next generation (Stewart et al., 2008a). Mouse proto-oocytes containing a higher proportion of frameshift mutant mtDNA that severely affected oxidative phosphorylation were eliminated by selection before ovulation (Fan et al., 2008). The authors concluded that taking into account that apoptosis in preovulatory follicles is thought to be induced by oxidative stress (Tsai-Turton and Luderer, 2006), it is conceivable that the proto-oocytes with the highest percentage of severe mtDNA mutations produce the most ROS and thus are preferentially eliminated by apoptosis.

These selection mechanisms are far from being faultless, as human mitochondrial diseases clearly demonstrate. The higher tolerance to mitonuclear mismatch in mammals, compared to birds, appears to play a role (Lane, 2011 a; b). Recent studies have suggested the presumed asexuality of mitochondrial

genomes as responsible for their high mutational load (Jansen and de Boer, 1998; Stewart et al., 2008b). However, asexuality, per se, may not be the primary determinant of the high mutation load in mtDNA. Very little sex and recombination is required to counter mutation accumulation (Pamilo et al., 1987; Charlesworth et al., 1993; Green and Noakes, 1995; Hurst and Peck, 1996; Chasnov, 2000; Keightley and Eyre-Walker, 2000; Bengtsson, 2003; D'Souza et al., 2006; Beukeboom, 2007; Haddrill et al., 2007; D'Souza and Michiels, 2010; Lampert and Scharf, 2010), and recent evidence suggests that mitochondrial genomes do experience occasional recombination (Lunt and Hyman, 1997; Ladoukakis and Zouros, 2001; Burzynski et al., 2003; Rokas et al., 2003; Kraysberg et al., 2004; Piganeau et al., 2004; Barr et al., 2005; Tsaousis et al., 2005; White et al., 2008; Neiman and Taylor, 2009). Instead, a high rate of accumulation of mildly deleterious mutations in mtDNA may result from the small effective population size associated with effectively haploid inheritance (Neiman and Taylor, 2009). The asymmetry in mtDNA inheritance becomes problematic in the case of traits that affect exclusively males and shared traits that, if compromised, have a disproportionately greater effect on males than females (Frank and Hurst, 1996; Zeh and Zeh, 2005). In this instance mutations that harm males but leave females unaffected will escape purifying selection and lead to the accumulation of a mutational load in the mitochondrial genome detrimental to male-specific traits; a scenario described as "mother's curse" (Ruiz-Pesini et al., 2000b; Gemmell et al., 2004; Wolff and Gemmell, 2012).

Conversely, the "internal quality control" of mtDNA takes place in specific physiological conditions (maturation of oocytes) and does not act in all possible situations of energy requirements of the organism (embryo, fetus, adult, restricted diet, cold environment, etc.). Energy demands do differ and are contradictory, imposing specific "trade-offs" for each functional state of the oxidative phosphorylation machinery (Das, 2006).

In *Drosophila*, a selective transfer of a subgroup of mitochondria with some specific feature from nurse cells to a specific position of the oocyte does occur (Cox and Spradling, 2006; Zhou et al., 2010). The colossal purge of female germ cells in humans, mice and *Drosophila* may play an important role in eliminating deleterious mtDNAs if wild-type mtDNA or mtDNA with advantageous characteristics has been selectively transported into the destined oocytes before the purge takes place (Zhou et al., 2010).

The competition between follicles to deliver the oocyte that will be fertilized has a mitochondrial component (Jansen and Burton, 2004). Mitochondria play an important role in nuclear and cytoplasmic oocyte maturation since they provide the main supply of ATP (Krisher and Bavister 1998; Stojkovic et al., 2001). Dysfunctional mitochondria and subsequent low ATP production is one of the major factors that compromise oocyte quality and fertilization (Van Blerkom et al., 1995; Stojkovic et al., 2001; Dumollard et al., 2004; 2006; 2007b; Tamassia et al., 2004; Van Blerkom, 2004; Brevini et al., 2005; Takeuchi et al., 2005; Zeng et al., 2007; Yu et al., 2010). Levels of mtDNA deletions are greater in unselected preovulatory human oocytes than in early embryos (Brenner et al., 1998; Perez et al., 2000), arguing for selection at the ovulation or/and early embryo stage (Jansen and Burton, 2004). Intracytoplasmic injection of 'normal' mitochondria can overcome mitochondrial dysfunctions (Nagai et al., 2004) and inhibit oocyte apoptosis (Perez et al., 2000), while injection of abnormal mitochondria induces oocyte apoptosis (Perez et al., 2007). Selection of functional mtDNA genomes likely involves a mechanism for functional testing to prevent transmission of mutated genomes to the offspring (Stewart et al., 2008a; b). Low mitochondrial DNA content, due to inadequate mitochondrial biogenesis or cytoplasmic maturation, may also adversely affect oocyte fertilizability (Reynier et al., 2001).

The existence of a female germline filter for severely deleterious mtDNA mutations makes evolutionary sense. Assuming that mtDNA variation is pivotal to species adaptation to changing environments and that the uniparental mtDNA cannot generate diversity by recombination, then mtDNA diversity must be generated through a high mutation rate (Ruiz-Pesini et al., 2004; Ruiz-Pesini and Wallace, 2006; Wallace, 2007). However, a high mutation rate would generate many highly deleterious mutations that could create an excessive genetic load and endanger species fitness. This dilemma can be resolved by the addition of a graded filter in the female germline that eliminates the most severe mutations before fertilization (Fan et al., 2008; Stewart et al., 2008a; b; Zhou RR et al., 2010). For such a filter to succeed, multiple cell divisions resulting in a large population of proto-oocytes would be required to segregate out the new mtDNA mutations. Mitochondrial function may also represent a quality control system in the early embryo that will determine whether the embryo proceeds further into development or is quickly eliminated (Dumollard et al., 2007b; Lane, 2011b).

8.4 Gametic selection

According to Lewontin (1970), gametic (or gamete) selection means specifically the differential motility, viability, and probability of fertilization of gametes that arises from their own haploid genotype, independent of the genotype of the parents which formed them. Haploid selection gives the unique opportunity to expose haploid genes to selection in organisms with a predominant diploid stage in the life cycle. In haploid individuals, composed of a single set of chromosomes, all novel adaptive mutations are immediately 'seen' by evolution, and selection is very efficient. In diploids (composed of two sets) or polyploids (multiple sets), mutations generally arise in a single copy that can be partially or completely masked by wild-type alleles. The efficacy of selection depends on the dominance properties of the mutation in question (Orr and Otto, 1994). Selection may act quickly in the case of a fully dominant allele, or slowly if the mutation is recessive and must appear in the same genome in multiple copies before its effects are exposed. This may reduce the rate of adaptation in diploid populations (Gerstein and Otto, 2011) and may prevent the establishment of recessive or partially recessive adaptive mutations (Anderson and Sirjusingh, 2004). Comparing the effect size of 20 adaptive mutations in haploids and homozygous diploids of the budding yeast *Saccharomyces cerevisiae*, Gerstein (2012) found that the same mutations often had a much larger effect in haploids than homozygous diploids. Further, haploidy together with periods of epigenetic stripping during reprogramming (see chapter 10.3.4) can be expected to unmask alleles with deleterious effects. Opportunity for haploid gene expression is limited in eggs given that they spend little or no time in the haploid phase: in many animals the final meiotic division of egg development takes place after fertilization (McCarter et al., 1999), whereas in others it happens just before fertilization (Erickson, 1990). Selection on genes expressed in haploid phases may occur at quite different quantities: in pollen, up to 65% of the genome might be expressed and in spermatids of mammals just 1.3–3.8% (Joseph and Kirkpatrick, 2004). However, expression during the haploid phase is not necessary for haploid selection. Some parts of the genome that are silent in the haploid phase can nevertheless experience haploid selection. The extreme compaction of DNA in sperm is accomplished by protamine 1 and 2 (Fuentes-Mascorro et al., 2000), which interact with specific recognition sites scattered throughout the sperm genome (Gatewood et al., 1987). The number, location and sequence of these sites affects the density and conformation of the DNA in sperm and are likely to be under haploid selection,

even though they are transcriptionally silent (Joseph and Kirkpatrick, 2004). Sperm nuclear chromatin condensation during spermiogenesis is achieved through ROS-induced formation of disulfide bonds between cysteine residues in protamines (Aitken et al., 2004).

During yeast gametogenesis widespread apoptotic-like DNA fragmentation in coordination with an unusual form of autophagy occurs that is most similar to mammalian lysosomal membrane permeabilization and plant autophagic cell death (Eastwood et al., 2012). A remarkable feature of megasporogenesis, as seen in the heterosporous fern *Marsilea* and almost all seed plants, is the regular apoptotic abortion of three of the products of meiosis often shortly after meiosis (Bell, 1996; Wu and Cheung, 2000; Papini et al., 2011).

In *Hydra*, spermatogenesis is associated with massive apoptosis of pre-meiotic spermatocytes and post-meiotic spermatozoa (Kuznetsov et al., 2001). In teleosts, a certain level of apoptosis is normal and although fish spermatogenesis is comparatively efficient in this regard, still 30–40% of all germ cells that could be produced theoretically become apoptotic before differentiating to spermatozoa (Billard, 1969; Vilela et al., 2003; Schulz et al., 2010). In teleosts, apoptotic germ cells have been observed mainly during the spermiogenic phase (Billard, 1969; Vilela et al., 2003). Sertoli cells remove and recycle this material very efficiently, so that cellular debris rarely appears in spermatogenic tubules (Scott and Sumpter, 1989). Indeed, even when a loss-of-function of a protein required during meiosis leads to apoptotic loss of all spermatocytes in zebrafish (Feitsma et al., 2007), the fraction of apoptotic spermatocytes visible in histological sections from mutant males is only ~10% of the total number of spermatocytes, suggesting a rapid clearance of material phagocytosed by Sertoli cells (Schulz et al., 2010). In addition, in many seasonal breeders, Sertoli cells play an important role in the phagocytosis of residual sperm after the spawning season (Billard and Takashima, 1983; Besseau and Faliex, 1994; Grier and Taylor, 1998; Almeida et al., 2008).

The occurrence of spermatogenic cell apoptosis at various stages of spermatogenesis has been reported (Roosen-Runge, 1973; Clermont, 1972; de Kretser and Kerr, 1988; Allan et al., 1992; Kerr, 1992; Shikone et al., 1994; Brinkworth et al., 1995; Callard et al., 1995; Sinha Hikim and Swerdloff, 1999). Degeneration of different types of spermatogonia (A2–A4) and meiotic cells in rats has been reported to result in the depletion of up to 75% of the mature sperm pool (Kerr,

1992; Tapanainen et al., 1993). Overall, during mammalian spermatogenic differentiation, more than half of the differentiating spermatogenic cells die by apoptosis before maturation into spermatozoa (Huckins, 1978; Dunkel et al., 1997; Braun, 1998; Sinha Hikim and Swerdloff, 1999). Only a limited number of apoptotic spermatogenic cells, however, are detectable when testis sections are histochemically examined. This is probably due to the rapid elimination of apoptotic cells by phagocytosis. In fact, electron microscopic studies with rodent testis sections reveal that degenerating spermatogenic cells are engulfed by Sertoli cells (Russell and Clermont, 1977; Chemes, 1986; Pineau et al., 1991; Miething, 1992; Francavilla et al., 2002). Studies have demonstrated the existence of a 'pachytene checkpoint', the triggering of which at late meiotic prophase leads to the elimination of defective germ cells by apoptosis (Roeder and Bailis, 2000). Surprisingly, there is evidence that this checkpoint, compared to spermatogenesis, is missing or less stringent in mammalian oogenesis (Hunt and Hassold, 2002; Pacchierotti et al., 2007), another sign of a relaxed quality control in oogenesis. Gamete phosphatidylserine translocation is a sensitive marker for increased oxidative stress and DNA damage (Limoli et al., 1998; Barroso et al., 2000; Shamsi et al., 2009). Catalysis of selective phosphatidylserine oxidation during apoptosis by cytosolic cytochrome c precedes its translocation from the inner to the outer leaflet of the plasma membrane (Vermes et al., 1995; Kagan et al., 2000; 2002; Tyurina et al., 2000; 2004; Jiang J et al., 2003). This translocation of phosphatidylserine is one of the earliest features of cells undergoing apoptosis (Martin SJ et al., 1995; Rimon et al., 1997). Sertoli cells recognize apoptotic spermatogenic cells through the binding of their surface receptor, class B scavenger receptor type I, to phosphatidylserine that is expressed on the surface of spermatogenic cells during apoptosis (Mizuno et al., 1996; Shiratsuchi et al., 1997; 1999; Kawasaki et al., 2002). These relationships link germ cell redox homeostasis with mutagenesis/DNA damage and ensure the quality control aspect of apoptotic removal that is mediated by ROS-dependent phosphatidylserine externalization. The limitation of trophic testosterone plays an essential role in spermatid apoptosis (Russell and Clermont, 1977; O'Donnell et al., 1994; 1996). The Bcl2 modifying factor (Bmf) is a pro-apoptotic member of the Bcl2 family of apoptosis-related proteins that has been shown to initiate apoptosis in response to the loss of attachment of cells from their basal lamina (anoikis). Experimental reduction in intratesticular testosterone

concentration brings about the death of spermatids that express Bmf as a consequence of their sloughing from Sertoli cells (Show et al., 2004). The ubiquitin-dependent sperm quality control, residing in the epididymal epithelium, has the ability to detect spermatozoa with apoptotic or necrotic DNA, while spermatozoa with defects other than DNA fragmentation are also recognized and ubiquitinated (Sutovsky et al., 2001; 2002).

Mammalian oocytes exhibit increased abnormalities in fertilization, chromosome segregation, cleavage divisions, and stress response with age (Tarin, 1996; Blondin et al., 1997; Goud et al., 1999; te Velde and Pearson, 2002; ESHRE Capri Workshop Group, 2005; Jones, 2008; Tamura et al., 2008). In humans, reproductive cessation occurs a decade before menopause, suggesting that declining oocyte quality, rather than quantity, is the major cause of maternal age-associated infertility and birth defects (ESHRE Capri Workshop Group, 2005). Similarly, several *C. elegans* studies show that oocyte quality is the limiting factor for aging-related reproductive capacity decline (Andux and Ellis, 2008; Luo S et al., 2010; Luo and Murphy, 2011).

The inhibition of phagocytosis in live animals resulted in a decrease in the number of epididymal sperm, indicating that phagocytosis of apoptotic spermatogenic cells by Sertoli cells is required for the efficient production of sperm (Maeda et al., 2002; Nakanishi and Shiratsuchi, 2004).

The differing autosomal recombination rates in males and females, known as the Haldane-Huxley rule (Lenormand and Dutheil, 2005), may be a corollary of the differing mutation rates in male and female gametes keeping mutation and recombination effects separate and exposing the more mutated haploid to different selection pressures than the more recombined haploid. In more than 15% of animal species, most notably in Hymenoptera, normal males are haploid and arise from unfertilized eggs, while females are diploid. In these species the principles of haploid selection concerning beneficial and deleterious mutations extend to the adult period.

8.5 Fertilization selection

Sperm are the most diverse cell type known: varying not only among- and within-species, but also among- and within-ejaculates of a single male (Crean et al., 2012). While the aspects of between-male sperm competition have been widely covered (Short, 1979; Harcourt et al., 1981; Smith, 1984; Birkhead and Møller, 1998; Birkhead, 2000; Simmons, 2001; 2005; Anderson and Dixson, 2002), the issue of sperm

competition within a single male has been rarely taken into account (but see Sivinski, 1984; Manning and Chamberlain, 1994). Already the definition of sperm competition: "competition between the sperm from two or more males for the fertilization of the ova" (Parker GA, 1998) highlights this limited view. However, in the vast majority of taxa, males ejaculate much more sperm than would be required to fertilize each egg. Within-ejaculate variation in sperm phenotype is always present, and often substantial (Immler et al., 2008; Crean et al., 2012) but the adaptive value of this variation so far has remained unclear (Higginson and Pitnick, 2011). Within-ejaculate variation in sperm phenotype is generally attributed to developmental errors during spermatogenesis and/or poor quality control by the male (Hunter and Birkhead, 2002). Sperm numbers will be increased by: (i) the number of loci which affect sperm competitiveness in the haploid state; (ii) the mutation rate; and (iii) the recombination rate (Manning and Chamberlain, 1994). A correlation between recombination rates and sperm numbers is therefore to be expected. Thus, even when a single male mates with a female, sperm competition for fertilizations of the limited number of ova takes place. Sperm of an ejaculate bear a coefficient of relatedness of 0.5 to many or most of ejaculated siblings with quality variation as the basis for sperm selection. Given that sperm have undergone more or less extensive mutagenesis and consecutive quality control, there is harsh selection for the most viable sperm. Female spermicidal reproductive tracts are common in birds, mammals and invertebrates, and might permit females to bias fertilization in favor of robust or preferred sperm (Birkhead et al., 1993b; Holman and Snook, 2006; 2008). In birds, sperm selection occurs in the vagina soon after insemination, with only a few percent of inseminated sperm being retained by the female (Bakst et al., 1994; Birkhead and Brillard, 2007; Calhim et al., 2007). In the promiscuous fowl *Gallus gallus*, where social status determines copulation success, dominant males produce more sperm than subordinates but the quality of dominant males' sperm decreases over successive copulations, whereas that of subordinates remains constant. Experimentally manipulating male social status demonstrated that ejaculate quality is a response to the social environment rather than the result of intrinsic differences between dominant and subordinate males (Cornwallis and Birkhead, 2007). Dominant males increased ejaculate quality in response to female sexual ornamentation, which signals reproductive quality, by adjusting the number and quality of sperm they transferred, whereas subordinate males did not (Cornwallis and Birkhead, 2007). There may also be

selection at the level of the sperm storage structures since the length of sperm and length of the sperm storage structures positively covary across bird species (Briskie and Montgomerie, 1992; 1993; Briskie et al., 1997). Similar patterns have been reported in insects (Dybas and Dybas, 1981; Pesgraves et al., 1999; Morrow and Gage, 2000; Minder et al., 2005) and mammals (Gomendio and Roldan, 1993; Anderson et al., 2006) and have been interpreted as an example of male-female coevolution, possibly mediated by sexual conflict over fertilization.

In mammals, sperm have to survive the physical and chemical stresses within the fairly inimical environment of the female reproductive tract that ensures that only sperm with normal morphology and vigorous motility will be the ones to succeed (Suarez and Pacey, 2006). Basic mammalian biology dictates that survival of a species depends on the ability of sperm to fertilize eggs, which is influenced by many factors. At least in humans, one of these factors is the quality of mitochondria, as they determine the speed of sperm on its way towards the egg (Moore and Reijo-Pera, 2000; Ruiz-Pesini et al., 2000a; b; Jansen and Burton, 2004). This appears to be a race against time, since (i) sperm may be killed by mild acidity and natural osmotic decrease, (ii) a healthy human vagina has a pH of 4.0 to 4.5 and (iii) ejaculate acts as an alkaline buffer for several hours only (Olmsted et al., 2000; Chen and Duan, 2011). On the other hand, the physical contact to the female epithelial cells and the stress to which the spermatozoa are exposed is required for their capacitation (Kervancioglu et al., 1994; Smith, 1998; Ford, 2004). The female spermicidal reproductive tracts require a high sperm/egg ratio so that in hamster a consistent fertilization occurs only when the relative gamete ratio is above $10^{3.5}$ sperm/egg \times ml, due to reduced sperm survival at low sperm concentrations (Cummins and Yanagimachi, 1982; Stewart-Savage and Bavister, 1988). Intriguingly, spermatozoa may form, at least temporary, alliances (Moore et al., 2002; Immler et al., 2007; Pizzari and Foster, 2008; Pitnick et al., 2009; Fisher and Hoekstra, 2010; Higginson and Pitnick, 2011). Apparently, it is advantageous for sperm to cooperate either for faster locomotion (Moore et al., 2002) and/or to withstand the harsh conditions in the female reproductive tract. Male domestic cats appear to use two different reproductive strategies. Compared with normospermic counterparts, teratospermic cats have a higher sperm output achieved by more sperm-producing tissue, more germ cells per Sertoli cell, and reduced germ cell loss during spermatogenesis. Gains in sperm quantity are produced at the expense of sperm quality (Neubauer

et al., 2004). From a 50- to 500-million spermatozoa in a human male ejaculate less than 1000 will find their way to the neighborhood of a competent oocyte in the oviduct of a fertile partner and these should be the 'best of the best' (Suarez and Pacey, 2006; Anand-Ivell and Ivell, 2011). Similarly, outcome of assisted reproductive techniques is predicted by sperm DNA quality (Duran et al., 2002; Morris et al., 2002; Agarwal and Allamaneni, 2004; Sharma et al., 2004).

Another fertilization selection concerns sperm mitochondria. Mammals inherit mitochondria from the mother only, even though the sperm contributes nearly one hundred mitochondria to the fertilized egg. This strictly maternal inheritance of mitochondrial DNA arises from the selective destruction of sperm mitochondria (Hutchinson et al., 1974; Giles et al., 1980) that are tagged by the recycling marker protein ubiquitin (Ciechanover, 1994). This imprint is a death sentence that is written during spermatogenesis and executed after the sperm mitochondria encounter the egg's cytoplasmic destruction machinery (Sutovsky et al., 1999).

Polyandry is widespread, with females of most taxa mating with more than one male (Birkhead and Møller, 1998). When females copulate with multiple males during a single reproductive episode, sperm from these males compete to fertilize the female's ova (Parker, 1970; Dziuk, 1996; Rowe and Pruett-Jones, 2011). Sperm competition offense occurs when a male copulates with a previously-mated female, and can be quantified as the proportion of offspring sired by the second male to mate a female (P2) (Simmons, 2001). Under conditions of sperm competition, male fertilization success is commonly determined by the number of sperm, relative to rival males, transferred during copulation (Laskemoen et al., 2010; Martin et al., 1974; Parker, 1982; Birkhead and Pizzari, 2002; Boschetto et al., 2011). *Drosophila* males produce seminal fluid proteins that have substantial effects on sperm transfer, sperm storage, female receptivity, ovulation, and oogenesis (Wolfner, 1997). P2 appears to be condition-dependent, e.g. affected by rearing conditions of the rival males (Amitin and Pitnick, 2007; McGraw et al., 2007; Clark NL et al., 2012). Social stress and dominance hierarchy also determine the competitive success of inseminations (Montrose et al., 2008; Thomas and Simmons, 2009). Across a diverse range of taxa, comparative and experimental studies have demonstrated that a common evolutionary response to sperm competition is an increase in testes size (Møller, 1991; Harcourt et al., 1995; Hosken, 1997; Stockley et al., 1997; Hosken and Ward, 2001;

Byrne et al., 2002; Simmons and García-González, 2008; Rowe and Pruett-Jones, 2011). In addition to testes size, sperm competition may select for increases in sperm production: species under higher sperm competition have a greater proportion of sperm-producing tissue within the testes (Schultz, 1938; Lüpold et al., 2009; Rowe and Pruett-Jones, 2011). Furthermore, inter- and intra-specific studies suggest that sperm competition is positively associated with greater numbers of sperm (i.e. sperm reserves or ejaculate size) (Stockley et al., 1997; Gage, 1991; Birkhead et al., 1993a; Firman and Simmons, 2010; Rowe and Pruett-Jones, 2011), at least partially because larger testes produce more sperm (Amann, 1970; de Reviers and Williams, 1984; Møller, 1988a; b; 1989).

Sperm swimming velocity is positively correlated with successful fertilizations in a number of vertebrate species. Sperm motility influences paternity success in birds (Birkhead et al., 1999; Donaghue et al., 1999; Burness et al., 2004; Denk et al., 2005; Pizzari et al., 2008), fish (Gage et al., 2004; Gasparini et al., 2010; Boschetto et al., 2011), and mammals (Holt et al., 1989; Moore and Akhondi, 1996; Malo et al., 2005). In 42 North American and European free-living passerine bird species, sperm swimming speed was positively related to the frequency of extrapair paternity (a proxy for the risk of sperm competition) and negatively associated with clutch size (a proxy for the duration of female sperm storage) suggesting both sperm competition and female sperm storage duration as evolutionary forces driving sperm swimming speed (Kleven et al., 2009).

Mollusks and teleosts employ external or internal fertilization. Sperm competition in the course of external fertilization is mainly provided through the sperm number (Yund, 2000). Yet, sperm quality may also play a role. In a marine invertebrate with external fertilization, *Styela plicata*, offspring sired by longer-lived sperm had higher performance compared to offspring sired by freshly-extracted sperm of the same ejaculate (Crean et al., 2012). Sperm longevity is negatively related to sperm length. Mean sperm length is shorter in free spawners compared to teleosts with internal fertilization (Ball and Parker, 1996). Across fish species, there is a positive association between the intensity of sperm competition and sperm swimming speed (Fitzpatrick et al., 2009). In the swordtail *Xiphophorus nigrensis*, an internally fertilized fish with alternative reproductive tactics, males with greater sperm viability sired more offspring than their rival, as predicted if the number of fertilization-capable sperm influences sperm

competition in a numerical raffle (as tickets in a raffle = lottery). In contrast, males with faster swimming sperm sired fewer offspring, but only when sperm were stored prior to fertilization (Smith CC, 2012).

In insects, sperm viability has been shown to influence competitive fertilization success (García-González and Simmons, 2005), and polyandrous species have been shown to have a greater proportion of viable sperm available for ejaculates relative to monandrous species (Hunter and Birkhead, 2002). Female yellow dung flies (*Scathophaga stercoraria*) control the rate of sperm release from the spermatheca, utilizing sperm more efficiently when it is limited. This mechanism is likely to explain the greater female effects on paternity observed in second clutches compared with first clutches (Sbilordo et al., 2009). Similarly, in situ observation of the female reproductive tract in a polyandrous moth revealed that contractions of the spermatheca eject around 50% of sperm from the first mate, explaining the strong last male precedence (Xu and Wang, 2010). Up to 4000 sperm are transferred to a *Drosophila* female during mating but only 25–35% of sperm enter the sperm-storage organs. Before the first egg is ovulated, unstored uterine sperm are expelled (Bloch Qazi et al., 2003). Postcopulatory gametic selection in *D. melanogaster* includes the early release of resident sperm from specialized sperm-storage organs, the heterogeneous distribution of competing sperm proportions in different storage organs and fair raffle sperm use in the seminal receptacle (Manier et al., 2010; Schnakenberg et al., 2012). From a single mating, females can lay between 300 and 400 eggs and remain fertile for nearly two weeks (Schnakenberg et al., 2012). In *C. elegans* hermaphrodites, fertilization occurs in the spermatheca by the first sperm to contact the oocyte. Not every oocyte is fertilized because oocytes are made in excess (Ward and Carrel, 1979). Since apoptosis during gametogenesis only occurs in the female and not in the male germline (Gumienny et al., 1999; Gartner et al., 2000; Jaramillo-Lambert et al., 2010), at least in hermaphrodites, *C. elegans* gamete quality selection may be exerted only in the female germline. Hermaphrodites make smaller sperm than males (LaMunyon and Ward, 1998; 1999). When males copulate with hermaphrodites, they displace the hermaphrodite sperm from the spermathecal walls and preferentially fertilize the oocytes. This preferential fertilization appears to be due in part to inhibition of hermaphrodite sperm fertility by the male sperm (Ward and Carrel, 1979). Moreover, larger sperm outcompete smaller sperm and male sperm competition favors larger sperm (LaMunyon and Ward, 1998; 1999; 2002).

In most entelegyne spiders (e.g., orb web spiders, jumping spiders, and wolf spiders), female genitalia are bilaterally symmetrical with paired copulatory openings, each leading into separate sperm storage organ. The sperm of 2 males could be therefore stored separately, avoiding direct sperm competition (Herberstein et al., 2011). Genital damage in male spiders is surprisingly common in araneoid spiders, including in the genus *Argiope* (Miller JA, 2007). Males break off parts or the entire pedipalp, which then becomes lodged as a plug in the female genitalia, preventing another male from utilizing this copulatory opening (Nessler et al., 2007; Foellmer, 2008; Uhl et al., 2010). Storage in different sites provides the female with a relatively easy mechanism to favor ejaculates of one male over another by selectively storing, activating, or utilizing sperm of one or the other spermatheca (Hellriegel and Ward, 1998; Herberstein et al., 2011). Indeed *A. bruennichi* females favor males that provided longer courtship by allowing them greater paternity shares (Schneider and Lesmono, 2009). Furthermore, female *A. lobata* store less sperm from related males if they fill the second spermatheca (Welke and Schneider, 2009). Male spiders are able to produce secretion in the testis and/or deferent duct, with one or several types of seminal secretion present (Michalik and Uhl, 2005; Michalik and Huber, 2006) that may influence fertilization success (Aisenberg and Costa, 2005).

Polyandry remains one of the most controversial topics in evolutionary biology (Yasui, 1997). This is primarily because in most species, females derive no direct benefits from mating with many males, but frequently incur direct costs (Chapman et al., 1995; Blanckenhorn et al., 2002). Field studies of vertebrates suggest, and laboratory experiments on invertebrates confirm, that even when males provide no material benefits, polyandry can enhance offspring survival (Madsen et al., 1992; Tregenza and Wedell, 1998; 2000; Jennions and Petrie, 2000; Zeh and Zeh, 2001; Ivy and Sakaluk, 2005; Fisher et al., 2006). Superior sperm competitors sire higher-quality young (Hosken et al., 2003; Fisher et al., 2006).

Benthic marine animals also compete for fertilizations (Yund and McCartney, 1994). In angiosperms, the interaction between pollen and stigma is one of the most important stages in the life cycle of a flowering plant, because its outcome determines whether fertilization will occur and thus whether seed will be set. For fertilization to be achieved, pollen must establish molecular congruity/compatibility with the stigma and then, following production of a pollen tube, with the transmitting tissue of the style and ovary as the pollen

tube grows through the pistil to deliver its two sperm cells to an ovule. Gametophytic competition among growing tubes may produce more vigorous or more competitive progeny, apparently because faster growing pollen genotypes, in a pollen-tube race, fertilize ovules first and transmit their metabolic superiority to the seeds (Mulcahy 1974; Lee, 1984; Mulcahy and Bergamini-Mulcahy, 1987; Thomson, 1989; Hormaza and Herrero, 1994; Mulcahy et al., 1996). This process has been linked to the evolutionary success of angiosperm (Mulcahy, 1979). In addition to pollen-tube growth rate selection, maternal sorting of donor pollen has been observed (Marshall and Ellstrand, 1988). Stigmas from various different angiosperms were found to accumulate ROS, predominantly H_2O_2 , constitutively, possibly as a means to select for stress-resistant pollen. ROS/ H_2O_2 amounts appeared reduced in stigmatic papillae to which pollen grains had adhered (McInnis et al., 2006). The measured outcrossing rate is frequently higher than that expected from the relative amounts of self versus cross pollen deposited on the stigma (Husband and Schemske, 1996). This selective filtering of pollen or zygotes can occur in a variety of forms, including the rejection of self pollen or selfed ovules with self-incompatibility (Seavey and Bawa, 1986; Dickinson, 1994; de Nettancourt, 1997; Lipow and Wyatt, 2000), and cryptic self-incompatibility caused by differential pollen-tube growth (Weller and Ornduff, 1977; Cruzan and Barrett, 1993; Jones, 1994; Eckert and Allen, 1997).

8.6 Embryo and offspring selection

Embryo and offspring selection is another level of quality selection.

A general pattern of angiosperm reproduction is that parental provisioning of offspring (seed filling) is delayed until after fertilization. The ability to assess offspring quality establishes the basis for the maternal sporophyte to provision only the highest quality offspring (Temme, 1986). Evidence suggests that higher quality offspring are preferentially provisioned and sired (Bertin, 1982; Bookman, 1984; Bertin and Peters, 1992), the differential provisioning of outcrossed versus selfed embryos or fruits (Stephenson, 1981; Marshall and Ellstrand, 1986; Stephenson and Winsor, 1986; Rigney, 1995; Korbecka et al., 2002), and the death of selfed embryos expressing lethal recessive alleles (Lande et al., 1994; Husband and Schemske, 1996). Offspring of lower quality are selectively aborted in a variety of plants (Andersson, 1993; Kärkkäinen et al., 1999; Ramsey and Vaughton, 2000; Melsner and Klinkhamer, 2001; Korbecka et al., 2002; Berg, 2003). In

gymnosperm such as cycads or conifers as the spruce there are several embryos that engage in an intense life and death competition during their development. Only one embryo reaches its full term of growth to become the seed embryo, while the weaker individuals are aborted in the earlier stages (Buchholz, 1922; Mock and Parker, 1997).

In plants and benthic aquatic invertebrates, a persistent seed bank may be an additional level of zygote selection. In the wild, plant species, particularly annual ones, may have strongly fluctuating population sizes due to poor survival or seed set and, to avoid extinction, have to rely on a persistent seed bank (Lunt, 1990; Thompson K et al., 1997; Bekker et al., 1998). A seed bank has the effect of overlapping the generations of the population, integrating the effects of selection over long periods of time (Templeton and Levin, 1979; Nunney, 2002). Plants are subject to strong interspecific competition that substantially limits seed recruitment (Harradine and Whalley, 1980; Morgan, 1995; Hitchmough et al., 1996; Miriti et al., 2001; Petit and Froend, 2001; Silvertown et al., 2002; Fréville and Silvertown, 2005). Mortality selection on plants is probably strongest at the seed and seedling stages (Huey et al., 2002).

Because variation in maternal investment directly impacts the number of surviving offspring (Williams, 1994), it can have strong implications for the fitness of both parents. The 'differential allocation hypothesis' predicts that parents trade-off their current and future reproduction and that the attractiveness of the mate affects the optimal trade-off between these two components of reproduction (Burley, 1986; 1988; Simmons, 1987; Sheldon, 2000; Harris and Uller, 2009; Pischedda et al., 2011). Female reproductive investment increases when they mate with males of larger size in seed beetles (Fox et al., 1995), dung beetles (Kotiaho et al., 2003), house crickets (Head et al., 2006), crayfish (Galeotti et al., 2006) and Australian rainbowfish (Evans et al., 2010). Also, male attractiveness and ornamentation influences female reproductive investment in several bird species (Burley, 1986; 1988; De Lope and Møller, 1993; Petrie and Williams, 1993; Gil et al., 1999; Cunningham and Russell, 2000; Limbourg et al., 2004; Uller et al., 2005; Velando et al., 2006; Helfenstein et al., 2008). The majority of these examples provided females several opportunities to assess male quality, either by lengthy male–female interactions, nuptial gifts to the female or extensive parental care, enabling females to alter their reproductive investment accordingly. If the reproductive value of some of the young is low, parents might decrease investment to them, and so

either increase the investment given to survivors or enhance their capacity for future reproduction (O'Connor, 1978; Tait, 1980; Gosling, 1986; Wright et al., 1988; Haig, 1990; Mappes et al., 1997).

Intriguingly in both invertebrates and vertebrates, DNA lesions that are carried by spermatozoa can be repaired in the embryo by maternal gene products (Generoso et al., 1979; Brandriff and Pedersen, 1981; Ashwood-Smith and Edwards, 1996; Marchetti et al., 2007). DNA repair does not occur post-meiotically in male *D. melanogaster*, but DNA damage carried in sperm can be repaired post-fertilization in *D. melanogaster* embryos via maternal repair enzymes. Agrawal and Wang (2008) exposed either high or low-condition females to sperm containing damaged DNA and then assessed the frequency of lethal mutations on paternally derived X chromosomes transmitted by these females. The rate of lethal mutations transmitted by low-condition females was 30% greater than that of high-condition females, indicating reduced repair capacity of low-condition females (Agrawal and Wang, 2008).

In many taxa of invertebrates and vertebrates, postfertilization selection includes the cannibalism/killing of eggs and/or newborns by siblings or parents (Polis, 1981; Simmons, 1988; 1997; Smith and Reay, 1991; Elgar and Crespi, 1992; Mock and Parker, 1997; 1998; Hausfater and Hrdy, 2008). *Drosophila* larvae often face high densities and competition for limited food in these ephemeral habitats (Atkinson, 1979; Nunney, 1990). Similar to the selection for sperm motility and speed, this type of selection is often based on hatching speed. As eggs hatch and the larvae develop, food is consumed and waste products produced. High quality individuals with elevated growth rates reduce the availability of food and contaminate the medium, making the environment a harsher place for slower-developing individuals (Bakker, 1961; Dawood and Strickberger, 1969). In aquatic and terrestrial invertebrates and vertebrates that rely on mass spawning and fertilizations, selective survival of high quality larvae and juveniles has been identified (Dobzhansky, 1947; Travis et al., 1985; Houde, 1987; 1997; Haag and Garton, 1995; Sogard, 1997; Searcy and Sponaugle, 2001; Bergenius et al., 2002; Vigliola and Meekan, 2002; Wilson and Meekan, 2002; Marshall et al., 2003; Takasuka et al., 2003; McCormick and Hoey, 2004; Hoey and McCormick, 2004; Marshall and Keough, 2007; Johnson et al., 2010). The exposure of propagules to natural selection is related to the concept of 'selection arenas' (Kozłowski and Stearns, 1989). The selection arena hypothesis—also called progeny choice

hypothesis—has been proposed to explain the observation that many organisms produce more fertilized zygotes than they ever support in growth (Stearns, 1987b; Kozlowski and Stearns, 1989; Bruggeman et al., 2004). It states that overproduction of zygotes could be explained as part of a bet-hedging and quality control mechanism which operates in the following manner: An enlarged array of zygotes is created of which only a genetically superior subset will fully develop; zygotes with a low future fitness fail, while zygotes with a high future fitness thrive. In this way, parental energy for reproduction is invested in the most promising zygotes. Essential in the hypothesis is that the potential members of the next generation are tested at a crucial moment, namely just before substantial parental investment starts. This hypothesis further assumes that (1) zygotes are cheap to produce, (2) parental time, energy and/or risk are invested in the zygotes, (3) offspring vary in fitness, and (4) this fitness difference can be identified. Natural selection will favor such a selection arena only if the benefits of high-quality progeny outweigh the cost of overproduction. Especially if the initial cost of a zygote is low relative to the cost of an independent offspring, zygote overproduction pays off and will skyrocket (Kozlowski and Stearns, 1989). Bell and Koufopanou's (1991) exposure of propagules to natural selection is related to the concept of 'selection arenas'. Yet, Kozlowski and Stearns (1989) missed the point that gamete overproduction is much higher than overproduction of zygotes and, most importantly, that gamete overproduction is subjected to a stringent quality control during sexual selection cascades that act independently of natural selection. Thus, the bet-hedging and quality aspect of zygote/offspring overproduction was only discussed in relation to environmental variability and its natural selection pressures but not in terms of sexual reproduction, its evolutionary rationale, the mutagenic origin of the genetic variability and selection regimes that are unrelated to natural selection, i.e. sexual selection cascades. Due to this oversight, the theory did not allow to dismiss the flawed genetic theories of sexual reproduction (see chapter 18.1), and overall could not contribute much to the debate over the evolutionary rationale of sexual reproduction. In higher taxa with internal fertilizations the action of natural selection in 'selection arenas' has been largely replaced by sexual fertilization- and embryo-selection.

The complex life cycles of many organisms create the potential for interactions between conspecifics that vary greatly in size, age, and experience (e.g., insects, Cameron et al., 2007; amphibians, Eitam et al., 2005; aquatic invertebrates, McCauley and Murdoch, 1987;

scleractinian corals, Edmunds and Elahi, 2007; marine algae, Schroeter et al., 1995; marine fishes, Bjørnstad et al., 1999; Webster, 2004; D'Alessandro et al., 2013). These inter-cohort competitions drive density-dependent juvenile selective bottlenecks. In fishes, juvenile growth and survival is determined by density-dependent competition with conspecific adults, with inter-cohort predation (i.e., cannibalism; Murdoch, 1994; Bjørnstad et al., 1999), and competition for limited resources, such as food or enemy-free space (Szabo, 2002; Samhuri et al., 2009). In marine fishes a high larval growth rate can 'carry-over' to affect fitness of subsequent developmental stages (Searcy and Sponaugle, 2001; Bergenius et al., 2002; Shima and Findlay, 2002; Wilson and Meekan, 2002; McCormick and Hoey, 2004; Holmes and McCormick, 2006; McCormick and Meekan, 2007; Samhuri et al., 2009; Smith and Shima, 2011). In some bird species, parents are rarely capable of rearing all chicks produced, some of which are actively or passively eliminated by either parents or earlier hatching siblings (Nelson, 1978; Stinson, 1979; Edwards and Collopy 1983; Drummond et al., 1986; Simmons, 1988; 1997; Anderson, 1989; Mock and Parker, 1997; 1998; Hausfater and Hrdy, 2008). Mauck et al. (2004) found a positive correlation between early hatching and early breeding success with longevity in a 40-year demographic study of Leach's storm-petrel, *Oceanodroma leucorhoa*.

Selective embryo abortion is also suspected in mammals. Mitochondrial function may well represent a quality control system in the early embryo that will determine whether the embryo proceeds further into development or is quickly eliminated (Dumollard et al., 2007b; Lane, 2011b). Many DNA repair and damage response genes are expressed in early mammalian embryos. DNA repair in the newly fertilized preimplantation embryo is believed to rely entirely on the oocyte's machinery (mRNAs and proteins deposited and stored prior to ovulation) (Zheng et al., 2005; Jaroudi and SenGupta, 2007). Notably, elevated levels of NER, MMR and HR gene transcripts were detected in preimplantation rat embryos developing from DNA-damaged sperm (Harrouk et al., 2000). Embryos possessing greater cellular/molecular damage are consuming more nutrients, such as amino acids for repair processes while embryos with the highest developmental capacity are characterized by a low amino acid turnover (Houghton et al., 2002; Leese, 2002; Brison et al., 2004; Baumann et al., 2007; Sturmey et al., 2009). Low levels of some repair proteins, however, indicate that the embryo's ability to repair DNA damage may be limited (Zheng et al., 2005). Mouse and human appear to prefer

conceptuses incompatible with their own MHC (major histocompatibility complex) antigens (Bolis et al., 1985; Wedekind, 1994). This has been extensively investigated in Hutterite woman, who experience increased fetal losses when married to men with similar human leucocyte antigens (HLA) alleles (Ober, 1999; Ober et al., 1992). In coypu there seems to be selective abortion of entire litters with respect to quality and sex (Gosling, 1986). In female common shrews the large numbers of offspring per litter that often exceed the number that are reared to weaning may be related to patterns of dispersal and inbreeding in this species. Matings between genetically similar individuals occur frequently in natural populations, and females appear unable to avoid costs associated with inbreeding by selecting mates or their sperm on the basis of genetic compatibility. Production of more offspring than are weaned, coupled with multiple mating, may therefore be a strategy to promote sibling competition for maternal investment and hence selection of the most genetically fit young from mixed paternity litters (Stockley and Macdonald, 1998). Reduced litter sizes have been reported to result when male mammals are subjected to a variety of ionizing radiation or heat stress regimes (Jannes et al., 1998; Rockett et al., 2001; Zhu and Setchell, 2004; Fatehi et al., 2006; Yaeram et al., 2006; Paul et al., 2008a). These regimes did not prevent fertilization but did cause apoptosis in the two- to eight-cell stage thus preventing further development of the embryos (Zhu and Setchell, 2004; Fatehi et al., 2006). In humans, less than one-third of fertilized embryos have a chance of surviving up to a term delivery (Ruder et al., 2008). The sporadic miscarriage rate of recognized pregnancies in the general population is about 20 to 30% (Wilcox et al., 1988; Bulletti et al., 1996; Wang X et al., 2003) but based on the assumption that many pregnancies abort spontaneously with no clinical recognition (e.g. Wilcox et al., 1988; Elish et al., 1996; Zinaman et al., 1996), only 50 to 60% of all conceptions advance beyond 20 weeks of gestation (Baird et al., 1986; Wilcox et al., 1988; Norwitz et al., 2001). Using current *in vitro* procedures, less than half of inseminated bovine and human oocytes reach the blastocyst stage (Hardy et al., 1989; Xu et al., 1992; Keskinetepe and Brackett, 1996) and of these many do not implant or attach following embryo transfer. Genetic factors are responsible for most losses in clinically recognized pregnancies and most losses before preclinical recognition (Leigh Simpson, 1999). There is strong evidence for uterine selection against genetically disadvantaged embryos (Warburton et al., 1983; Stein et al., 1986; Neuhäuser and Krackow, 2007). In case of sperm genetic damage, a few

embryos may reach the blastocyst stage, but embryo selection will ensure that most of them will abort before growing to term (Ahmadi and Ng, 1999; Sakkas et al., 1999; Morris ID et al., 2002). However, the incidence of certain birth defects — most notably Down's syndrome — rises with maternal age with strongly accelerating rate when mothers approach menopause (Penrose, 1934; Hook, 1981; Morris JK et al., 2002; 2005). Conventional explanations have focused on a rising production of defective zygotes; in contrast, an evolutionary approach suggests a relaxed maternal screen. Relaxed screening potentially explains the rising incidence of chromosomal abnormalities in live-births, the incidence of normal embryos in spontaneous abortions, and the incidence of spontaneous abortions with maternal age (Kloss and Nesse, 1992; Stein et al., 1986; Forbes, 1997; Neuhäuser and Krackow, 2007). Aneuploidy is a form of stress-inducible mutation in eukaryotes, capable of fuelling rapid phenotypic evolution as bet-hedging strategy (Chen G et al., 2012). Increased levels of cortisol are associated with a higher risk of very early pregnancy loss in humans (Nepomnaschy et al., 2006).

8.7 Sexual selection

Sexual selection is defined as selection arising from competition for access to reproductive opportunities, which can occur either through competition with members of the same sex for access to mates (intrasexual selection) or through mate choice by the opposite sex (intersexual selection) (Andersson, 1994; Borgia, 1979; Clutton-Brock, 2007). Male and female reproductive optima invariably differ because the potential reproductive rate of males almost always exceeds that of females: females are selected to maximize mate 'quality', while males can increase fitness through mate 'quantity' (Clutton-Brock and Vincent, 1991). A dynamic, sexually selected conflict therefore exists in which 'competitive' males are selected to override the preference tactics evolved by 'choosy' females (Gage et al., 2002). Darwin (1859) wrote "Amongst many animals, sexual selection will give its aid to ordinary selection, by assuring to the most vigorous and best adapted males the greatest number of offspring." Sexual selection is that special variety to natural selection which is responsible for the evolution of traits that promote success in competition for mates. Theoretical evaluation of sexual selection suggests that the strength of selection is dependent on the amount of effort that is invested in access to mates (usually by males) versus taking part in other parental activities such as maturing eggs or rearing offspring (Sutherland, 1985; 1987). Mate choice is the process

leading to the tendency of members of one sex to mate nonrandomly with respect to one or more varying traits in members of the other sex (Heisler et al., 1987). Precopulatory sexual selection in animals, in which males (generally) compete to mate with (generally) choosy females has generated traits that promote the transmission of one individual's genes at the expense of another's (Eberhard, 1996; Birkhead and Møller, 1998; Simmons, 2001; but see Bonduriansky, 2009). In many species, females are highly selective when it comes to mating (Darwin, 1871; Bateson, 1983; Andersson, 1994; Kokko et al., 2003). In some of these species, females are congruent in their mate preference for a particular male, while in other species females are incongruent in their preference, with each preferring a different male. Female mate preferences, like male ornaments, are condition dependent, high quality females showing the strongest mate preference (Jennions and Petrie, 1997; Hunt et al., 2005; Cotton et al., 2006).

Sexual selection theory distinguishes between two types of genetic benefits, additive and nonadditive effects, mediated by preferences for good and compatible genes, respectively. Good genes preferences should imply directional selection and mating skew among males, and thus reduced genetic diversity in the population. In contrast, compatible genes preferences should give balancing selection that retains genetic diversity. The least controversial models of female mate choice emerged from resource-based mating systems. In mating systems in which males provide direct benefits to the female or her offspring, such as food or shelter, the answer seems straightforward — females should prefer to mate with males that are able to provide more or better resources. The finding that, based on human mtDNA (transmitted only from mother to child) “The Time to the Most Recent Common Ancestor” is estimated to be twice as long as the one based on the non-recombining part of the Y chromosome (passed from father to son) indicates that in human ancient populations males faced a highly competitive context, while females were facing a much smaller female-female competition (Favre and Sornette, 2012). Females that chose a male based on direct benefits appear to have simultaneously chosen a male of higher genetic quality (Kokko et al., 2003; Hunt et al., 2004). However, there are many other mating systems (and perhaps most mating systems) in which females receive no resources from males (called nonresource-based mating systems), yet females still express a preference among males. For example, in some taxa, males display at fixed courtship, territories known as leks and these males provide only genes (i.e.

sperm) to their mates. A striking characteristic of lek mating is the large variance in males assembled on any one area. On a typical vertebrate lek, as few as 5% of the males may account for as many as 70% of the matings (Bradbury et al., 1985; Höglund and Alatalo, 1995). This congruence appears paradoxical given that a female receives only genes from the male she selects (termed the ‘paradox of the lek’; reviewed in Kirkpatrick and Ryan, 1991; Tomkins et al., 2004).

Good-genes sexual selection, especially viability-based sexual selection, is important in a variety of animal species (Andersson, 1994; Kirkpatrick, 1996; Møller and Thornhill, 1998; Petrie and Kempenaers, 1998; Petrie et al., 1998; Wilkinson et al., 1998; Møller and Alatalo, 1999). The condition-dependence of male ornaments is vindicated by studies showing that the expression of traits, such as tail ornaments and combs in birds, and carotenoid pigmentation in fishes and birds, correlates with condition, particularly immunocompetence, and survival (von Schantz et al., 1989; Milinski and Bakker, 1990; Zuk et al., 1990; Hill, 1991; Houde and Torio, 1992; Nicoletto, 1993; Andersson, 1994; Møller, 1994; Thompson CW et al., 1997). The good-genes models are specifically supported by studies showing that female birds can increase offspring fitness by mating with more ornamented males without obtaining any direct benefits (Norris, 1993; Møller, 1994; Petrie, 1994; von Schantz et al., 1994; Hasselquist et al., 1996). Little genetic variance in fitness traits is expected, however, because directional selection tends to drive beneficial alleles to fixation (Fisher, 1930; Falconer, 1989; Roff, 1997). Nevertheless, evidence shows that genetic variance persists despite directional selection (Houle, 1992; Pomiankowski and Møller, 1995; Rowe and Houle, 1996) and genetic benefits and offspring fitness provided by female choice (Alatalo et al., 1998; Møller and Alatalo, 1999; von Schantz et al., 1999; Jennions et al., 2001; Byers and Waits, 2006; Simmons and Kotiaho, 2007; García-González and Simmons, 2011). A theoretical solution to the lek paradox has been proposed on the basis of two assumptions (Rowe and Houle, 1996): that traits are condition-dependent, and that condition (a summary of characteristics that reflect the general health and vigor of an individual) shows high genetic variance. Condition-dependence as evidenced by sexual ornamentation may be related to immunocompetence, stress resistance and oxidative stress susceptibility (von Schantz et al., 1999; Buchanan, 2000; Velando et al., 2008; Dowling and Simmons, 2009; Cotton, 2009; Monaghan et al., 2009; Helfenstein et al., 2010) and may be used for premating and postmating cryptic choice (Velando et

al., 2008; Cotton, 2009). Various experimental approaches to manipulate or quantify the levels of oxidative stress/damage and ROS production, and then to examine the associations between these parameters and sexual trait expression and immunocompetence (Alonso-Alvarez et al., 2004b; Constantini et al., 2007; Hörak et al., 2007; Kurtz et al., 2007; Pike et al., 2007; Torres and Velando, 2007) found evidence for ROS-mediated sexual selection (Dowling and Simmons, 2009). The condition capture model also predicts that over evolutionary time, the amount of genetic variation for sexual traits should increase as they become increasingly condition-dependent. Such an evolutionary association has been reported across species of stalk-eyed flies (Wilkinson and Taper, 1999). Ultimately, the theory relies on the assumption that condition is influenced by a large number of loci, resulting in a relatively high frequency of mutations in genes coding for condition (Rowe and Houle, 1996). Experiments showed that male courtship rate in the dung beetle *Onthophagus taurus* is a condition-dependent trait that is preferred by females. More importantly, male condition has high genetic variance and is genetically correlated with courtship rate (Kotiaho et al., 2001).

In addition to the female "good gene" mate choice (Møller and Alatalo, 1999; Kokko, 2001; Byers and Waits, 2006), the "compatible gene" mate choice has been proposed (Hamilton and Zuk, 1989; Zeh and Zeh, 1996; 1997; Brown, 1997; Tregenza and Wedell, 2000). Rather than providing good genes that improve offspring fitness traits, these males may be relatively more compatible with the choosing female's genotype (Zeh and Zeh, 1996; Brown, 1997; Tregenza and Wedell, 2000; Mays and Hill, 2004; Kempnaers, 2007). While good genes effects are additive and broadly speaking are expressed independently of the maternal genome, compatibility effects are nonadditive and are determined by the interaction between the parental genotypes (Zeh and Zeh, 1996; 1997). This leads to a key difference between the good genes and compatibility explanations for female choice: while females will usually agree about which males carry good genes, the most compatible male will vary depending on the genotype of the choosing female. Compatibility does, however, not equal with dissimilarity. The relationship between genetic dissimilarity and offspring fitness is such that the highest level of fitness (compatibility) is achieved at intermediate levels of genetic dissimilarity (Bateson, 1983; Wan et al., 2013). Maximal genetic dissimilarity between parents might not yield the highest fitness of offspring (Wegner et al., 2004). The main consequence of mating between genetically dissimilar

partners is increased heterozygosity of offspring (Brown, 1997; Griggio et al., 2011). Genetic heterozygosity can influence fitness via two main mechanisms: either because it avoids unmasking any deleterious recessive alleles carried by either parent (the dominance hypothesis), or because heterozygotes are inherently superior to homozygotes (overdominance: Charlesworth and Charlesworth, 1987). Particularly, disassortative mating preferences for genes of the major histocompatibility complex (MHC) have been observed in fish, reptiles, birds and mammals (Yamazaki et al., 1976; Potts et al., 1991; Brown, 1997; Penn and Potts, 1999; Landry et al., 2001; Aeschlimann et al., 2003; Freeman-Gallant et al., 2003; Olsson et al., 2003; Richardson et al., 2005; Milinski, 2006; Forsberg et al., 2007; Yamazaki and Beauchamp, 2007; Radwan et al., 2008; Agbali et al., 2010; Setchell et al., 2010; Griggio et al., 2011; Reichard et al., 2012). Whatever the underlying mechanism, homozygosity is frequently detrimental to reproductive success, having been shown to reduce hatching success or embryo survival, litter size, and survival of offspring in captive studies (Ralls et al., 1988; Pusey and Wolf, 1996; Bixler and Tang-Martinez, 2006). Accumulating data support the idea that genetic similarity among mating partners also has negative effects on offspring number and survival in the wild (Stockley et al., 1993; Coltman et al., 1998; Crnokrak and Roff, 1999; Keller and Waller, 2002; Slate and Pemberton, 2002). The detrimental effects of inbreeding may continue into adulthood, with inbred individuals suffering a reduction in survival (Jiménez et al., 1994; Keller et al., 1994; Coltman et al., 1999), ability to hold territories (Meagher et al., 2000), and reproductive success (Keller, 1998; Slate et al., 2000; Seddon et al., 2004).

Despite differences between the 2 models of mate choice for genetic quality, recent evidence suggests females might use both cues simultaneously, e.g. via both pre- and postcopulatory mechanisms, when choosing mates (Howard and Lively, 2004; Mays and Hill, 2004; Neff and Pitcher, 2005; Hoffman et al., 2007; Eizaguirre et al., 2009; Kawano et al., 2009) or alternate between the 2 cues (Roberts and Gosling, 2003; Puurtinen et al., 2005; Oh and Badyaev, 2006). Ultimately, optimal female choice and the strength of preference for genetic quality are likely influenced by the variability of heterozygosity and compatibility among potential mates and the relative costs of obtaining indirect benefits (Colegrave et al. 2002a; Roberts et al., 2006; Kempnaers, 2007). Several hypotheses propose that female birds benefit indirectly from extra-pair mating by enhancing the genetic quality of their offspring, through good genes or

genetic compatibility effects (Jennions and Petrie, 2000; Kokko, 2001; Griffith et al., 2002; Neff and Pitcher, 2005). Supporting this idea, recent studies have identified a range of fitness-related traits for which extra-pair offspring are superior to their within-pair half-siblings (Hasselquist et al., 1996; Kempnaers et al., 1997; Sheldon et al., 1997; Johnsen et al., 2000; Charmantier et al., 2004; Schmoll et al., 2005; Freeman-Gallant et al., 2006; Garvin et al., 2006; Bouwman et al., 2007; O'Brien and Dawson, 2007; Dreiss et al., 2008; Fossøy et al., 2008; Losdat et al., 2011). A recent study (Gohli et al., 2013) found that more promiscuous species of passerine birds had higher nucleotide diversity at autosomal introns, but not at Z-chromosome introns. In more promiscuous species, major histocompatibility complex class IIB alleles had higher sequence diversity, and therefore should recognize a broader spectrum of pathogens. The results suggest that female promiscuity in passerine birds targets a multitude of autosomal genes for their nonadditive, compatibility benefits. Also, as immunity genes seem to be of particular importance, interspecific variation in female promiscuity among passerine birds may have arisen in response to the strength of pathogen-mediated selection (Gohli et al., 2013).

Sexual selection may not only act in pre-mating but also in post-mating choice of sperm both following internal and external fertilization (Thornhill, 1983; Thornhill and Alcock, 1983; Eberhard, 1996; Olsson et al., 1996; Newcomer et al., 1999; Reyer et al., 1999; Radwan, 2004; Fisher et al., 2006; Birkhead, 2010). In polyandry, cryptic, post-copulatory female choice might be more likely to generate 'good gene' or 'compatible gene' benefits than female choice of mates based on the expression of secondary sexual traits (Eberhard, 1996; Radwan, 2004; Fisher et al., 2006; Slatyer et al., 2012). Theoretical studies indicate that condition-dependent sexual selection can elevate population mean fitness and accelerate the rate of adaptation, making the feedback between natural and sexual selection a particularly potent force in changing environments (Proulx, 1999, 2001, 2002; Whitlock, 2000; Agrawal, 2001; Siller, 2001; Lorch et al., 2003; Fricke and Arnqvist, 2007; Clark SCA et al., 2012). For instance, sexual selection has been shown to be a key component in the process of speciation (Lande, 1981; West-Eberhard, 1983; Hoy et al., 1988; McMillan et al., 1997; Seehausen et al., 1997; Civetta and Singh, 1999; Dieckman and Doebeli, 1999; Higashi et al., 1999; Panhuis et al., 2001; Kocher, 2004; Boul et al., 2007; van Doorn et al., 2009; Maan and Seehausen, 2011).

However, in well-adapted populations, sexually successful males sired unfit daughters, indicating sexual and natural selection were in conflict. However, in populations containing an influx of maladaptive alleles, attractive males sired offspring of high fitness, suggesting that sexual selection reinforced natural selection (Long et al., 2012). Theoretical and experimental evaluations suggest that a reduction in fitness due to sexual conflict, however, may offset the fitness gain related to sexual selection (Holland, 2002; Arnqvist and Rowe, 2005; Pischedda and Chippindale, 2006; Rundle et al., 2006; Tregenza et al., 2006; Fricke and Arnqvist, 2007; Hall et al., 2008; Whitlock and Agrawal, 2009; Connallon et al., 2010; Hollis and Houle, 2011; Arbuthnott and Rundle, 2012; but see García-González and Simmons, 2011) that may also be modulated by the species' sex chromosome system (Connallon, 2010). On the other hand, sexual selection may be opposed by antagonistic natural selection: antagonistic pleiotropy between male sexual and nonsexual fitness is likely to evolve, ultimately limiting male trait evolution (Hine et al., 2011). Thus, sexually antagonistic genes should weaken the potential indirect genetic benefits of sexual selection by reducing the fitness of opposite-sex progeny from high-fitness parents (Pischedda and Chippindale, 2006).

Using phylogenetic comparative data, indices of sexual selection were found positively related to altitudinal range and habitat range in taxa of birds and in agamid lizards. A plausible interpretation of this pattern was that sexual selection combines synergistically with natural selection, thereby increasing physiological tolerance or the propensity to adapt to novel environments (Badyaev and Ghalambor, 1998; Tobias and Seddon, 2009; Östman and Stuart-Fox, 2011). Moreover, sexual selection allowed a faster removal of deleterious genes from the population (Radwan, 2004; Sharp and Agrawal, 2008; Hollis et al., 2009; Whitlock and Agrawal, 2009). Female choice can actually increase genetic variability by supporting a higher mutation rate in sexually selected traits. Increasing the mutation rate will be selected against because of the resulting decline in mean fitness. However, it also increases the probability of rare beneficial mutations arising, and mating skew caused by female preferences for male subjects carrying those beneficials with few deleterious mutations ('good genes') can lead to a mutation rate above that expected under natural selection (Petrie and Roberts, 2007). From this perspective, the interaction between sexual selection and population mean fitness is positive, potentially leading to broader ecological niches (Badyaev and

Ghalambor, 1998; Proulx, 2002; Tobias and Seddon, 2009), accelerated rates of adaptation (Lorch et al., 2003; Fricke and Arnqvist, 2007), and a reduced likelihood of extinction (Whitlock, 2000). Finally, sexual conflict due to coevolution between the sexes may work to elicit a rapid evolution of reproductive barriers and increased speciation rates (Parker and Partridge, 1998; Arnqvist et al., 2000; Gavrillets, 2000; Martin and Hosken, 2003; McPeck and Gavrillets, 2006) (but see Gage et al., 2002 for contrasting evidence)

9. Coevolutionary dynamics of the germ-soma conflict

Natural selection may be said to be biased in favor of youth over old age whenever a conflict of interests arises.

George C Williams (1957)

Summary

From various biological levels of conflict it has become obvious that conflict breeds antagonistic coevolution that can be described by 'Red Queen' dynamics. Self-reinforcing adaptation/counter-adaptation chain reactions may lead to both a higher mutational robustness and higher evolvability of the genetic network. Conflicts may arise from competition among dividing cell lineages for opportunities to propagate or for access to the germline. Conflicts can also arise among the products of meiosis and between hosts and endosymbionts. A central conflict that has to be mediated in multicellular organisms with a germline-soma division revolves around the issue of resource allocation for both reproduction and somatic tissue maintenance and resolution of the transgenerational 'tragedy of commons' dilemma. The fundamental conflict between germline cells and soma over the transgenerational access to and control over limited resources resulting in somatic aging and death has been discussed recently (Heininger, 2002; 2012).

Evolutionary conflict arises in interactions when the individual optima of interactants cannot be satisfied simultaneously (Parker, 2006). This disparity between optima has been labeled the "battleground" of evolutionary conflict (Godfray, 1995; Cant, 2006; 2012). Invariably, access to and control over limited resources such as food, mates, reproduction, territories, are sources of conflict (Hirshleifer, 1988; Mock and Parker, 1998; Garfinkel and Skapaderas,

2007; Batchelor and Briffa, 2010; Heininger, 2012). Conflict arises at all levels of biological organization (e.g., between genes, cell organelles, cells, individuals, and groups) (Cosmides and Tooby, 1981; Alexander, 1987; Frank, 2003; Adams and Mesterton-Gibbons, 2003; Lachmann et al., 2003; Burt and Trivers, 2006; Garfinkel and Skapaderas, 2007; Reeve and Hölldobler, 2007; Queller and Strassman, 2009). From various biological levels of conflict (e.g. predator/prey, herbivore/plant, competitors, mating partners, host/pathogen, host/(endo)symbiont, mitonuclear, and intragenomic conflicts) it has become obvious that conflict breeds coevolution (Van Valen, 1973; Jaenike, 1978; Hamilton, 1980; Bell, 1982; Rice and Holland, 1997; Zeh and Zeh, 2000; Arnqvist and Rowe, 2002; 2005; Itoh et al., 2002; Rice and Chippindale, 2002; Eberhard, 2004; Hongoh et al., 2005; Lessells, 2006; Pal et al., 2007; Poulsen et al., 2007; Kikuchi et al., 2009; Lively, 2010; Paterson et al., 2010; Wilkins, 2010; Lane, 2011a; b). Mathematical models have shown that by competing with one another, coevolutionary systems evolve at increased rates (Fernández et al., 1998). Both theoretical modeling and ecological evidence indicate that evolutionary dynamics are accelerated by coevolutionary patterns (Dieckmann and Law, 1996; Marrow et al., 1996; Sorenson and Payne, 2001; Rice and Chippindale, 2002; Good-Avila et al., 2006). Thus, coevolution speeds the rate of evolution (Lack, 1947b; Holt, 1977; Brown and Vincent, 1992; Travis, 1996; Lutzoni and Pagel, 1997; Rice and Holland, 1997; Brodie and Brodie, 1999; Thompson, 1999; Abrams, 2000; Doebeli and Dieckmann, 2000; Schluter, 2000a, b; Arnqvist and Rowe, 2002; Itoh et al., 2002; Thompson and Cunningham, 2002; Summers et al., 2003; Buckling and Rainey, 2002a; Eberhard, 2004; Vamosi, 2005; Nosil and Crespi, 2006; Pal et al., 2007; Raffel et al., 2008; Kikuchi et al., 2009; Paterson et al., 2010; Gómez and Buckling, 2011; Heininger, 2012). Also intraspecific competition may lead to coevolutionary processes (Roughgarden, 1972; Rosenzweig, 1978; Gibbons, 1979; Wilson and Turelli, 1986; Doebeli, 1996; Dieckmann and Doebeli, 1999; Drossel and McKane, 2000; Bolnick, 2001; Wichman et al., 2005; Svanbäck and Bolnick, 2007). Van Valen (1973) proposed the Red Queen Hypothesis in which each species is competing in a zero-sum game against others; each game is a dynamic equilibrium between competing species where "no species can ever win and new adversaries grinningly replace the losers." The Red Queen is characterized by a coevolutionary chain reaction: adaptation by species A → counter-adaptation by enemy species B → counter-adaptation by species A → ..., which can lead

to a protracted period of coevolution (Ehrlich and Raven 1964; Vermeij, 1983; 1987; 1994; Arnqvist and Rowe, 2002). As a result, there is selection on each interacting partner to manipulate the trait towards its own optimum and resist such manipulation by the other partner (Lessells, 2006).

Conflicts may have both beneficial and disastrous consequences. The fitness-boosting value of coevolutionary systems has been demonstrated at various levels of biological organization (Spitze, 1991; Spitze et al., 1991; Clarke et al., 1994; Lynch and Spitze, 1994; Reznick et al., 2004a; Fisk et al., 2007; Pal et al., 2007; Paterson et al., 2010). Antagonistic coevolution is a cause of rapid and divergent evolution, and is likely to be a major driver of evolutionary change within and between species. When the bacterium *Pseudomonas fluorescens* and its viral parasite, phage Phi2 coevolved with each other, the rate of molecular evolution in the phage was far higher than when the phage evolved against a constant host genotype (Paterson et al., 2010). Guppies collected from stream environments lacking predators were found to be inferior in every aspect of their life history profile to those evolved in other, nearby sites with predators present (Reznick et al., 2004a). Fitness gains appear to accelerate under the challenge of moderate conflicts. Differences in the evolutionary interests of males and females, a well studied conflict of interest, may provide an important route to speciation (Chapman et al., 1995; Arnqvist and Rowe, 1995; 2005; Chapman and Partridge, 1996; Rice, 1996; 1998a; b; Alexander et al., 1997; Parker and Partridge, 1998; Holland and Rice, 1999; Arnqvist et al., 2000; Gavrillets, 2000; Martin and Hosken, 2003; Chapman, 2006) and, indeed, sexual conflict seems to be a key "engine of speciation" (Arnqvist et al., 2000; Martin and Hosken, 2003). When selection differs between the sexual conflict partners, a mutation beneficial to the one may be harmful to the other (sexually antagonistic) and can interfere with the other's adaptive evolution (Rice, 1984; 1992; 1998b; Chapman et al., 1995). Thus, conflicts may even result in extinction following disruptive selection (Rice, 1984; 1998b; Tanaka, 1996; Parker and Partridge, 1998; Arnqvist et al., 2000; Kisdí et al., 2001; Johansson, 2008; Heininger, 2012).

A parallel evolutionary chain reaction can occur between cell populations or non-allelic genes within the genome of a single organism. Mutation, fusion between different genotypes, and infection by symbionts are the key processes that can introduce genetic heterogeneity into the population of cells that constitutes a multicellular organism. The presence of

genetically distinct replicating units in a multicellular organism can lead to several different kinds of conflict among cell lineages. The conflicts may arise between dividing cell lineages competing for opportunities to propagate or for access to the germline (Buss, 1982; 1985; 1987). Conflicts can also arise among the products of meiosis (Haig and Grafen, 1991), and between hosts and (endo)symbionts (Bell and Koufopanou, 1991; Hurst and Hamilton, 1992; Frank, 1996a; Itoh et al., 2002; Hongoh et al., 2005; Kikuchi et al., 2009). Thus, like host and parasite, the gene products from the conflicting partners are part of the evolving, biotic environment of one another, and they can potentially coevolve in an antagonistic or correlational fashion (Ehrlich and Raven, 1964), via a Red Queen process (Van Valen, 1973; 1974; Stenseth and Maynard Smith, 1984; Vermeij, 1994; Rice and Holland, 1997; Rice et al., 2005; Decaestecker et al., 2007; Schulte et al., 2010). A key characteristic of antagonistic coevolution is that it can lead to a self-reinforcing adaptation/counteradaptation chain reaction that leads to both a higher mutational robustness and higher evolvability of the genetic network (Wagner, 2005a; Lenski et al., 2006; Hintze and Adami, 2008; 2010; Yukilevich et al., 2008; Kartal and Ebenhöf, 2009; Whitacre and Bender, 2010; Fierst, 2011; Whitacre, 2011). That is, it can lead to recurrent, even perpetual, gene substitutions at antagonistically interacting loci and thereby continually drive genetic and phenotypic divergence among related species, isolated populations, cell populations and genetic loci. Accordingly, coevolving populations have significantly higher levels of heterozygosity and allelic diversity (Buckling and Rainy, 2002a; Duncan and Little, 2007; Duffy MA et al., 2008; Koskella and Lively, 2009; Béréños et al., 2011). In general terms, antagonistic coevolution speeds the rate of evolution (Lutzoni and Pagel, 1997; Thompson and Cunningham, 2002; Harvell, 2004; Landry et al., 2005; Decaestecker et al., 2007; Paaby and Schmidt, 2008; Schulte et al., 2010; Fox et al., 2011; Béréños et al., 2012) whenever allelic substitution at one locus selects for a new allele at the interacting locus, and vice versa, so that no stable equilibrium can be achieved, or is only achieved after many iterations. As a consequence, an increased rate of allelic substitution is a footprint left behind by the antagonistic coevolution process (Rice and Holland, 1997; Itoh et al., 2002; Landry et al., 2005; Pal et al., 2007; Paterson et al., 2010; Schulte et al., 2010; Fox et al., 2011).

On all levels of biological organization, competition for limited resources is one of the most pervasive motors of evolution (Darwin, 1859; MacArthur and Levins,

1964; MacArthur, 1970; Pianka, 1974b; Lawlor and Maynard Smith, 1976a; Brown, 1981; Winther, 2005; Kopp and Hermisson, 2006; Fisher and Hoekstra, 2010; Heininger, 2012). Within plants and animals different structures may compete during development for a shared and limited pool of resources to sustain growth and differentiation (Parzer and Moczek, 2008; Sadras and Denison, 2009). Also germ cells and soma compete for resources (Renault et al., 2004), a feature that becomes particularly evident during dietary restriction when reproductive activity is delayed in favor of somatic maintenance (Heininger, 2012).

The idea that parents and their young can be in evolutionary conflict over the amount of parental resources invested in individual offspring was raised by Hamilton (1964) and discussed in more detail by Trivers (1974). Both were the first to realize that natural selection can act in different ways on genes expressed in the parent and in the young. In most animals, the specification of germ cells occurs very early during ontogeny by asymmetric distribution of germ plasm. A multi-level selection theory predicted that a reproductive division of labor is required to evolve prior to subsequent functional specialization. The frequency distribution of division of labor and the sequence of its acquisition confirm that reproductive specialization evolves prior to functional specialization (Simpson, 2012). Thus, organisms without a segregated germline (e.g. plants, benthic aquatic animals), have much less differentiated tissues than unitary animals with a segregated germline. The segregation of the germline underlies the germ-soma conflict that, on the other hand, accelerated the coevolutionary dynamics of taxa.

Many mammals, birds, fishes and insects are found living at densities at the carrying capacity of their environments (Sibly et al., 2005; Brook and Bradshaw, 2006). Populations of vertebrate and invertebrate taxa are in general regulated by the production of adult individuals being a decreasing function of population density (Klomp, 1964; Tanner, 1966; Harrison, 1995; Myers et al., 1995; Kuang et al., 2003; Sibly et al., 2005; Bassar et al., 2010) which explains the relative stability of animal populations that do not increase at rates their fertility would allow. In a variety of insects, birds and mammals, breeding density or parent nutritional stress as proxy of high parent density affect the number and quality of offspring (Anderbrant et al., 1985; Jann and Ward, 1999; Lindström, 1999; Van de Pol et al., 2006; Descamps et al., 2008). In bark beetles, more than 20 offspring per female were produced at the lowest density but only 0.6 per female at the highest density. The offspring from the lowest

density were about 50% heavier than those from the highest density and also the fat content increased with decreasing density. In the next generation, offspring from the highest density produced about half as many progeny as those from the lowest densities, showing an effect of density acting over more than one generation (Anderbrant et al., 1985). When vital rates are influenced by population density, population dynamics become nonlinear. The population is characterized not by an exponential growth rate, but by the existence and stability of equilibria, by bifurcations that occur when stability is lost, and by patterns of dynamics (cycles, quasicycles, chaos) that follow the bifurcations (Neubert and Caswell, 2000; Holland, 1995; Mitteldorf, 2010). As the quality of offspring affects the fitness of parents (see also chapter 3), species should have developed mechanisms of population control which prevent overutilization and destruction of their environment and therefore their own extinction (Christian, 1961).

Exploiters (parasites and predators) are thought to play a significant role in diversification, and ultimately speciation, of their hosts or prey (Darwin, 1859; Lack, 1947b; Schluter, 2000a; b). Exploiters may drive sympatric (within-population) diversification if there are a variety of exploiter-resistance strategies or fitness costs associated with exploiter resistance (Holt, 1977; Brown and Vincent, 1992; Abrams, 2000; Doebeli and Dieckmann, 2000; Schluter, 2000a). Exploiters may also drive allopatric (between-population) diversification by creating different selection pressures and increasing the rate of random divergence (Travis, 1996; Thompson, 1999; Buckling and Rainey, 2002a). Parasites increase diversification between populations through a combination of selection for resistance and chance: the morphotype in which the resistance mutation occurred (which varied between populations) swept to high frequencies and determined subsequent population evolutionary trajectories (Buckling and Rainey, 2002a).

The soma and germline cells are irreversibly dependent on each other by their mutual interests: reproduction of the soma is tied to germline cells and the germ cells require the soma to nurse and brood them and for mating (Heininger, 2012). Current theory suggests that mutualisms are best viewed as reciprocal exploitations that nonetheless provide net benefits to each partner (Nowak et al., 1994; Leigh and Rowell, 1995; Maynard Smith and Szathmáry, 1995; Herre and West, 1997; Doebeli and Knowlton, 1998; Herre et al., 1999; Sachs et al., 2004; Foster and Wenseleers, 2006; Leigh, 2010a; Jones et al., 2012). This view stresses the disruptive potential of

conflicts of interests among the erstwhile partners. The potential for conflicts of interest to shape or destabilize mutualistic associations will depend on the extent to which the survival and reproductive interests of the symbiont align with those of the host (Herre et al., 1999; Jones et al., 2012). Leigh and Rowell (1995) and Leigh (1999, 2010) pointed out that the crucial aspect of the evolution of mutualism is whether partners have a sufficient common interest. As long as partners have a sufficient common interest, they should continue to cooperate, but as soon as conditions change to boost selfish interests, one (or both) of the partners may defect and a struggle rather than a harmonious relationship ensues (van Baalen and Jansen, 2001; Jones et al., 2012). Competition for resources is a common feature of mutualisms (Holland et al., 2005; Holland and DeAngelis, 2010; Jones et al., 2012). Simple models of consumer–resource interactions revealed multiple equilibria, including one for species coexistence and others for extinction of one or both species, indicating that species' densities alone can determine the fate of interactions (Holland and DeAngelis, 2009; 2010).

The conflict between germline cells and the soma has a parasitic/endosymbiotic phenotype being fuelled by the transgenerational conflict over exploitation of limited resources. This conflict underlies the evolutionary programming of postreproductive aging and death of the soma (Heininger, 2012). Importantly, the germ-soma conflict depends on the segregation of germline cells from the soma and should arise in both sexually and asexually reproducing organisms. The twofold 'cost of meiosis' reduces parent–offspring relatedness from 1, in a female that reproduces parthenogenetically, to 0.5 in a sexually reproducing female (Williams, 1975; Uyenoyama, 1984; Rice, 2002). Relatedness may reduce conflict and hence attenuate coevolutionary dynamics (Lessells, 1999; Rankin, 2011). According to a theoretical model presented by Peters and Lively (1999; 2007), antagonistic coevolution can select for recombination. Thus, the germ-soma conflict per se may favor the evolution of sexual reproduction. In a bacterial and *Drosophila* coevolutionary model, deleterious mutations exacted higher costs than under non-coevolutionary conditions (Cooper et al., 2005; Buckling et al., 2006; Young et al., 2009) and increased the rate at which deleterious mutations were purged from the bacterial population (Buckling et al., 2006).

In plants and benthic marine animals that have somatic totipotent stem cells and may reproduce by agametic cloning, the adult body is itself a

reproductive unit that increases its fitness as a function of genet size. Accordingly, plants and immobile animals often exhibit labile sex expression but turn to sexual reproduction under environmental challenges (Harvell and Grosberg, 1988; Romme et al., 1997; Korpelainen, 1998; van Kleunen et al., 2001). The germ-soma conflict and, by consequence, antagonistic coevolution, can be expected to be boosted in sexually reproducing organisms. Theoretical models identified two general properties of antagonistically selected loci (Connallon and Clark, 2012). First, antagonistic selection inflates heterozygosity and fitness variance across a broad parameter range—a result that applies to alleles maintained by balancing selection and by recurrent mutation. Second, effective population size and genetic drift profoundly affect the statistical frequency distributions of antagonistically selected alleles. The efficacy of antagonistic selection (i.e., its tendency to dominate over genetic drift) is extremely weak relative to classical models, such as directional selection and overdominance. Alleles meeting traditional criteria for strong selection ($N_e s \gg 1$, where N_e is the effective population size, and s is a selection coefficient for a given sex or fitness component) may nevertheless evolve as if neutral. The effects of mutation and demography may generate population differences in overall levels of antagonistic fitness variation, as well as molecular population genetic signatures of balancing selection (Connallon and Clark, 2012).

Biotic interactions with 'Red Queen dynamics' often fuel chronic correlational selection, which is strong enough to maintain adaptive genetic correlations. Correlational selection builds favorable genetic correlations through the formation of linkage disequilibrium (LD) at underlying loci governing the traits (Sinervo and Svensson, 2002). However, LD built up by correlational selection are expected to decay rapidly (ie, within a few generations) due to recombination and segregation (Falconer and Mackay, 1996; Futuyma, 1998). Nevertheless, if correlational selection is strong and chronic, substantial linkage disequilibrium can be maintained owing to a balance between recombination, segregation and selection (Hartl and Clark, 1997; Lynch and Walsh, 1998). Thus, correlational selection favors optimal trait combinations (i.e. a single fitness peak). However, correlational selection is broader than this, encompassing fitness ridges or even saddles, with regions in which parallel changes in both traits (i.e. both increase or both decrease) have parallel rather than antagonistic effects on fitness (Phillips and Arnold, 1989; Roff and Fairbairn, 2007). Correlational selection can generate a suite of combinations that

have equal fitnesses rather than a single fitness peak, and this may help to maintain variation in fitness trade-offs (Roff and Fairbairn, 2007). Moreover, it may facilitate evolution in fitness landscapes with its potential peaks and valleys (Gokhale et al., 2009).

10. The redox regulation of gametogenesis: mutagenesis, epigenesis, canalization and gamete quality control

Summary

Reactive oxygen and nitrogen species are signaling molecules: speed and range of signaling, almost unlimited availability and close link to the energy status of the cell are their features. Oxidative/nitrosative stress is the final common pathway of responses to a variety of biotic and abiotic stressors. Gametogenesis is subject to waves of metabolic and oxidative stress that regulate developmental epimutagenesis during primordial germ cell reprogramming, mutagenesis through both oxidative DNA damage and modulation of DNA repair, double strand breaks that are requisite for recombination, canalization by capacitators, and finally apoptosis as ultimate gamete quality assurance. Epigenetic regulatory mechanisms (RNA interference, DNA methylation and histone modifications) are thought to have evolved as defense mechanisms against genomic invaders, such as viruses and transposable elements. The redox-dependent control of transposable element mobility, genetic stability and epigenetic modulation highlights the integrated transgenerational regulation of genotype and phenotype by redox balance.

Two systems are primarily responsible for general reduction-oxidation (redox) regulation, the thioredoxin (TRX) and glutaredoxin/glutathione (GRX/GSH) systems. They maintain the redox cellular homeostasis as well as regulate several cellular processes through a thiol–redox mechanism (Holmgren, 1995; Nakamura et al., 1997; Schafer and Buettner, 2001). Thiol-based redox mechanisms rely on the special properties of Cys residues, which can adopt 10 different sulfur oxidation states from +6 to -2 (the fully reduced state) (Giles et al., 2003; Jacob et al., 2003). Reactive oxygen and nitrogen species are signaling molecules: speed and range of signaling, almost unlimited availability and close link to the

energy status of the cell are their features. Environmental stress is the common denominator of the environmental modulation of a variety of developmental and life-history events (Heininger, 2001, 2012). Oxidative/nitrosative stress is the final common pathway of responses to a variety of biotic and abiotic stressors (Lindquist, 1986; Sanchez et al., 1992; Finkel and Holbrook, 2000; Heininger, 2001; Mittler, 2002; Mikkelsen and Wardman, 2003; Sørensen et al., 2003; Apel and Hirt, 2004; Ardanaz and Pagano, 2006; Rollo, 2007; Miller et al., 2008; Slos and Stoks, 2008; Jaspers and Kangasjärvi, 2010; Steinberg, 2012; Choudhury et al., 2013).

10.1 Mutagenesis

Mutagenesis has two components: generation and repair of DNA damage. Repair of DNA plays a major role in regulating mutant frequency (Klungland et al., 1999; Wang et al., 2006; Ikehata et al., 2007). The accumulation of DNA damage through misrepair or incomplete repair may determine the extent of mutagenesis (Kryston et al., 2011). Importantly, there exists a mutagenic synergism between the ability of RONS to generate DNA damage and their ability to inhibit the repair of this damage (Hu et al., 1995). Mutagens paradoxically favor loss of DNA repair, and the underlying logic comprises the metaphor ‘don’t stop for repairs in a war zone’ (Hu et al., 1995; Breivik, 2001). The key role of RONS in the generation of mutations is well established (Mello-Filho and Meneghini, 1984; Goldstein and Czapski, 1986; Imlay and Linn, 1987; 1988; Ziegler-Skylakakis and Andrae, 1987; Chevion, 1988; Imlay et al., 1988; Kazakov et al., 1988; Tachon, 1989; Blakely et al., 1990; Aruoma et al., 1991a; b; McBride et al., 1991; Juedes and Wogan, 1996; Oikawa and Kawanishi, 1996; Tamir and Tannenbaum, 1996; Rodriguez H et al., 1997; 1999; and see chapter 4.1). Genomic data mining revealed that germline caretakers that maintain DNA integrity/repair gene function are relatively dispensable for survival, and implied that milder (e.g., epimutational) male prezygotic repair defects could enhance sperm variation—and hence environmental adaptation and speciation—while sparing fertility (Zhao and Epstein, 2008). It was concluded that tumor suppressor genes that maintain DNA integrity and repair genes are general targets for epigenetically initiated adaptive evolution (Zhao and Epstein, 2008). One of the manifold relations between oxidative stress and mutagenesis converge in the base excision repair enzyme apurinic/apyrimidinic endonuclease 1 (APE1). APE1 is a key player in its role as a redox signaling factor and in the redox regulation of DNA repair (Luo M et al., 2010; Kelley et al., 2012). APE1 is the main

apurinic/aprimidinic endonuclease in eukaryotic cells, playing a central role in the DNA base excision repair (BER) pathway of all DNA lesions (uracil, alkylated and oxidized, and abasic sites), including single-strand breaks (Tell et al., 2009). APE1 is induced by oxidative stress (Grösch et al., 1998; Ramana et al., 1998) and has a pleiotropic role in controlling cellular response to oxidative stress including mitochondrial function and cell death signaling pathways. APE1 is directly responsible for the control of the intracellular ROS levels through inhibiting the ubiquitous small GTPase Rac1, the regulatory subunit of the NADPH oxidase system (Angkeow et al., 2002; Ozaki et al., 2002). APE1 protein upregulation is associated with an increase in both redox and AP endonuclease activity, followed by an increase in cell resistance toward oxidative stress and DNA damaging agents (Grösch et al., 1998; Ramana et al., 1998; Tell et al., 2005; McNeill and Wilson, 2007; Mitra et al., 2007). APE1 also coordinates recruitment of other DNA-repair proteins involved in BER through a complex network of direct protein-protein interactions and indirect interactions. In addition to its repair function in BER as an AP endonuclease, APE1, in its role as redox factor, regulates a number of transcription factors, including AP-1, Egr-1, tumor necrosis factor- α , NF- κ B, p53, ATF/CREB, HIF-1 α , STAT3, Myb, PEBP2, HLF, NF-Y, nuclear respiration factor 1 (NRF1) and others (Xanthoudakis and Curran, 1992; Xanthoudakis et al., 1992; Huang and Adamson, 1993; Mitomo et al., 1994; Huang et al., 1996; Nakshatri et al., 1996; Akamatsu et al., 1997; Jayaraman et al., 1997; Tell et al., 1998a; b; 2000; 2009; Ema et al., 1999; Gaidon et al., 1999; Hirota et al., 1999; Ueno et al., 1999; Lando et al., 2000; Hall et al., 2001; Cao et al., 2002; Nishi et al., 2002; Ziel et al., 2004; Ando et al., 2008; Bhakat et al., 2009; Ray et al., 2010; Cardoso et al., 2012; Li et al., 2012). Thus, APE1 controls the redox status of several transcription factors that in turn regulate expression of APE1 (Grösch and Kaina, 1999; Fung et al., 2001; 2007; Haga et al., 2003; Pines et al., 2005; Zaky et al., 2008).

The biological activities of APE1 are sensitive to oxidative and nitrosative stress (Qu et al., 2007; Luo M et al., 2010; Kelley et al., 2012; Tang et al., 2012). APE1 DNA repair activity is redox dependent and can be completely abolished by higher ROS levels (Kelley and Parsons, 2001; Azam et al., 2008; Bhakat et al., 2009; Luo M et al., 2010). Paradoxically, an unbalanced increase in APE1 protein leads to genetic instability (Hofseth et al., 2003; Sossou et al., 2005). Overexpression of APE1 protein disrupts the repair of DNA mismatches and results in microsatellite instability (Chang et al., 2005). Elevated APE1 levels

have been demonstrated in a variety of cancers and are typically associated with malignant transformation and progression, aggressive proliferation, genetic instability, increased resistance to therapeutic agents, and poor prognosis (Xu et al., 1997; Evans et al., 2000; Moore DH et al., 2000; Guo and Loeb, 2003; Hofseth et al., 2003; Wang D et al., 2004; Sossou et al., 2005; Yang S et al., 2007; Kim et al., 2013).

Noncytotoxic levels of H₂O₂ dramatically reduced the activities of the human DNA mismatch repair (MMR) system in repairing both single-base and insertion/deletion loop mismatches in a dose-dependent manner (Chang et al., 2002) and suppressed DNA MMR enzyme expression in rheumatoid arthritis (Lee SH et al., 2003). The main defense against the mutagenic effect of 8-oxoG is the BER pathway, which in eukaryotes is initiated by the OGG1 protein, a DNA glycosylase in the BER pathway that catalyzes the excision of 8-oxoG from DNA (Boiteux and Radicella, 2000). Acute oxidative stress results in nearly complete but reversible inactivation of the 8-oxoG DNA glycosylase activity of human OGG1 (Bravard et al., 2006; 2009). Chronic ROS exposure lowers the cellular activity of OGG1 in animal models (Potts et al., 2001; 2003) or in human cells (Youn et al., 2005) resulting from inhibition of gene expression at the transcriptional level. Likewise NO and RONS inhibit various DNA repair pathways (Laval and Wink, 1994; Wink and Laval, 1994; Graziewicz et al., 1996; Laval et al., 1997; Wachsman, 1997; Jaiswal et al., 2001a; b; Phoa and Epe, 2002; Sidorkina et al., 2003; Tang et al., 2012).

Hypoxia induces changes in the expression of several genes involved in DNA repair pathways. Chronic hypoxia induces the epigenetic downregulation of MMR (Jiricny 1998; Edwards et al., 2009). The expression of key genes within the MMR pathway and several critical mediators of HR, BRCA1, BRCA2, and RAD51 is downregulated by hypoxia (Mihaylova et al., 2003; Bindra et al., 2004; 2005a; b; 2007; Koshiji et al., 2005; Meng et al., 2005; Bindra and Glazer, 2007a; b; Bristow and Hill, 2008). BRCA1 is a caretaker gene that is responsible for repairing DNA, and it is able to upregulate several genes involved in the antioxidant response by controlling the activity of the transcription factors Nrf2 and Nf κ B (Benezra et al., 2003; Bae et al., 2004). HIF-1 α is involved in the regulation of genetic instability at the nucleotide level by inhibiting the expression of a variety of DNA repair genes (Kim et al., 2001; Mihaylova et al., 2003; Bindra et al., 2005a; Koshiji et al., 2005; Meng et al., 2005; Shahrzad et al., 2005; To et al., 2005; 2006; Bindra and Glazer, 2007a; Huang LE et al., 2007; Crosby et

al., 2009; Rezvani et al., 2010; Babar et al., 2011). A functional impairment of repair pathways, independent of gene expression, was also involved (Yuan et al., 2000; Bindra et al., 2004; 2005b). Defective MMR is associated with a mutator phenotype (Branch et al., 1993; 1995; Bhattacharyya et al., 1994; Eshelman and Markowitz, 1996). For example, in the absence of a MMR system targeted for oxidatively induced lesions, mutation rate is elevated 1,000 times relative to that of normal cells (Simpson, 1997). Since the same pathway is also responsible for repairing base:base mismatches, defective cells also experience large increases in the frequency of spontaneous transition and transversion mutations (Glaab et al., 1998; Umar et al., 1998; Aquilina and Bignami, 2001).

Downregulation of DNA repair under stress is adaptive at the cellular level. Embryonic stem (ES) cells deficient in DNA mismatch repair responded abnormally when exposed to oxidative DNA damage. ES cells derived from mice carrying either one or two disrupted Msh2 alleles displayed an increased survival following protracted exposures to low-level ionizing radiation as compared with wild-type ES cells. The increases in survival exhibited by ES cells deficient in DNA mismatch repair appeared to have resulted from a failure to efficiently execute cell death (apoptosis) in response to radiation exposure (DeWeese et al., 1998). Loss of MMR renders cells both resistant to the cytotoxicity of H₂O₂ and hypersensitive to the mutagenic effect of this oxidative stress (Lin et al., 2000). Hypoxia, along with its associated low pH, enriches for MMR-deficient cells in the surviving population and makes cells sensitive to some forms of hypoxia-induced genomic instability (Kondo et al., 2001). Hypoxic cells can acquire a mutator phenotype that consists of decreased DNA repair, an increased mutation rate and increased chromosomal instability, a phenomenon which has been well established in tumor progression (Huang LE et al., 2007; Bristow and Hill, 2008).

10.2 Recombination

As mentioned earlier, homologous recombination by itself does not generate sequence polymorphisms. However, recombination does prevent the reduction in variability caused by selective sweeps and sequential bottlenecks, thus increasing the polymorphism in a population (Suerbaum et al., 1998). Meiotic recombination is inherently hazardous because it is initiated by developmentally programmed DSBs at multiple sites in the genome (Keeney, 2007). DSB or free ends require oxidative stress for their generation (Henle and Linn, 1997; Aitken et al., 1998a; Lopes et al., 1998; Wang et al., 1998; Haber, 1999; Kemal Duru

et al., 2000; Karanjawala et al., 2002; Sawyer DE et al., 2003; Barzilai and Yamamoto, 2004). ROS-induced DNA damage is recombinogenic (Brennan and Schiestl, 1998). p53 is activated by multiple cellular stress signals and oxidative stress (Lu and Lane, 1993; Wang and Ohnishi, 1997; Vousden and Lu, 2002; Murray-Zmijewski et al., 2006; 2008; Berns, 2010; Hölzel et al., 2010; Marchenko et al., 2010; Lu et al., 2011) and is involved in the control of meiotic recombination (Rotter et al., 1993; Sjöblom and Lähdetie, 1996; Stürzbecher et al., 1996; Habu et al., 2004; Di Giacomo et al., 2005; Ghafari et al., 2009; Lu et al., 2010). In many, if not most eukaryotes, crossing-over recombination can also occur during mitosis (Pontecorvo and Käfer, 1958). Mitotic recombination during spermatogenesis was observed both in *Drosophila* (Becker, 1974; Dewees, 1982; McKee, 2004; 2009), amphibians (Yamamoto et al., 1999) and mammals (Kelus and Steinberg, 1991; Högstrand and Böhme, 1997; Leeftang et al., 1999; Hsia et al., 2003). Likewise, mitotic recombination occurs in oogenesis of vertebrates and invertebrates (Wieschaus and Szabad, 1979; Busson et al., 1983; Perrimon et al., 1984; Hsia et al., 2003). Single-strand DNA (ssDNA) lesions, double-strand breaks (DSB) or free ends are prerequisites for mitotic and meiotic recombination (Szostak et al., 1983; McGill et al., 1993; Pâques and Haber, 1999; Cromie et al., 2001; Bleuyard et al., 2006). During the meiotic prophase, DSBs are induced in a controlled manner by the action of a specific topoisomerase II variant, Spo11. This protein is conserved from yeast to humans, and its expression is strongly induced in meiotic cells (Sun et al., 1989; Zenvirth et al., 1992; Bergerat et al., 1997; Keeney et al., 1997; 1999; Romanienko and Camerini-Otero, 1999; Celerin et al., 2000; Baarends et al., 2001; Keeney, 2007). Crossing over initiates with the appearance of DSBs in leptotene and is completed by late pachytene (Sun et al., 1989; Mahadevaiah et al., 2001; Zenvirth et al., 2003). The importance of forming DSBs to allow the process of recombination is illustrated by the observation that deletion of Spo11 results in infertility in both sexes. In males, loss of Spo11 results in failure of germ cells to progress beyond the zygotene stage of meiotic prophase and is associated with increased rates of germ cell apoptosis (Baudat et al., 2000; Romanienko and Camerini-Otero, 2000). Meiotic recombination, which promotes proper homologous chromosome segregation at the first meiotic division, normally occurs between allelic sequences on homologues (Keeney, 2007). However, recombination can also take place between non-allelic DNA segments that share high sequence identity. Such non-allelic

homologous recombination can markedly alter genome architecture during gametogenesis by generating chromosomal rearrangements (Sasaki et al., 2010). In humans, DSBs are thought to resolve as crossover events in only 5–25% of the time (Jeffreys and May, 2004). Consequently, SNPs lying near the centre of a recombination hotspot (see chapter 12.2) are liable to be included within gene conversion tracts and will experience much higher effective recombination rates than predicted from crossover rates alone (The International HapMap Consortium, 2007). Meiotic gene conversion has an important role in allele diversification and in the homogenization of gene and other repeat DNA sequence families (Clarke et al., 1982; Jinks-Robertson and Petes, 1985; Powers and Smithies, 1986; Ogasawara et al., 2001; Rozen et al., 2003), sometimes with pathological consequences (Collier et al., 1993; Watnick et al., 1998).

10.3 Epimutagenesis

It is now widely recognized that heritable changes in gene expression can occur without accompanying changes in DNA sequence. Epigenetics refers to a collection of mechanisms and phenomena that define the phenotype of a cell without affecting the genotype (Wolffe and Matzke, 1999; Wolffe and Guschin, 2000; Goldberg et al., 2007). In molecular terms, it represents a range of chromatin modifications including DNA methylation, histone modifications, non-coding RNAs, remodelling of nucleosomes and higher order chromatin reorganization that determine whether, where and when genes are expressed (Jirtle and Skinner, 2007; Mattick, 2012).

Genotoxic stressors have an effect on both the genome and the epigenome (Kovalchuk and Baulch, 2008). From fungi and plants to humans, oxidative stress-dependent cellular differentiation (Sohal et al., 1986; Allen, 1991; 1998; Zs.-Nagy, 1992; Blackstone, 1999; 2009; Heininger, 2001; 2012; Orzechowski et al., 2002; Foyer and Noctor, 2005; de Magalhães and Church, 2006; Gapper and Dolan, 2006; Pitzschke et al., 2006; Hitchler and Domann, 2007; Covarrubias et al., 2008; Nasution et al., 2008; Scott and Eaton, 2008; Owusu-Ansah and Banerjee, 2009; Hernández-García et al., 2010; Vincent and Crozatier, 2010; Sardina et al., 2012) is associated with epigenetic changes. Epigenetic profiles, including DNA methylation, histone modifications, and non-coding RNA-mediated regulatory events, are modifiable during cellular differentiation but are phylogenetically conserved to effect the heritable and long-lasting changes in gene expression (Wu and Sun, 2006; Hitchler and Domann, 2007; Sasaki and Matsui, 2008; Singh et al., 2009; Feng et al., 2010; Hu B et al., 2010; Iorio et al., 2010;

Mahpatra et al., 2010; Ficz et al., 2011; Wu and Zhang, 2011; Briones and Muegge, 2012; Hu et al., 2012; Sabin et al., 2013). A major part of the epigenetic variation is triggered by (oxidative) stress or changes in the environment (Lertratanangkoon et al., 1997; Finnegan, 2002; Labra et al., 2002; Wada et al., 2004; Rapp and Wendel, 2005; Grant-Downton and Dickinson, 2006; Richards, 2006; Choi and Sano, 2007; Bossdorf et al., 2008; Boyko and Kovalchuk, 2008; Mason et al., 2008; Jablonka and Raz, 2009; Turner, 2009; Angers et al., 2010; Halfmann and Lindquist, 2010; Verhoeven et al., 2010a; Flatscher et al., 2012; Grativol et al., 2012). Moreover, if conditions return to their original state, spontaneous back-mutation of epialleles can restore original phenotypes [e.g., in position-effect variegation (Richards, 2006; Flatscher et al., 2012)]. The discovery of position-effect variegation (PEV) by H. J. Muller in 1930 provided the first description of a phenomenon with an underlying epigenetic basis (Wakimoto, 1998).

Epigenetics is closely linked to cellular bioenergetics (Xie et al., 2007; Naviaux, 2008; Smiraglia et al., 2008; Minocherhomji et al., 2012) and is, at least in part, regulated by mtDNA copy number as a component of retrograde signaling from mitochondria to the nucleus. Growth and replication of the nucleus are limited by mitochondrial energy production and thus calorie availability. The regulation of nuclear replication and gene expression by calorie availability is mediated by mitochondrial energetics. This is achieved by coupling of nDNA chromatin structure and function by modification via high energy intermediates: phosphorylation by ATP, acetylation by acetyl-Coenzyme A (ac-CoA), deacetylation by nicotinamide adenine dinucleotide (NAD⁺), and methylation by S-adenosyl-methionine (SAM). Numerous characterized epigenetic marks, including histone methylation, acetylation, and ADP-ribosylation, as well as DNA methylation, have direct linkages to central metabolism through critical redox intermediates such as NAD⁺, SAM, and 2-oxoglutarate (Wallace and Fan, 2010; Cyr and Domann, 2011). SAM is produced in the cytosol by the reaction L-methionine + ATP to give SAM + Pi + PPi. Thus, SAM links energy production to the methylation of lysines and arginines in proteins and cytosines in DNA (Wallace and Fan, 2010). SAM has both antioxidant (Evans et al., 1997; Caro and Cederbaum, 2004) and pro-oxidant (Wang and Frey, 2007) properties. A significant percentage of proteins across all organisms are enzymes that catalyze the redox-dependent transfer of a methyl group from the cofactor SAM to a substrate (Cheng and Blumenthal, 1999; Martin and McMillan, 2002;

Katz et al., 2003; Schubert et al., 2003; Petrossian and Clarke, 2009). Members of this superfamily, the radical SAM enzymes, contain an iron-sulphur (Fe-S) cluster and use SAM to catalyse a variety of radical reactions (Wang and Frey, 2007). Fe-S clusters are used as cofactors by many redox proteins and radical SAM enzymes (Boyd et al., 2009), and are important for electron transfer reactions and gene regulation as they sense changes in redox status and oxidative stress (Beinert and Kiley, 1999; Fontecave, 2006; Outten, 2007; Kaur et al., 2010). Prevalent calories increase ATP, acetyl-CoA, SAM and NADH, causing the modification of histones, the opening of the chromatin, increased gene expression, and the stimulation of growth and reproduction. Reduced calorie levels deplete ATP, ac-CoA, SAM, and increase NAD⁺, reducing histone modification, compacting the chromatin, and reducing gene expression, growth and reproduction (Wallace and Fan, 2010).

10.3.1 DNA methylation

Almost 40 years ago, it was proposed that cytosine DNA methylation in eukaryotes could act as a stably inherited modification affecting gene regulation and cellular differentiation (Holliday and Pugh, 1975; Riggs, 1975). The percentage of methylated cytosines ranges from 0–3% in insects, 2% to 8% in mammals and birds, 10% in fish and amphibians to up to 50% in higher plants (Doerfler, 1983; Adams, 1996). Whereas DNA methylation in plants can occur at C bases in diverse sequence contexts, in mammals DNA methylation occurs almost exclusively in symmetric CpG (C followed by G) dinucleotides and is estimated to occur at ~70–80% of CpG dinucleotides throughout the genome (Ehrlich et al., 1982; Law and Jacobsen, 2010). DNA methyl transferases (DNMTs) fall under two categories: de novo and maintenance (Goll and Bestor, 2005). Patterns of DNA methylation are initially established by the de novo DNA methyltransferases DNMT3A and DNMT3B during the blastocyst stage of embryonic development (Okano et al., 1998b; 1999). These methyl marks are then faithfully maintained during cell divisions through the action of the maintenance methyltransferase, DNMT1, which has a preference for hemi-methylated DNA (duplex DNA in which only one of the two strands is methylated), copying pre-existing methylation patterns onto the newly synthesized DNA strands during DNA replication and repair (Bestor and Ingram, 1983; Bestor et al., 1988; Hermann et al., 2004; Mortusewicz et al., 2005; Chen and Li, 2006; Wu and Zhang, 2010). Both the establishment and maintenance of DNA methylation patterns are crucial for development as mice deficient in DNMT3B or

DNMT1 are embryonic lethal (Li et al., 1992; Okano et al., 1999) and DNMT3A-null mice die by 4 weeks of age (Okano et al., 1999). In general, the presence of DNA methylation, in and around the promoter regions of genes, is associated with gene silencing, and loss of methylation accompanies transcription (Bird, 2002). Exposure to ROS can alter DNA methylation profiles (Panayiotidis et al., 2004; Lim et al., 2008; Tunc and Tremellen, 2009; Donkena et al., 2010; Min et al., 2010; Quan et al., 2011; Ziech et al., 2011). DNA oxidative injury, like other types of DNA damage (alkylation of bases, abasic sites, photodimers, etc.), plays a causal role in the formation of DNA methylation patterns (Weitzman et al., 1994; Cerda and Weitzman, 1997; Wachsmann, 1997; Dalton et al., 1999; Franco et al., 2008; Tunc and Tremellen, 2009). Oxidative stress can cause both DNA methylation and demethylation (Lertratanangkoon et al., 1997; Panayiotidis et al., 2004; Campos et al., 2007; Franco et al., 2008; Lim et al., 2008; Bhusari et al., 2010; Donkena et al., 2010; Min et al., 2010; Quan et al., 2011; Ziech et al., 2011; Bernal et al., 2013). High doses of ionizing radiation, a known inducer of oxidative stress, result in epigenetic modifications in adult mice (Tawa et al., 1998). They also induce genomic instability and the bystander effect, a phenomenon in which nonirradiated cells exhibit radiation damage even though they are not directly exposed (Koturbash et al., 2008; Kovalchuk and Baulch, 2008). The bystander effect is dependent on epigenetic signaling, since targeted disruption of Dnmt1 and Dnmt3a in cultured cells eliminates the transmission of genomic instability (Rugo et al., 2011). Hydroxyl radical-induced DNA lesions, such as 8-oxoguanine (8-oxoG) and 8-OHdG (Kuchino et al., 1987; Weitzman et al., 1994; Turk et al., 1995; Turk and Weitzman, 1995; Cerda and Weitzman, 1997), O6-methylguanine (Tan and Li, 1990; Hepburn et al., 1991) and single stranded DNA (Christman et al., 1995) have all been shown to contribute to decreased DNA methylation by means of interfering with the ability of DNA to function as a substrate for the DNMTs and thus resulting in global hypomethylation (Panayiotidis et al., 2004; Franco et al., 2008). Oxidative damage of parental strand guanines would permit normal copying of methylation patterns through maintenance methylation, while oxidative damage of guanines in the nascent (and unmethylated) strand DNA, one or two bases 3' to the target cytosine, would inhibit such methylation resulting in differences in methylation rates as great as 13-fold (Turk et al., 1995). DNA methylation also appears to affect factors such as chromatin organization (Jones and Wolffe, 1999; Segal and Widom, 2009; Chodavarapu et al.,

2010). Aberrant DNA methylation patterns induced by oxidative insult could therefore further alter oxidative susceptibility of regions of DNA as well as affect DNA repair activity (Evans and Cooke, 2004). DNA hypomethylation affects point mutation rates in mammalian cells (Chan et al., 2001) and elicits an increased rate of rearrangements and gene loss by mitotic recombination (Chen et al., 1998).

An additional modified base, 5-hydroxymethylcytosine (5hmC), has been found to be a normal component of mammalian DNA (Kriaucionis and Heintz, 2009; Tahiliani et al., 2009) and appears to be generated by oxidation of m5C in a reaction catalyzed by the ten eleven translocation (Tet)-family of enzymes (Tahiliani et al., 2009). Tet proteins can convert 5mC into 5hmC, 5-formylcytosine, and 5-carboxylcytosine through three consecutive oxidation reactions. Recent studies have raised the possibility that 5hmC is an intermediate during DNA demethylation and that the Tet family enzymes are critical for this process (Guo et al., 2011; He YF et al., 2011; Ito et al., 2011; Williams et al., 2011; Wossidlo et al., 2011; Wu and Zhang, 2011).

DNA methylation via SAM can also be modulated by mitochondrial function (Wallace and Fan, 2010). ROS can lead to de novo DNA methylation (Campos et al., 2007; Lim et al., 2008; Donkena et al., 2010; Min et al., 2010; Quan et al., 2011; Ziech et al., 2011), e.g. by recruiting histone deacetylase 1 and DNA methyltransferase 1 as well (Lim et al., 2008). The level and pattern of 5-mC are determined by both DNA methylation and demethylation processes (He XJ et al., 2011). Demethylation of DNA can be passive and/or active. Passive DNA demethylation occurs when maintenance methyltransferases are inactive during the cell cycle following DNA replication, which results in a retention of the unmethylated state of the newly synthesized strand. Active DNA demethylation involves one or more enzymes and can occur independently of DNA replication (Zhu, 2009).

These epigenetic modifications constitute a unique profile in each cell and define cellular identity by regulating gene expression. Importantly, DNA methylations are not gene-locus specific and have a substantial stochastic component (Silva et al., 1993, Ushijima et al., 2003; Reiss and Mager, 2007; Raj and van Oudenaarden, 2008; Huang, 2009; Mohn and Schübeler, 2009; Feinberg and Irizarry, 2010; Petronis, 2010). The degree of fidelity in epigenetic transmission is about three orders of magnitude lower than that of DNA sequence (an error rate of 1 in 10^6 and 1 in 10^3 for DNA sequences and DNA modification, respectively) (Ushijima et al., 2003; Laird et al., 2004;

Riggs and Xiong, 2004; Genereux et al., 2005; Fu et al., 2010; Petronis, 2010). The cardinal signs of epigenetic effects on gene transcription are variable expression of a gene in a population of isogenic individuals (variable expressivity) and/or a mosaic pattern among cells of the same type within an individual (variegation) (Whitelaw and Martin, 2001). The term "metastable epialleles" was coined to describe alleles with more than one stable epigenetic state driving variable expressivity and variegation (Rakyan et al., 2002). At each new generation, the establishment of a metastable epiallele's epigenetic state is probabilistic (Peaston and Whitelaw, 2006). Metastable epialleles are most often associated with retroelements and transgenesis, resulting in ectopic or aberrant transcription of nearby genes (Ekram et al., 2012; Faulk et al., 2013). Thus, in addition to genetic variation, epigenetic variation that is higher than genetic variation, represents another level of diversity (Petronis et al., 2003; Wong et al., 2005; Peaston and Whitelaw, 2006; Rakyan and Beck, 2006; Richards, 2006; 2011; Zhai et al., 2008; Lister et al., 2009; Feinberg and Irizarry, 2010; Tal et al., 2010; Verhoeven et al., 2010a; Bell and Spector, 2011; Massicotte et al., 2011; Schmitz et al., 2011; Ekram et al., 2012; Havecker et al., 2012; Faulk et al., 2013). Variation in epigenetic modifications is at least partly independent from variation in the DNA sequence (e.g. Cubas et al., 1999; Cervera et al., 2002; Riddle and Richards, 2002; Keyte et al., 2006; Shindo et al., 2006; Vaughn et al., 2007; Bossdorf et al., 2008). For instance, Cervera et al. (2002) and Vaughn et al. (2007) found large and consistent ecotypic variation of DNA methylation in *A. thaliana* that was not correlated with genetic variation. Keyte et al. (2006) explored DNA methylation polymorphism in 20 accessions of cotton and found that the levels of epigenetic variation greatly exceeded genetically based estimates of variation (Bossdorf et al., 2008).

10.3.1.1 CpG mutation bias

ROS react with 5-methylcytosine to oxidize the 5,6-double bond; the intermediate product, 5-methylcytosine glycol, then deaminates to form thymine glycol. Thymine glycol base pairs with A and results in a C→T transition (Marnett and Plastaras, 2001). There is a large body of evidence implicating cytosine-5 DNA methylation in transition mutations at CpG dinucleotides in vertebrates (Gojobori et al., 1982; Wang et al., 1982; Li et al., 1984; Bulmer, 1986; Cooper and Krawczak, 1990; Sved and Bird, 1990; Laird and Jaenisch, 1996; Yang et al., 1996a; O'Neill and Finette, 1998; Chan et al., 2001). Methylated CpGs are mutational hotspots and undergo mutation

at a higher rate than the 4 unmodified bases. Cytosine methylation followed by a spontaneous deamination event creating TpG or CpA dinucleotides induces 40–70% of all spontaneous somatic mutations of the multiple classes at CpG and CpNpG sites and flanking nucleotides (Razin and Riggs, 1980; Holliday and Grigg, 1993; Mazin, 2009; Cooper et al., 2010). The net result is that methyl-CpGs mutate at 10–50 times the rate of C in any other context (Coulondre et al., 1978; Bird 1980; Duncan and Miller, 1980; Razin and Riggs 1980; Bulmer, 1986; Sved and Bird, 1990; Walser and Furano, 2010), or of any other base (Hwang and Green, 2004). In both eukaryotes (Fryxell and Zuckerkandl, 2000; Galtier et al., 2001; Birdsell, 2002) and prokaryotes (Birdsell, 2002), mutation processes produce more AT mutations than GC mutations, which may, at least in part, be compensated by the GC-biased gene conversion system (Marais, 2003). With much higher efficiency than other types of mutational events, CpG deamination events can create new transcription factor-binding sites in promoters of human genes, transposons, and in genomic regions bound by key transcription factors, contributing to variability in gene regulation (Zemojtel et al., 2009; 2011). That in vertebrates the mutation of cytosine to thymine (C→T) in the context of CpG dinucleotides has the highest rate among all base substitutions, is reflected in the ongoing genomic depletion of CpG dinucleotides and has led to a decrease in frequency of amino acids coded by CpG dinucleotides in organisms with CpG methylation (Sved and Bird, 1990; Jones PA et al., 1992; Schorderet and Gartler, 1992; Yang et al., 1996b; Pfeifer, 2006). Notably, in humans CpG dinucleotides occur at a frequency ~21% of that predicted by random chance (International Human Genome Consortium, 2001).

Fully 30–40% of all human germline point mutations are thought to be methylation-induced even though the CpG dinucleotide is under-represented (Jones PA et al., 1992). Thus, CpG transition mutations are responsible for approximately one-third of all human hereditary disease mutations (Cooper and Krawczak, 1990). CpG transition mutations represent the single most common type of somatic point mutation of the p53 gene in human cancer (Greenblatt et al., 1994; Hollstein et al., 1994; Denissenko et al., 1997; Hussain and Harris, 1999; Pfeifer, 2000). CpG transition mutations are the most common type of point mutation found in mutation assays *in vivo* and *in vitro* (Jackson-Grusby et al., 1997; O'Neill and Finette, 1998; Ikehata et al., 2000; Ono et al., 2000). Work with cytosine-5 methyltransferases has shown that the enzymes themselves can contribute to deamination of

cytosines in the target recognition sequence e.g. under conditions involving a limiting supply of the methyl donor S-adenosylmethionine (Shen et al., 1992; Laird and Jaenisch, 1994; Bandaru et al., 1996; Zingg et al., 1996; Okano et al., 1998a; b; 1999). There is a repair mechanism which specifically recognises G•T mismatches, and replaces thymine with cytosine. However, this repair is not fully efficient, because the 5mC→T transition mutation occurs about 10 times as frequently as other transitions (Holliday and Grigg, 1993). CpG deamination has been ascribed a role in silencing of transposons and induction of variation in regional methylation. CpG deamination events can create transcription factor-binding sites with much higher efficiency than other types of mutational events (Zemojtel et al., 2009; 2011).

Comparison of the human and chimpanzee genomes has shown that 14% of the single amino acid changes are due to the biased instability of CpG sequences, which can be subject to methylation and thence to mutations (Misawa et al., 2008). The methylation of CpGs is a major contributing factor to mutation in RB1, a gene in which allelic inactivation leads to the developmental tumor retinoblastoma (Mancini et al., 1997). Intriguingly, the CpG content is strongly correlated with a higher rate of neutral mutation at non-CpG sites (Walser et al., 2008; Walser and Furano, 2010), which suggests that CpGs play a role in influencing the mutation rate of DNA not containing CpG, perhaps by influencing the chromatin conformation surrounding the CpG and making it more accessible to other modifying processes. Furthermore, CpG content also appears to influence the type of mutation that occurs, with a higher ratio of transition-to-transversion mutations observed in parallel with the non-CpG mutation rate (Walser and Furano, 2010).

However, there are local exceptions to the hypermutability of CpG sequences. Short sequences (~1kb) in which CpGs appear in high density in a mostly unmethylated form are termed CpG islands (CGIs) (Antequera and Bird, 1993). CGIs, though only representative of a fraction of all CpG dinucleotides, occur in the promoter sequences of a vast number of human genes (Illingworth and Bird, 2009; Illingworth et al., 2010). These islands are thought to persist based upon methylation status; since they remain largely unmethylated, minimal deamination takes place and the islands maintain their integrity. On the other hand, a subset of CGIs appear to have tissue-specific roles due to cell type-specific DNA methylation at CGIs during differentiation (Deaton et al., 2011; Deaton and Bird, 2011).

10.3.2 Histone modifications

Histone modifications including acetylation, methylation, ADP-ribosylation, SUMOylation, phosphorylation, ubiquitylation, and deamination are other redox-dependent key mechanism in transcriptional regulation, which are well conserved through a host of plant and animal species (Bird and Wolffe, 1999; Kornberg and Lorch, 1999; Cheung et al., 2000; Strahl and Allis, 2000; Jenuwein and Allis, 2001; Rice and Allis, 2001; Turner, 2002; Verdin et al., 2003; Bode and Dong, 2005; Causevic et al., 2006; Kondo, 2009; Sundar et al., 2010; Cyr and Domann, 2011). The “histone code” hypothesis has been formulated to account for the vast capacity of histones for transient information storage on top of DNA sequence (Strahl and Allis, 2000; Jenuwein and Allis, 2001; Musselman et al., 2012). Histone modifications have both active and repressive effects on chromatin function (Chen et al., 1999; Strahl et al., 2001; Wang H et al., 2001; Arney et al., 2002; Cowell et al., 2002; Erhardt et al., 2003; Reik et al., 2003; Kourmouli et al., 2004; Lepikhov and Walter, 2004; Liu et al., 2004; Yu MC et al., 2006; Berger, 2007; Klose and Zhang, 2007; Lin H et al., 2010; Musselman et al., 2012). For instance, a common mark associated with active chromatin is the trimethylation of histone 3 (H3) at lysine 4 (K4), or H3K4me3, which is often found at promoters of actively transcribed genes (Black et al., 2012). Conversely, marks associated with silenced heterochromatin include di- and trimethylated H3K9, as well as trimethylation of H3K27 (Black et al., 2012). Histone methylation patterns define the vast majority of mammalian recombination hotspots (Borde et al., 2009; Buard et al., 2009; Grey et al., 2011; Ségurel et al., 2011; Smagulova et al., 2011). It is generally assumed that chromatin condensation and gene repression are linked to the activity of histone deacetylases (HDAC), whereas chromatin relaxation and the promotion of gene expression involve the activity of histone acetyltransferases (HAT) (Davie and Spencer, 1999). Acetylation by HATs of specific lysine residues on the N-terminal tail of core histones results in uncoiling of the DNA and increased accessibility to transcription factor binding. In contrast, histone deacetylation by HDAC represses gene transcription by promoting DNA winding thereby limiting access to transcription factors. ROS are involved in histone acetylation and deacetylation and their balance (Rahman et al., 2002; 2004; Tomita et al., 2003; Ito et al., 2004; Adcock et al., 2005; Sundar et al., 2010). Accumulating evidence suggests that an epigenetic cross-talk, i.e. interplay between DNA methylation and histone modification, is involved in the process of gene transcription and gene silencing (Fuks, 2005; Viré et al., 2006; Rush et al., 2009; Margueron and Reinberg,

2011). The hierarchical order of events and dependencies leading to gene silencing, however, remains largely unknown. While some studies suggest that DNA methylation patterns guide histone modifications during gene silencing, other studies argue that DNA methylation takes its cues primarily from histone modification states (Causevic et al., 2006; Vaissière et al., 2008; Kondo, 2009). H3K9 methylation, for example, is a prerequisite for DNA methylation in *Neurospora crassa* and guides maintenance DNA methylation in *Arabidopsis* (Malone and Hannon, 2009; Law and Jacobsen, 2010).

Recent evidence links hypoxia-elicited oxidative stress and epigenetic regulation via histone methylation/demethylation and acetylation/deacetylation (Kato et al., 2004; Maltepe et al., 2005; Chen et al., 2006; Johnson and Barton, 2007; Beyer et al., 2008; Johnson et al., 2008; Wellmann et al., 2008; Pollard et al., 2008; Baccarelli and Bollati, 2009; Xia et al., 2009; Yang J et al., 2009; Krieg et al., 2010; Watson et al., 2010; Zhong et al., 2010). ROS have been shown to inhibit binding of methyl-CpG binding protein 2, a critical epigenetic regulator that recruits cytosine methyl transferases and histone deacetylases to DNA (Valinluck et al., 2004). It is becoming increasingly apparent that epigenetics plays a crucial role in the cellular response to hypoxia relayed by the hypoxia-induced transcription factor (HIF) family (Wellmann et al., 2008; Watson et al., 2010). This includes the role of epigenetics in both the stabilization and binding of HIF to its transcriptional targets, the role of histone demethylase enzymes following direct HIF transactivation, and the impact of hypoxic environments on global patterns of histone modifications and DNA methylation (Pollard et al., 2008; Watson et al., 2010). In addition to the traditional transcriptional regulation by HIF, recent studies have shown that epigenetic modulation such as histone methylation, acetylation, and DNA methylation can change the regulation of the response to hypoxia (Mimura et al., 2011).

The epigenetic, selectable variation might enable a lineage to adapt and “hold” the adaptation until genetic changes take over; thus, the heritable epigenetic variations in protein architecture pave the way for genetic adaptation (True et al., 2004; Sangster et al., 2004; Jablonka and Raz, 2009).

10.3.3 Noncoding RNA

Around 70 to 90% of the genome is transcribed in a variety of eukaryotes from fission yeast to humans (Carninci et al. 2005; Cheng et al. 2005; Willingham and Gingeras 2006; Birney et al., 2007; Wilhelm et al.

2008; Bühler, 2009) and plants (Chekanova et al., 2007; Matzke et al., 2009). Most of the transcripts correspond to nonprotein-coding (nc) RNAs of unknown function. Increasing evidence suggests, however, that the ncRNAs themselves and/or the act of transcription play key roles in establishing and maintaining the epigenetic architecture of eukaryotic genomes. In some cases, long ncRNAs are involved directly in recruiting chromatin factors (Nagano et al., 2008; Pandey et al., 2008; Lee, 2012), whereas in other instances they are processed by the RNAi machinery to generate short interfering RNAs that guide chromatin modifications to homologous regions of the genome (Kloc and Martienssen, 2008; Bühler, 2009). Small non-coding RNAs (sncRNAs), ranging from 19 to 30 nucleotides (nt) in length, constitute a large family of regulatory molecules with diverse functions in invertebrates, vertebrates, plants, and fungi (Bartel, 2004; Nakayashiki, 2005; Großhans and Filipowicz, 2008; Kawaji and Hayashizaki, 2008). The growing family of small RNAs, including microRNA (miRNA), small interfering RNA (siRNA), piwi-interacting RNA (piRNA), repeat-associated-siRNA (rasiRNA) and heterochromatic small RNA (hcRNA), forms the most abundant class of endogenous RNA in metazoans (Joly-Tonetti and Lamartine, 2012), but has also been characterized in plants, unicellular algae (Zhao et al., 2007), DNA viruses (Pfeffer et al., 2004) and, controversially, in retroviruses (Klase et al., 2007). All of the known sncRNA species have been found to be abundantly expressed in the testis (Aravin et al., 2006; Girard et al., 2006; Grivna et al., 2006a; b; Kim, 2006; Lau et al., 2006; Ro et al., 2007a; b; Kuramochi-Miyagawa et al., 2010; Linsen et al., 2010; Song R et al., 2011) and play critical roles in testicular development and spermatogenesis in mice (Deng and Lin, 2002; Hayashi et al., 2008; Kuramochi-Miyagawa et al., 2008; Ma et al., 2009; Frost et al., 2010; Korhonen et al., 2011; Romero et al., 2011; Pillai and Chuma, 2012). Although a variety of small RNAs have a host of functions in germline cells (e.g. Zhou X et al., 2010), here my focus is on miRNA and piRNA. MicroRNA (miRNA) was discovered nearly 20 years ago in *C. elegans* (Lee et al., 1993; Wightman et al., 1993). miRNAs are ~22-nt-long non-coding RNAs (Lagos-Quintana et al., 2001; Lau et al., 2001; Lee and Ambros, 2001) that regulate gene expression in eukaryotes and have been identified in various organisms including primates, rodents, birds, fish, worms, flies and viruses (Cullen, 2006; Kim and Nam, 2006; Ibanez-Ventoso et al., 2008). In metazoa, miRNAs target the RNA-induced silencing complex (RISC) usually to the 3' untranslated region of mRNA

genes in a sequence-specific manner leading to mRNA cleavage (RNA interference). Or they target transcripts that are being translated, leading to inhibition of translation or changes in mRNA stability (Ambros, 2004; Bartel, 2004; Rana, 2007). miRNA-mediated translational repression is a reversible process in mammalian cells. The miRNA mode of action seems to be more of a fine-tuning of expression rather than degradation of mRNA, a mechanism by which RNA interference works (Engels and Hutvagner, 2006). Recently it was shown that miRNAs have the potential to activate translation under certain conditions (Henke et al., 2008; Jopling et al., 2008; Orom et al., 2008) and have the ability to switch from translational repression to translational activation in cell-cycle-arrested cells (Vasudevan et al., 2007; 2008; Vasudevan and Steitz, 2007). miRNAs are currently thought to regulate the expression of most genes and consequently play critical roles in the coordination of a wide variety of processes, including differentiation, proliferation, metabolism, inflammation and cancerogenesis (Pasquinelli and Ruvkun, 2002; Bartel and Chen, 2004; Karp and Ambros, 2005; Miska, 2005; Kloosterman and Plasterk, 2006; Bushati and Cohen, 2007; Schetter et al., 2010).

Many miRNA genes were found to be evolutionarily conserved and this was thought to be a general characteristic of miRNAs. However, a number of nonconserved miRNAs have been recently discovered (Bentwich et al., 2005). miRNA controlled genes evolve under extremely high constraints and are more likely to undergo intense purifying selection than other genes (Chen and Rajewsky, 2006; Hertel et al., 2006; Sempere et al., 2006; Prochnik et al., 2007; Saunders et al., 2007; Heimberg et al., 2008; Nielsen et al., 2009). Importantly, after a positive selection-driven allele replacement is over, positive selection transforms into negative selection (Bazykin and Kondrashov, 2011). miRNAs are estimated to comprise 1%–5% of animal genes (Bartel, 2004; Bentwich et al., 2005; Berezikov et al., 2005), making them one of the most abundant classes of regulators: e.g., there are more than 1,000 miRNAs in humans (Bentwich et al., 2005; Berezikov et al., 2005; Xie et al., 2005; Rigoutsos et al., 2006) that are conserved throughout evolution with constitutive or spatially and temporally regulated expression. Target site predictions (Enright et al., 2003; Rajewsky, 2006) reveal that these human miRNAs have the potential to regulate thousands of human genes. Computational analyses suggest that a single transcript may be regulated by multiple miRNAs (Lindow and Gorodkin, 2007) and that each miRNA can target tens to hundreds of transcripts (Baek et al., 2008; Selbach et

al., 2008), leading to the conclusion that miRNAs as a whole regulate the expression of at least 30% of human gene transcripts (Lewis et al., 2005; Rajewsky, 2006).

Recent evidence indicates that ncRNAs play an important role in both the generation and repair of DSBs (Shaham et al., 1999; Adamo et al., 2012; Adamo and Volpe, 2012). The DNA-damage response is a signaling pathway that originates from a DNA lesion and arrests cell proliferation. Evolutionarily conserved, ncRNA have been shown to function in the DNA-damage response (Francia et al., 2012; Liu and Lu, 2012; Tang and Ren, 2012; Kang HC et al., 2013). DSBs trigger production of ~21-nucleotide small RNAs from sequences flanking DSB sites in Arabidopsis, Drosophila and human cells (Michalik et al., 2012; Wei et al., 2012). Mutations in proteins involved in the biogenesis of DSB-induced small RNAs caused significant reduction in DSB repair efficiency (Wei et al., 2012). The small RNAs can repress homologous sequences in trans and may therefore—in addition to putative roles in repair—exert a quality control function by clearing potentially truncated messages from genes in the vicinity of the break (Michalik et al., 2012).

10.3.4 Epigenetic reprogramming

Epigenetic reprogramming is the process by which most genomic methylation patterns are erased and re-established in a sex-specific fashion. The methylation status of plant genomes was thought to be not reset each generation to the same degree as mammalian genomes are, and a considerable proportion of the methylation marks are stably transmitted across generations (Cervera et al., 2002; Riddle and Richards, 2005; Vaughn et al., 2007). However, more recent evidence suggests that epigenetic reprogramming also occurs in plant gametogenesis (Gehring et al., 2009; Hsieh et al., 2009; Slotkin et al., 2009; Jullien and Berger, 2010; Gutierrez-Marcos and Dickinson, 2012; Jullien et al., 2012). Importantly, epigenetic modifications, such as DNA methylation, are not entirely erased between generations and could underlie transgenerational epigenetic inheritance (Hadchouel et al., 1987; Reik, et al., 1987; Sapienza et al., 1987; Swain et al., 1987; Kearns et al., 2000; Sutherland et al., 2000; Lane et al., 2003). Two periods of mammalian epigenetic reprogramming have been detected: during primordial germ cell (PGC) migration (Hajkova et al., 2002; Yamazaki et al., 2003; Seki et al., 2007) and immediately after fertilization when the paternal genome is preferentially and actively demethylated (Monk et al., 1987; Mayer et al., 2000; Oswald et al., 2000; Abdalla et al., 2009; Okada et al., 2010;

Smallwood and Kelsey, 2012). In the mouse male germline, the establishment of novel methylation marks for imprinted genes begins around day 15.5 post conceptionem, but is finished only after birth (Davis et al., 1999; 2000; Li JY et al., 2004). The SAM radical domain (see chapter 10.3) is involved in the **active** process of paternal genome demethylation (Okada et al., 2010). After fertilization, the one-cell zygote undergoes several cell divisions that ultimately lead to formation of the blastocyst. During this developmental period, maternally contributed DNMT1 is excluded from the nucleus (Carlson et al., 1992) and the maternal genome undergoes **passive** DNA demethylation (Li, 2002). A gradual loss of DNA methylation occurs with each cell division (Monk et al., 1987) in a replication-dependent manner (Howlett and Reik, 1991). During germ cell development, epigenetic reprogramming resets parent-of-origin based genomic imprints and restores totipotency to gametes. In PGCs, epigenetic reprogramming occurs on a genome-wide scale, which includes demethylation of DNA and remodeling of histones and their modifications (Reik et al., 2001; Surani, 2001; Hajkova et al., 2002; 2008; 2010; Li, 2002; Allegrucci et al., 2005; Morgan et al., 2005; Ohinata et al., 2006; Sasaki and Matsui, 2008; Feng et al., 2010; Popp et al., 2010; Guibert et al., 2012; Smallwood and Kelsey, 2012). Demethylation in PGCs is global and encompasses genic, intergenic and transposon sequences, with a median methylation level of 16.3% and 7.8% in male and female mouse PGCs, respectively (Popp et al., 2010). Methylation levels in fetus, embryonic stem cells and sperm are high (73.2–85%), whereas those in placenta are intermediate (42.3%) (Popp et al., 2010). PGCs at the endpoint of reprogramming have therefore attained a unique epigenetic state, with genome-wide demethylation of DNA, and loss of the repressive histone marks H3K9me2 and H2A/H4R3me2 together with H2AZ, as well as loss of the active histone mark H3K9ac (Seki et al., 2007; Hajkova et al., 2008; Popp et al., 2010; Guibert et al., 2012). DNA hypomethylation can impart genomic instability with elevated mutation rates, an increased rate of rearrangements and microsatellite slippage, activation of endogenous retroviral elements and gene loss by mitotic recombination (Jähner et al., 1982; Chen et al., 1998; Gaudet et al., 2003; Eden et al., 2003; Kim M et al., 2004; Wang and Shen, 2004; Howard et al., 2008). A link between DNA hypomethylation, chromosomal and genomic instability and carcinogenesis has been established (Chen et al., 1998; Saito et al., 2002; Fan et al., 2003; Kisseljova and Kisseljov, 2005; Shvachko, 2009; Kanai, 2010).

A recent study in *C. elegans* highlights the importance

of reprogramming between generations (Daxinger and Whitelaw, 2012). Mutants that are null for the H3K4me2 demethylase *spr-5* (the mammalian orthologue is KDM1A) exhibit progressive sterility over many generations (Katz et al., 2009). This sterility correlates with the misregulation of genes in spermatogenesis and the transgenerational accumulation of H3K4me2, suggesting that H3K4me2 needs to be cleared between generations.

Ectopic expression of the reprogramming factors Oct4, Sox2, Klf4, and c-Myc or Oct4, Sox2, and Klf4 allows the reprogramming of somatic cells to a pluripotent state (Takahashi and Yamanaka, 2006; Park et al., 2008; Hochedlinger and Plath, 2009; Yamanaka and Blau, 2010; Okita and Yamanaka, 2011). This reprogramming-induced pluripotency allows important inferences on the processes and states of PGC and embryonal reprogramming. There is a direct link between epigenetic reprogramming and increased DNA DSBs (González et al., 2013). p53 integrates several stress response pathways and coordinates the cellular response to a wide range of insults (Vazquez et al., 2008). A key role of p53 in PGC early mammalian embryo reprogramming has been identified (Kanatsu-Shinohara et al., 2004; Menendez et al., 2010). In contrast, wild type p53 operates in preventing reprogramming in somatic cells (Kawamura et al., 2009; Tapia and Schöler, 2010; Yi et al., 2012). Reprogramming to a pluripotent state has been shown to increase the number of cells with phosphorylated histone H2AX nuclear foci, one of the earliest cellular responses to DSBs (Huang and Darzynkiewicz, 2006; Kawamura et al., 2009; Marion et al., 2009; Müller et al., 2012; González et al., 2013). Demethylation of DNA involves potentially mutagenic DNA modifications that need to be processed through DNA repair mechanisms (Teperek-Tkacz et al., 2011; González et al., 2013). Thus, efficient reprogramming requires key homologous recombination genes, including *Brca1*, *Brca2*, and *Rad51* (González et al., 2013) and possibly additional DNA repair pathways (Fong et al., 2011). Overall, reprogramming increases genomic instability and is mutagenic (Mayshar et al., 2010; Ramos-Mejia et al., 2010; Blasco et al., 2011; Gore et al., 2011; Hussein et al., 2011; Laurent et al., 2011; Pasi et al., 2011; Chen Z et al., 2012; Liang et al., 2013b; González et al., 2013). Importantly, single cell transcriptional profiling revealed an increased heterogeneity of reprogrammed pluripotent stem cells (Narsinh et al., 2011).

BORIS is a sperm cell-specific protein and cancer/testis gene (see chapter 7.3.2) with an 11-zinc-finger domain which interacts with

demethylases to remove DNA methylation patterns by epigenetic reprogramming during the final round of mitosis in spermatogenesis (Klenova et al., 2002; Loukinov et al., 2002; Vatolin et al., 2005). Tet protein-mediated oxidative loss of 5mC and prevention of unwanted DNA methyltransferase activity is central to PGC and early mammalian embryo epigenetic reprogramming (Wossidlo et al., 2011; Wu and Zhang, 2011; Xu et al., 2011). Studies in plants (Choi et al., 2002; Gong et al., 2002; Kapoor et al., 2005; Zhu, 2009), zebrafish (Rai et al., 2008) and mammalian cells (Barreto et al., 2007; Zhu, 2009; Cortellino et al., 2011) have suggested that active DNA demethylation can occur through various DNA repair mechanisms. DNA demethylation in the mouse PGCs is mechanistically linked to the appearance of single-stranded DNA breaks and the activation of the BER pathway (Hajkova et al., 2010). The most commonly recognized effect of global hypomethylation is to facilitate genomic instability (Gaudet et al., 2003; Kim M et al., 2004; Hoffmann and Schulz, 2005; Weber and Schübeler, 2007; Daskalos et al., 2009), probably mediated by hypomethylated genome-associated replication-independent DNA DSB error-prone repair (Pornthanakasem et al., 2008; Kongruttanachok et al., 2010). The importance of maintaining methylation on various types of repeats has been demonstrated in a number of methyltransferase-deficient systems. DNA methylation in mammals is associated with repeat stability: demethylation of minor satellites, subtelomeric satellites, microsatellites and selfish repeats appears to lead to increased recombination and mutagenesis and may result in destabilisation of the chromosome on which they reside (Hansen et al., 1999; Okano et al., 1999; Xu et al., 1999; Bourc'his and Bestor, 2004; Guo G et al., 2004; Kazazian, 2004; Kim M et al., 2004; Wang D et al., 2004; Gonzalo et al., 2006; Lees-Murdock and Walsh, 2008). During PGC reprogramming single-copy and imprinted sequences are demethylated, presumably by active demethylation (Kafri et al., 1992; Brandeis et al., 1993; Lee J et al., 2002; Hajkova et al., 2002; Popp et al., 2010). Some demethylation of the transposable Intracisternal A Particle (IAP) elements and Line1 elements was also reported in PGC (Walsh et al., 1998; Hajkova et al., 2002; Lane et al., 2003). In PGC both IAP and Line1 methylation was fairly high (74%, 65%), followed by considerable demethylation of Line1 (to 32% and 17% for combined male and female cells, respectively) and IAPs (40% male, 34% female) (Lane et al., 2003).

A high level of transposable element (TE) expression is usually deleterious for the organism, leading to double-strand breaks, disruption of protein-coding

genes, mutations, chromosomal rearrangements, and an alteration in the transcription network (McClintock, 1951; Kidwell and Lisch, 2001; Gilbert et al., 2002; Symer et al., 2002; Deininger et al., 2003; Kazazian, 2004; Brookfield, 2005; Gasior et al., 2006; Hedges and Deininger, 2007; Goodier and Kazazian, 2008; Konkel and Batzer, 2010). Notably, the number of L1-induced DSBs is greater than the predicted numbers of successful insertions, suggesting a significant degree of inefficiency during the integration process (Gasior et al., 2006; Hedges and Deininger, 2007). Therefore, activity of mobile elements is thought to be under keen cellular control. Transcription of TEs is restricted in most differentiated tissues of animals and plants due to silencing directed by DNA methylation, histone modifications and RNA interference (Matzke et al., 2000; Miura et al., 2001; Slotkin and Martienssen, 2007; Law and Jacobsen, 2010). In germline cells, silencing of selfish elements is realized through short RNA species, called both repeat associated short interfering RNAs (rasiRNAs) (Aravin et al., 2003; 2004; Saito et al., 2006; Vagin et al., 2006; Gunawardane et al., 2007) and Piwi-interacting RNAs (piRNAs) (Brennecke et al., 2007). piRNAs of 24–32 nt in length are longer than 21–22 nt siRNAs derived from dsRNA or 21–23 nt endogenous miRNAs (Aravin et al., 2003; 2004). piRNAs play evolutionarily conserved roles in the regulation of TE in insects, mammals and zebrafish (Aravin et al., 2007a; Carmell et al., 2007; Houwing et al., 2007) and are accumulated specifically in the germline (Aravin et al., 2006; Girard et al., 2006; Lau et al., 2006; Klenov et al., 2007). Approximately 80% of the piRNAs in *D. melanogaster* are rasiRNAs with a sequence that corresponds to or is complementary to TEs (Aravin et al., 2003; Saito et al., 2006; Brennecke et al., 2007; Gunawardane et al., 2007). piRNAs are specialized in the repression of mobile elements in the germline (Aravin et al., 2006; Girard et al., 2006; Grivna et al., 2006b; Saito et al., 2006; Vagin et al., 2006; Brennecke et al., 2007). A lack of piRNAs has been shown to be incompatible with normal spermatogenesis and male fertility (Carmell et al., 2007; Frost et al., 2010; Zheng et al., 2010; Watanabe et al., 2011). In plant meristems and gametogenesis, similar TE mobilization processes may be operative (Van Ex et al., 2011; Bucher et al., 2012; Martínez and Slotkin, 2012; Migicovsky and Kovalchuk, 2012).

Classical theory holds that parental-origin specific DNA methylated regions necessitate a process of epigenetic reprogramming during gamete development to ensure the successful development of future offspring (Radford et al., 2011). However, if sexual reproduction requires epigenetic

reprogramming that not only serves to reset parental-origin-specific imprinting but also carries the increased risk of TE mobilization, this increased risk should be considered as an additional cost of sexual reproduction. Doesn't evolution play here Russian roulette with a loaded and unlocked gun, particularly in cells that are thought to be vital for the transmission of stable genetic information?

10.4 Canalization

Living things must be able to dampen variable inputs (in nutrition, temperature, humidity, genetic background, etc.) to achieve the remarkable stability in the output (development, physiological responses, gene expression, etc.) (Wu et al., 2009). If organisms always produce the same phenotype, regardless of variation in genotype or environment, the relationship is described as canalization. Genetic canalization describes the insensitivity of a character to mutations, insensitivity to environmental factors is called environmental canalization (Wagner et al., 1997). The major fitness benefit driving the fixation of canalizing alleles derives from a reduction in environmental influences on phenotypic variation (Meiklejohn and Hartl, 2002). Canalization is therefore recognized as a property of organisms that influences their variability, or their propensity to vary (Wagner and Altenberg, 1996), a property that is selected for under fluctuating selection regimes (Kawecki, 2000). The terms 'phenotypic plasticity' (see chapter 12.5) and 'canalization' indicate whether environmental variation has a large or small effect on the phenotype. The heat shock protein 90 is considered the key mediator of canalization (Rutherford and Lindquist, 1998; Wagner et al., 1999).

A main feature of the heat shock response from bacteria to man is the vigorous but transient activation of a small number of specific genes previously either silent or active at low levels. New mRNAs are actively transcribed from these genes and translated into proteins which are collectively referred to as the heat shock proteins, or hsp (Schlesinger et al., 1982; Burdon, 1986). An intriguing feature is that the hsp have been highly conserved from yeast to plants and animals (Ingolia et al., 1982; Hackett and Lis, 1983; Farrelly and Finkelstein, 1984; Hunt and Morimoto, 1985; Rochester et al., 1986). A number of isoforms as members of several hsp families has been described and in eukaryotic cells the endomembrane systems [endoplasmic reticulum (ER), mitochondria, chloroplasts] harbor their own sets of proteins related to the hsp families (Nover and Scharf, 1997). The heat shock response is controlled by heat shock transcription factors (Hsfs) that act by binding to the

highly conserved heat shock element (HSE) in the promoters of target genes. It is known that, besides heat, hsps and Hsfs are involved in cellular response to various forms of stress. Hsfs are also involved in different pathological conditions, cellular responses to oxidative stress, heavy metals, amino acid analogues and metabolic inhibitors, wounding, pathogen infection, and certain developmental and differentiation processes (Sorger and Pelham, 1988; Park and Craig, 1989; Jedlicka et al., 1997; Morimoto, 1998; Hahn et al., 2004; Swindell et al., 2007). An intimate relationship appears to exist between oxidative stress and the heat shock response (Jacquier-Sarlin and Polla, 1996; Liu and Thiele, 1996; McDuffee et al., 1997; Ahn and Thiele, 2003; Miller and Mittler, 2006). Hsfs may function as one of the hydrogen peroxide sensors in plants and animals (Manalo et al., 2002; Ahn and Thiele, 2003; Miller and Mittler, 2006; Volkov et al., 2006; Vandenbroucke et al., 2008).

Hsps act as molecular chaperones. Chaperones are proteins that assist other proteins in folding, and that can help refold misfolded proteins (Hartl, 1996; Young et al., 2001; Walter and Buchner, 2002). Protein misfolding can result from mutations in protein coding regions (Walter and Buchner, 2002; Peterson et al., 2010) or from environmental changes, such as heat stress, which can lead to protein denaturation (McClellan et al., 2007). Because proteins are involved in forming and maintaining every phenotypic trait, misfolded proteins often have detrimental effects on phenotypes (Hartl, 1996; Walter and Buchner, 2002). Proteins that can mitigate these effects can render organisms more robust against genetic or environmental perturbations. Thus, chaperones are one of several ways in which phenotypes can become robust to genetic, epigenetic and environmental change (Wagner, 2005a; Salathia and Queitsch, 2007; Chen and Wagner, 2012). Robustness to genetic and environmental change is often associated with one another (Queitsch et al., 2002; Milton et al., 2003; Hermisson and Wagner, 2004; Masel and Siegal, 2009; Jarosz and Lindquist, 2010). On evolutionary time scales, robustness to genetic change has an important consequence on the genetic constitution of a population: It allows mutations to accumulate that are not phenotypically visible, precisely because phenotypes are robust to such mutations. The resulting genetic variation is often also called cryptic variation (Gibson and Dworkin, 2004; Schlichting, 2008; McGuigan and Sgrò, 2009; Chen and Wagner, 2012). Such variation need not stay cryptic forever, however. It can become phenotypically visible in the presence of yet other mutations or after environmental change (Rutherford and Lindquist, 1998; Queitsch et

al., 2002; Gibson and Dworkin, 2004; Sangster et al., 2008; Schlichting, 2008; Chen and Wagner, 2012). The resulting phenotypic change can be detrimental, but also beneficial, leading to new evolutionary adaptations (Maisnier-Patin et al., 2005; Sangster et al., 2008; Masel and Siegal, 2009; Jarosz and Lindquist, 2010). Cryptic genetic variation is likely to be an effective source of useful adaptations at a time of environmental change, relative to an equivalent source of variation that has not spent time in a hidden state (Masel, 2006).

The Hsp90 stress response protein is an ancient, abundant and nearly ubiquitous protein chaperone that interacts in an ATP-dependent system with more than 100 'client proteins' in the cell, most of which are involved in signaling pathways, including protein kinases, transcription factors and others, and either facilitates their stabilization and activation or directs them for proteasomal degradation. Both genetic (Cossins, 1998; Wagner et al., 1999; Marshall, 2002; Mitchell-Olds and Knight, 2002; Stearns, 2002; Velkov, 2002) and epigenetic (Pigliucci, 2003; Ruden et al., 2003; 2005; Rutherford and Henikoff, 2003; Sangster et al., 2003; Sollars et al., 2003) mechanisms likely explain the evolutionary capacitor function of Hsp90. By this means, Hsp90 displays a multifaceted ability to influence signal transduction, chromatin remodelling and epigenetic regulation, development and morphological evolution in nearly every organism and cell type examined (Rutherford and Zuker, 1994; Richter and Buchner, 2001; Nollen and Morimoto, 2002; Carey et al., 2006; Pearl and Prodromou, 2006; Salathia and Queitsch, 2007; Yeyati et al., 2007; Pearl et al., 2008). Hsp90 is extremely abundant – constituting ~1% of total protein under normal growth conditions (Welch and Feramisco, 1982) – and these levels are increased approximately twofold by environmental stress in yeast (Borkovich et al., 1989) and may even increase up to tenfold both in prokaryotes and in eukaryotes (Buchner, 1999). Complete loss of Hsp90 function is lethal, as multiple essential pathways are inactivated (Rutherford et al., 2007a). Hsp90 is constitutively expressed (Lindquist and Craig, 1988; Welch, 1990) and Hsp90 protein function is required at all times in eukaryotic cells (Borkovich et al., 1989; Cutforth and Rubin, 1994), but under stress conditions higher levels are achieved through induction of a heat shock response (Borkovich et al., 1989). By linking genetic variation to phenotypic variation via environmental stress, the Hsp90 protein folding reservoir might promote both stasis and change (Jarosz and Lindquist, 2010). The Hsp90 chaperone system alters relationships between genotypes and phenotypes under conditions of

environmental stress (Rutherford and Lindquist, 1998; Queitsch et al., 2002; Cowen and Lindquist, 2005; Carey et al., 2006; Sangster et al., 2007; Sangster et al., 2008; Jarosz et al., 2010; Jarosz and Lindquist, 2010; Chen G et al., 2012) and, in so doing, provide at least two routes to the rapid evolution of new traits: (i) Acting as a potentiator, Hsp90's folding reservoir allows individual genetic variants to immediately create new phenotypes; when the reservoir is compromised, the traits previously created by potentiated variants disappear. (ii) Acting as a capacitor, Hsp90's excess chaperone capacity buffers the effects of other variants, storing them in a phenotypically silent form; when the Hsp90 reservoir is compromised, the effects of these variants are released, allowing them to create new traits. A variety of morphological abnormalities are expressed when Hsp90 is partially disabled in heterozygous *Drosophila* mutants or when developing flies or *Arabidopsis* seedlings are treated with sublethal doses of Hsp90-inhibitory drugs—conditions expected to mimic natural reductions of Hsp90 function by more extreme environmental stress (Rutherford and Lindquist, 1998; Nollen and Morimoto, 2002; Queitsch et al., 2002; Milton et al., 2003; 2006; Rutherford et al., 2007b; Sangster et al., 2007; Sangster et al., 2008). Modulation of Hsp90 activity not only is able to unmask cryptic, pre-existing variation but also to create the expression and assimilation of novel morphological phenotypes (Ruden et al., 2003; Sollars et al., 2003; Tariq et al., 2009; Mittelman and Wilson, 2010). Proteotoxic stress, caused by transient Hsp90 inhibition or heat shock, markedly increased chromosome instability to produce a yeast cell population with high karyotype diversity. Continued growth in the presence of an Hsp90 inhibitor resulted in the emergence of drug-resistant colonies with chromosome XV gain. Short-term exposure to Hsp90 stress potentiated fast adaptation to unrelated cytotoxic compounds by means of different aneuploid chromosome stoichiometries (Chen G et al., 2012). These findings demonstrate that aneuploidy is a form of stress-inducible mutation in eukaryotes, capable of fuelling rapid phenotypic evolution and drug resistance, and reveal a new role for Hsp90 in regulating the emergence of adaptive traits under stress. The loss of Hsp90 function under high stress may be due to its ATP-dependent functioning when ATP becomes limiting energetic stress-dependently (Csermely and Kahn, 1991; Csermely et al., 1993; Obermann et al., 1998; Panaretou et al., 1998; 2002; Buchner, 1999; Rutherford et al., 2007b), and possibly cochaperone-dependently (Stankiewicz and Mayer, 2012). Moreover, ROS-dependent degradation of

Hsp90 protein may result in the loss of Hsp90 chaperone function, leading to client protein degradation (Pantano et al., 2003; Panopoulos et al., 2005; Shen et al., 2008; Beck et al., 2009; 2011; 2012), possibly by an ADP- and iron-dependent local generation of hydroxyl radicals through a Fenton-type reaction (Beck et al., 2012). Thus, canalization and phenotypic plasticity are two sides of the same coin. Under environmental stress the function of Hsp90 breaks down affecting the odds for a change of the redox-dependent canalization-phenotypic plasticity balance. HSP90 has also been shown to impact genomic stability and TE activity through regulation of the Piwi-interacting RNA pathway (Specchia et al., 2010; Gangaraju et al., 2011).

Numerical simulations of complex gene networks, as well as genome-scale expression data from yeast single-gene deletion strains illustrated that most, and perhaps all, genes reveal phenotypic variation when functionally compromised, and that the availability of loss-of-function mutations accelerates adaptation to a new optimum phenotype. However, this effect does not require the mutations to be conditional on the environment. Thus, there might exist a large class of evolutionary capacitors whose effects on phenotypic variation complement the systemic, environment-induced effects of Hsp90 (Hartman et al., 2001; Bergman and Siegal, 2003; Wagner, 2003; Kitani, 2004; Cooper et al., 2006; Suzuki and Nijhout, 2006; Wang GZ et al., 2011). For instance, microRNAs mediate another mechanism of canalization (Stark A et al., 2005; Hornstein and Shomron, 2006; Wu et al., 2009).

10.5 Apoptosis

Earlier, I presented compelling evidence that both compulsory measures and deceit succeeded to coerce cells into, and trap them in, stress pathways with “dead-ends” (Heininger, 2001). Thus, apoptosis is no “altruistic suicide” but programmed cytocide in which social control and cellular competition turn signaling networks that evolved as survival pathways into “programmed cell death” (Heininger, 2001). Gamete quality control is exerted by germ cell life and death decision pathways. There is no doubt that ROS can be a double-edged sword: depending on the cellular context they exert signaling and executive functions in cellular survival and apoptosis decisions (Heininger, 2001; Martin and Barrett, 2002; Martindale and Holbrook, 2002; Fruehauf and Meyskens, 2007; Moreira da Silva et al., 2010; Maryanovich and Gross, 2013). Thus, regulation and execution of cell death is controlled by oxidative stress in both fungi, plants and animals (Buttke and Sandstrom, 1994; Jacobson,

1996; Tan et al., 1998; Jabs, 1999; Kannan and Jain, 2000; Simon et al., 2000; Jones, 2001; Ueda et al., 2002; Kern and Kehrer, 2005; Le Bras et al., 2005; Gechev et al., 2006; Orrenius, 2007; Matés et al., 2008; Trachootham et al., 2008; Circu and Aw, 2010; Doyle et al., 2010).

10.6 Transposable elements and epigenetics

In contrast to the relatively modest changes in the proteome through evolution, the amount of non-protein-coding DNA has increased dramatically and accounts for >98% of the human genome sequence (Taft et al., 2007). Transposable elements (TEs) are DNA sequences that can move (transpose) from one chromosomal location to another within the genome. While the genome of the nematode *C. elegans* has less than 5% (Kidwell and Lisch, 2000), and the *Drosophila* genome 7–8% (Smith et al. 2007), in mammals TEs account for nearly half of the genome (International Human Genome Consortium, 2001; Mouse Genome Sequencing Consortium, 2002), and in some plants they may constitute more than 90% of the genome (Leeton and Smyth, 1993; SanMiguel et al., 1996; Wessler, 2006; Tenailon et al., 2010). TEs can be broadly categorized as retrotransposons (class I), which move via an RNA intermediate by a “copy and paste” mechanism, or DNA transposons (class II), which mobilize through a “cut-and-paste” mechanism (Slotkin and Martienssen, 2007; Goodier and Kazazian, 2008). As a consequence, class I retroelements generate an additional copy with every transposition, whereas the transposition of class II DNA transposons is conservative, where one site loses the transposon while another gains it. Long interspersed element-1, LINE-1 or L1 retrotransposons have successfully populated and modified eukaryotic genomes for hundreds of millions of years (Singer and Skowronski, 1985; Dombroski et al., 1991; Smit et al., 1995; Han and Boeke, 2005). L1, the most abundant class of retrotransposons in mammals, has approximately 500,000 copies in the haploid genome and about 100 and 3000 of them are estimated to be functional in humans and mice, respectively (Kazazian, 2004). The other major component of mammalian repetitive DNA is short interspersed nuclear elements (SINEs), comprising predominantly Alu and Alu-like elements (Singer, 1982). Such active TEs are typically expressed in the metazoan germline, wherein they generate newly transposed copies and pass them onto the next generation. L1 expression in the germline and cells that are closely associated with the germline has been previously reported (Branciforte and Martin, 1994; Trelogan and Martin, 1995; Ergun et al., 2004). DNA methylation is one important mechanism involved in

the silencing of transposons in plant, mammalian, and fungal germlines (Yoder et al., 1997; Martienssen and Colot, 2001; Selker, 2004). Once thought to be purely selfish genomic entities (Doolittle and Sapienza, 1980; Orgel and Crick, 1980), TEs are now recognized to occupy a continuum of relationships, ranging from parasitic to mutualistic, with their host genomes (Zeh et al., 2009). For instance, a number of formerly selfish or parasitic element sequences have been exapted to provide regulatory and/or coding sequences that serve to increase the fitness of the host (Kidwell and Lisch, 2000; Kazazian, 2004; Feschotte, 2008; Huda et al., 2010). TEs can regulate host genes by serving as the targets of epigenetic histone modifications that spread into adjacent gene loci (Lippman et al., 2004; Mikkelsen et al., 2007).

In a variety of taxa, TE activity increases in response to extrinsic stress and oxidative stress (McClintock, 1984; Ratner et al., 1992; Arnault and Dufournel, 1994; Hirochika et al., 1996; Wessler, 1996; Grandbastien, 1998; Capy et al., 2000; Jiang N et al., 2003; Kikuchi et al., 2003; Lu and Ramos, 2003; Nakazaki et al., 2003; Jorgensen, 2004; Farkash et al., 2006; de la Vega et al., 2007; Slotkin and Martienssen, 2007; Bouvet et al., 2008; Cam et al., 2008; Desalvo et al., 2008; Oliver and Greene, 2009a; Zeh et al., 2009; Rebollo et al., 2010; 2012; Stoycheva et al., 2010; Belancio and Roy-Engel, 2011; Casacuberta and González, 2013). TEs serve as broad-spectrum mutator elements and are responsible for genetic variation in the host genome (Kidwell and Lisch, 1997; Miller and Capy, 2004; Kidwell, 2005). Thus, TEs have a major role in generating intraspecies genetic variability at the level of cytosine methylation and through insertions and non-homologous recombination events between elements, leading to various chromosomal rearrangements, duplications and deletions (Deininger et al., 2003; Sandovici et al., 2005; Boissinot et al., 2006; Rangwala et al., 2006; del Carmen Seleme et al., 2006; Wang and Dooner, 2006; Reiss and Mager, 2007; Slotkin and Martienssen, 2007). Like new mutations produced by any mutator mechanism, the majority of new TE-induced mutations are expected to be deleterious to their hosts (Kidwell and Lisch, 1997). TEs produce their mutagenic effects not simply on initial insertion into host DNA but may also produce mutations when they excise, leaving either no identifying sequence or only small “footprints” of their previous presence (Kidwell and Lisch, 1997). In *E. coli*, TEs increase mutational supply and occasionally generate variants with especially large phenotypic effects, e.g. by activating cryptic genes (Reynolds et al., 1981; Hall, 1999), but may be outcompeted by mismatch repair mutator

alleles (Fehér et al., 2012). It has been estimated that 80% of the spontaneous mutations seen in *Drosophila* genetics result from TEs (Ashburner, 1992) that constitute 7–8% of the genome (Smith et al., 2007). TEs have repeatedly contributed regulatory and coding sequences to their hosts, leading to the emergence of new lineage-specific gene regulations and functions and were domesticated as drivers of genomic and biological diversity and evolution (Bowen and Jordan, 2002; 2007; Miller and Capy, 2004; Volff, 2006; Muotri et al., 2007; Piriyaongsa et al., 2007a; Böhne et al., 2008; Bourque, 2009; Sinzelle et al., 2009; Lankenau and Volff, 2009; Nakayashiki, 2011), including speciation (Rebollo et al., 2010). TEs have been implicated in the evolution of several key innovations, including acquired immunity in vertebrates (Kapitonov and Jurka, 2005) and placentation in mammals (Harris, 1998; Sekita et al., 2008). Thus, it is thought that the transposable element, MER20, contributed to the rewiring of gene regulatory networks and to the evolution of pregnancy in mammals (Lynch et al., 2011). Regulatory regions of heat shock genes are associated with constitutively uncondensed chromatin that not only facilitates rapid up-regulation in response to thermal stress, but also enables any TEs present in the region to escape transcriptional silencing, with few options for host countermeasures. In *Drosophila*, promoters of heat shock genes are indeed enriched for P elements whose effects contribute substantially to phenotypic variation (Chen B et al., 2007). In mammals, global epigenetic reprogramming occurs during preimplantation embryonic development and PGC development and coincides with dramatic increases in TE expression (Dupressoir and Heidmann, 1996; Loebel et al., 2004; Peaston et al., 2004; Svoboda et al., 2004; Taruscio and Mantovani, 2004; Maksakova et al., 2008; Leung and Lorincz, 2012). Developmentally regulated demethylation thus enables TEs to escape from transcriptional repression during critical stages and cause heritable transposition mutations. TE expression at these pre-meiotic stages can also yield clusters of progeny carrying identical transposition-induced mutations (Woodruff and Zhang, 2009). Such pre-meiotic clusters have major implications for transposon-mediated host evolution because they increase the fixation probability of a new mutant allele and the likelihood that the new mutation will precipitate reproductive isolation and speciation (Woodruff and Thompson, 2002; Rebollo et al., 2010). TE transposition has been revealed to take place during cellular differentiation in neuronal cells creating cellular diversity and neuronal plasticity (Muotri et al., 2005; 2007; 2009; Muotri and Gage, 2006; Vogel,

2011; Thomas et al., 2012) and involving both the DNA damage response (Coufal et al., 2011) and DNA methylation/demethylation machinery (Zhao et al., 2003; Muotri et al., 2010).

Because all known epigenetic pathways act on all TEs, it is likely that the specialized epigenetic regulation of regular host genes was co-opted from this ubiquitous need for the silencing of TEs and viruses. Growing evidence indicates that epigenetic regulation evolved to suppress TE (Bestor, 2003; Slotkin and Martienssen, 2007; Huda et al., 2010). It was argued that epigenetic regulatory mechanisms (RNA interference, DNA methylation and histone modifications) originally evolved as defense mechanisms against genomic invaders, such as viruses and TEs, and genome defense by suppressing TE mobilization (an immune system for the genome) appears to remain the primary function of this class of regulatory mechanisms (Barlow, 1993; Yoder et al., 1997; Plasterk, 2002; Vagin et al., 2006; Brennecke et al., 2007; Aravin et al., 2008; Obbard et al., 2009; Lisch and Benetzen, 2011). Only later, gene silencing mechanisms were co-opted to serve the regulatory needs of the host organism (Yoder et al., 1997; Matzke et al., 2000; Lippman et al., 2004; McDonald et al., 2005; Piriyaongsa et al., 2007b; Piriyaongsa and Jordan, 2008; Obbard et al., 2009; Lisch and Benetzen, 2011). However, physiological stress, induced by climate change or invasion of new habitats as well as oxidative stress disrupt epigenetic regulation and unleash TE (McClintock, 1984; Ratner et al., 1992; Arnault and Dufournel, 1994; Wessler, 1996; Grandbastien, 1998; Capy et al., 2000; Ikeda et al., 2001; Chen et al., 2003a; Daboussi and Capy, 2003; Lu and Ramos, 2003; Jorgensen, 2004; Farkash et al., 2006; McGraw and Brookfield, 2006; de la Vega et al., 2007; Bouvet et al., 2008; Cam et al., 2008; Desalvo et al., 2008; Perez-Hormaeche et al., 2008; Oliver and Greene, 2009a; Zeh et al., 2009; Rebollo et al., 2010; Stoycheva et al., 2010; Casacuberta and González, 2013).

Increasingly, non-coding RNAs have been identified to originate from within already characterized sequences such as genes and TEs (Matzke et al., 2000; Aravin et al., 2001; Sijen and Plasterk, 2003; Vastenhouw and Plasterk, 2004; Slotkin et al., 2005; Smalheiser and Torvik, 2005; 2006; Vagin et al., 2006; Brennecke et al., 2007; Piriyaongsa and Jordan, 2007; 2008; Piriyaongsa et al., 2007b; Conley et al., 2008; Zhang R et al., 2008; Kuang et al., 2009). TE-derived small RNAs have been traditionally treated as functionally distinct from gene-regulating small RNAs, such as miRNAs (Slotkin and Martienssen, 2007; Czech and

Hannon, 2010; Saito and Siomi, 2010; McCue and Slotkin, 2012). TEs are major producers of endogenous small interfering RNAs (endo-siRNAs) in plants and animals and piRNAs in animals (Cox et al., 2000; Saito et al., 2006; Vagin et al., 2006; Brennecke et al., 2007; Yin and Lin, 2007). These two classes of small RNAs act to repress TE mRNA accumulation post-transcriptionally (Saito and Siomi, 2010) and, in some cases, to induce DNA methylation and repressive histone tail modifications at TE loci to maintain the element in a transcriptionally repressed heterochromatic state (Zilberman et al., 2003; Xie et al., 2004; Aravin and Bourc'his, 2008; Wang and Elgin, 2011). In contrast to TE-regulating small RNAs, gene-regulating small RNAs, such as miRNAs and the plant-specific tasiRNAs, are derived from single-copy or low-copy regions of the genome and are processed by different pathways compared with TEs (Montgomery et al., 2008; Felippes and Weigel, 2009; Czech and Hannon, 2010; McCue and Slotkin, 2012). However, two recent reports in *Drosophila* and *Arabidopsis* (Rouget et al., 2010; McCue et al., 2012; McCue and Slotkin, 2012) that experimentally revealed the direct regulation of a host gene mRNA by TE small RNAs have blurred the lines of this distinction. In both examples, epigenetically and developmentally regulated bursts in TE expression produced gene-regulating small RNAs (McCue et al., 2012). Recent data have also uncovered the less expected role of piRNAs in the regulation of gene expression through the control of mRNA stability (Rouget et al., 2010; Simonelig, 2011). Several lines of evidence indicate that piRNA-based gene regulation is likely to be widespread. For instance, a proportion of piRNAs is not produced from transposable element sequences, but from either intergenic sequences or 3' UTR of cellular mRNAs (Senti and Brennecke, 2010; Siomi et al., 2011).

10.6.1 Role of microRNAs in gametogenetic DNA instability

Dicer, an RNaseIII endonuclease that is required for miRNA and small interfering RNA biogenesis, is required for primordial germ cell development and spermatogenesis (Hayashi et al., 2008). Selective ablation of Dicer in mouse Sertoli cells leads to infertility due to complete absence of spermatozoa and progressive testicular degeneration and Dicer and Dicer-dependent small RNAs have a continuous and cumulative effect on the process of spermatogenesis (Maatouk et al., 2008; Papaioannou et al., 2009; Korhonen et al., 2011; Romero et al., 2011; Liu D et al., 2012). Induction of miRNAs by hypoxia/HIF and ROS has been documented in a wide range of taxa

(Hua et al., 2006; Donker et al., 2007; Hebert et al., 2007; Kulshreshtha et al., 2007; 2008; Fasanaro et al., 2008; Gaedicke et al., 2008; Kenneth and Rocha, 2008; Dekanty et al., 2010). On the other hand, miRNAs can also activate the generation of ROS (Chen et al., 2010; Favaro et al., 2010). Some studies have identified a miRNA signature associated with hypoxia in certain cell types (Kulshreshtha et al., 2007; 2008; Chan and Loscalzo, 2010; Loscalzo, 2010).

Hypoxia induces specific microRNAs collectively referred to as hypoxamirs (Chan and Loscalzo, 2010). A study investigating mechanistic manipulations of miRNAs in hypoxia has been conducted recently (Fasanaro et al., 2008). The study focused on one particular miRNA, miR-210, the master hypoxamir (Chan et al., 2012) that is consistently upregulated in all published studies, in both normal and transformed hypoxic cells (Kulshreshtha et al., 2007; Camps et al., 2008; Corn, 2008; Giannakakis et al., 2008; Ivan et al., 2008; Pulkkinen et al., 2008, Crosby et al., 2009; Pocock, 2011). miR-210 is involved in repressing mitochondrial respiration (Chan et al., 2009; Favaro et al., 2010) exaggerates production of undesired mitochondrial ROS (Favaro et al., 2010) and antagonizes DNA repair (Crosby et al., 2009). Intriguingly, VEGF that is central to oogenesis and follicular quality control (see chapters 7.2.4 and 8.2) is one of the most prominent miRNA targets, particularly of miR-210 (Hua et al., 2006; Foekens et al., 2008; Liu F et al., 2012; Yamasaki et al., 2012). miR-210 expression has been identified in gametogenesis of *Drosophila*, *Xenopus*, fishes and mammals (Grün et al., 2005; Madison-Villar and Michalak, 2011; Torley et al., 2011; Ambady et al., 2012; Bizuayehu et al., 2012; El Naby, 2012; Miles et al., 2012). In addition, several of the transcription factors activated by hypoxia including p53, NF-kappaB, as well as c-Myc can induce miRNAs (O'Donnell et al., 2005; Taganov et al., 2006; Chang et al., 2007; Raver-Shapira et al., 2007). miRNAs are up- or down-regulated in biotic and abiotic stress responses in plants (Phillips et al., 2007; Shukla et al., 2008; Sunkar, 2010) and animals (Babar et al., 2008; Leung and Sharp, 2010; Suzuki and Miyazono, 2010). Tumor suppressors p53, p63, and p73 that bind to conserved p53 response elements in promoter DNA, function as both positive and negative regulators of miRNAs maturation in response to DNA damage (Suzuki HI et al., 2009; Boominathan, 2010; Knouf et al., 2012). Various hypoxia- and oxidative stress-dependent miRNAs downregulate homologous recombination-mediated DNA repair, nucleotide excision repair and mismatch repair, enhance genomic instability and induce a mutator phenotype (Crosby et al., 2009; Lal et al., 2009; Valeri et al., 2010a; b;

Moskwa et al., 2011; Tili et al., 2011).

miR-155, has emerged as a “master-regulator” of numerous biological processes, most notably those involved in immune function and cancer development (Rodriguez et al., 2007; Thai et al., 2007; Teng and Papavasiliou, 2009; Tili et al., 2009). miR-155 is an oncogenic miRNA product in humans or Bic in mice and is deregulated in a number of different cancers, most of which are of B cell origin. miR-155 downregulates MMR (Valeri et al., 2010a; Chang et al., 2011; Chang and Sharan, 2012; Yamamoto et al., 2012) and induces a mutator phenotype (Tili et al., 2011). Hypoxia and HIF-1 upregulate miR-155 suggesting that hypoxia-induced genomic instability may in part be mediated via miR-155 induction (Babar et al., 2011). Moreover, miR-155 acts to upregulate glycolysis in breast cancer cells (Jiang et al., 2012). miR-155 expression was significantly higher in sexually mature than immature porcine testes (Luo L et al., 2010). miR-743a that plays a role in the oxidative stress response in mitochondria (Shi and Gibson, 2011) was found up-regulated fourfold in mouse spermatogonial cell populations compared to gonocytes (McIver et al., 2012).

miR-18 that belongs to the Oncomir-1 cluster, is an oncogene that is intimately associated with the occurrence and progression of different types of cancer, including B-cell lymphomas, lung, breast, and colorectal carcinomas (Ota et al., 2004; Hayashita et al., 2005; Dews et al., 2006; Volinia et al., 2006; Mendell, 2008). miR-18a impairs the DNA damage response (DDR) through downregulation of ataxia telangiectasia mutated (ATM) kinase which functions as the primary sensor and transducer of DNA damage response signal (Song L et al., 2011). DDR related genes have been reported to play important roles in the maintenance of genomic stability and dysregulations of these genes were frequently found in many cancer types (Weinert and Lydall, 1993; Zhou and Elledge, 2000; Myung et al., 2001; Bartek and Lukas, 2003; Shiloh, 2003; Smith et al., 2010). miR-18 is highly abundant in testis, displaying distinct cell-type-specific expression during the epithelial cycle that constitutes spermatogenesis. Expression of HSF2 and of miR-18 exhibit an inverse correlation during spermatogenesis, indicating that, in germ cells, HSF2 is downregulated by miR-18 (Björk et al., 2010).

Several families of miRNA, dubbed “apoptomirs”, are involved in the regulation of apoptosis (Vecchione and Croce, 2010). miR-29 family members upregulate p53 levels and induce apoptosis in a p53-dependent manner (Park et al., 2009). Myeloid cell leukemia sequence 1 (MCL1), encodes an antiapoptotic Bcl2

family protein that promotes cell survival by interfering at an early stage in a cascade of events leading to the release of cytochrome c from mitochondria (Michels et al., 2005). MCL1 is also known to be the target of miR-29 members sensitizing cells to TNF-related apoptosis-inducing ligand (Mott et al., 2007). miR-29 members are thought to promote apoptosis through a mitochondrial pathway that involves p53, Mcl-1 and Bcl-2 (Xiong et al., 2010). Moreover, the miR-29 family influences de novo DNMTs, DNMT3a and DNMT3b expression directly and possibly maintenance DNMT1 indirectly (Fabbri et al., 2007; Takada et al., 2009; Filkowski et al., 2010; Meunier et al., 2012; Sandhu et al., 2012). DNMTs may also be involved directly and/or indirectly in the apoptotic process, because their alterations induce germ cell death (Doerksen et al., 2000). miR-29 downregulated expression of de novo methyltransferases, DNA methyltransferase 3a and 3b, could directly affect methylation patterns (Fabbri et al., 2007; Filkowski et al., 2010; Meunier et al., 2012) and induce global DNA hypomethylation (Garzon et al., 2009). miR-29 family members are expressed in the male and female germline (Takada et al., 2009; Filkowski et al., 2010; Meunier et al., 2012). In the testes of adult irradiation-exposed mice, miR-29a and miR-29b upregulation was paralleled by a significant downregulation of DNMT3a, profound hypomethylation of transposable LINE1 and SINE B2 sequences and genomic instability (Filkowski et al., 2010). Neonatal exposure to xenoestrogen induced a dose-dependent increase in miR-29a, miR-29b, and miR-29c expression. Increased miR-29 expression resulted in a decrease in DNMT1, DNMT3a, and DNMT3b, and a concomitant increase in transcript levels of DNA methylation target genes in correlation with their pattern of methylation (Meunier et al., 2012). Moreover, increased miR-29 expression decreased antiapoptotic Mcl-1 protein levels and induced adult germ cell apoptosis (Meunier et al., 2012)

11. Sexual mutagenesis-selection cascades (SMSC): there is more than meets the eye

Eldredge and Gould argued that both phases of punctuated equilibrium are inconsistent with natural selection as a single underlying cause....First, natural selection is posited as being effective only in fine-tuning organisms to small-scale changes in their environment. Second, some process other than

natural selection must come into play to cause punctuations. The frequent association between punctuations and the appearance of new species suggests to Gould and Eldredge that this process, whatever it is, causes both phenomena...

Travis and Reznick, 2009

Summary

The Modern Synthesis and population genetics orthodoxy hold that (i) germline mutations are random carrying a high risk of being deleterious, (ii) cells within a multicellular individual are closely related, with little expected variation, so that selection between these cells can be ignored and therefore (iii) the gamete bottleneck (out of a huge number of gametes only a small number succeeds to become offspring) is stochastic, (iv) Muller's ratchet operates in organisms with stochastic bottlenecks. Within this conceptual framework it can be inferred that Muller's ratchet should operate in sexually reproducing organisms with narrow, stochastic gamete bottlenecks resulting in mutational meltdown. Sexual reproduction solved the "mutator-population size dilemma" by subjecting a huge population of germ cells and gametes to a selection cascade whose pre-selection principle is based on stress resistance (insensitivity to disturbance) and resilience (the rate of recovery after disturbance), competitiveness, and viability of the selected units. Thus, the molecular processes associated with sexual reproduction reveal a complexity that goes far beyond the simple sexual reproduction = meiotic recombination scenario.

The RNA virus quasispecies model can be viewed as a simple framework that contains all the basic ingredients of Darwinian evolution. Genomes are not independent entities due to mutational coupling among variants, and instead, the entire mutant distribution forms an organized cooperative structure which acts like (quasi) a single unit (species). The quasispecies target of natural selection has been proposed to be 'the mutant distribution as a whole,' as opposed to individual variants. The level of genetic diversity in a viral population, termed the quasispecies cloud size, is an intrinsic property of the quasispecies. The theoretical advantage of maintaining a diverse quasispecies is that, when the virus is shifted to a new environmental niche or selective regimen, a variant may already be present in the population which will be more fit in the new environment. When the mutation rate is adjusted upwards, the rate of adaptation increases. Quasispecies genetic

variation can be reduced by purifying selection and by genetic bottlenecks. What is left by purifying selection and transmission bottlenecks to the action of natural selection is only the proverbial "tip of the iceberg" of quasispecies genetic variation. Muller's ratchet operates in stochastic bottlenecks resulting in fitness losses and, eventually, in the extinction of the population. On the other hand, selective bottlenecks increase or at least do not attenuate the fitness of the transmitted viruses. The quasispecies concept is also applicable to other biological systems such as prions, bacteria and tumor cells.

Sexual mutagenesis and selection cascades and gamete bottlenecks are mutually interdependent and are finely tuned to each other and to the actions of natural selection. A general pattern can be recognized that allows to distinguish between three broad categories of organisms that differ with regard to body size, population size, size of the quasispecies cloud due to (epi)mutagenesis, stringency of gamete and offspring quality control and importance of natural selection. Sexual reproduction generated a process that, in its consequence, is a beneficial-mutation enrichment system. However, the quality check regime is far from optimal (Hartshorne et al., 2009). This may have several reasons: (i) the quality checks based on cellular stress-resistance cannot reflect the complexity of the environment and its manifold adaptive challenges; (ii) the system cannot check the proper functioning of differentiated cells in a multicellular organism with its division of labor; (iii) although the stochasticity of the gametic bottleneck is attenuated by the manifold quality checks, a residual stochastic, possibly fitness-eroding, element remains and (iv) the system relies on the bet-hedging strategy that must allow for a less than optimal quality check to create e.g. "hopeful monsters".

Adherents to scientific paradigms self-censor their thinking within the boundaries of their beliefs. The following dogmas of the Modern Synthesis and population genetics made the proponents of these doctrines blind to the evolutionary potential of sexual reproduction: (i) natural selection is "the only direction-giving factor in evolution" (Mayr, 1980); (ii) selection within an individual can be ignored since all cells within a multicellular individual are recently derived from a common single-celled ancestor (the zygote or spore) and are hence closely related with little expected variation (Maynard Smith and Szathmáry, 1995, p. 244); (iii) mutations are accidental;

(iv) due to the unfavorable ratio of deleterious and beneficial mutations, mutation rate should be as low as possible; and (v) as a result of the deleterious/beneficial mutation ratio, genetic variation largely depends on slightly deleterious and neutral mutations (Ohta, 1973; 1992; 2011).

So far, evolutionary theories of sexual reproduction focused on, and were limited to, the role of recombination. Recombination results in the exchange of genetic information between non-sister chromatids resulting in crossovers that are essential for the correct segregation of the chromosomes and by combining paternal and maternal alleles creates genetic diversity among individuals within a population (Baarends et al., 2001; Agrawal, 2006b). Real population sizes are generally significantly less than one billion individuals. This finding is important for discussions of the evolution of genetic recombination, especially when the expected numbers of double mutations in natural populations is considered (Ackerman et al., 2010). Maynard Smith (1968, 1978) pointed out that double mutants could be produced by mutation alone provided that the population size is large enough, making the generation of doubly favorable mutants by recombination unnecessary. But for this to happen in practice, the population size would have to be of the order of 10^{16} , and for triple mutants population sizes of 10^{24} are needed (Ackerman et al., 2010). These numbers are based on the estimate of 10^{-5} favorable mutations per genome per generation (Perfeito et al., 2007), which translates into a per-gene rate of 10^{-8} , assuming that there are at least 1000 genes per haploid genome. The projected population numbers are clearly unrealistic for the majority of eukaryotic species, especially multicellular eukaryotes (Ackerman et al., 2010). Although it is often impossible to measure population sizes directly, and impossible to measure historical effective population sizes, indirect measures can be obtained because the effective size N of a population is related to the genetic diversity that is maintained in the population (Kimura and Crow, 1964; Frankham, 1996). Such analyses of polymorphism data yield an estimated effective population size of approximately 10,000 for the modern human lineage (e.g., Takahata, 1993; Yu et al., 2001) and less than 100,000 for other primate lineages (Burgess and Yang, 2008). Traditional population genetics suggests that, given that the mutation rate for favorable alleles is orders of magnitude less than the reciprocal of the population size, new favorable mutants in a given gene are essentially unique and are, for all practical purposes nonrecurring. This problem is less acute for prokaryotes and single-celled eukaryotes that can

have very large population sizes and that have rapid doubling times (20 min in *Escherichia coli* vs. 20 years in humans). Consequently, without recombination most of the favorable mutants that occur in finite populations—even very large finite populations—will eventually be lost. Barrick and Lenski, (2009) showed that, in asexual populations, some beneficial mutations can be lost through competition with other beneficial mutations.

Like for recombination, an important feature of “non-accidental” mutagenesis is the “necessity” of large population sizes to account for the randomness of mutagenesis and its large excess of deleterious mutations. In unicellular organisms with their large population sizes this is not a restriction, but it may be a huge hurdle in multicellular organisms and it certainly would not be an adaptive response in small-size populations. Sexual reproduction solved this problem by subjecting a huge population of germ cells and gametes to a selection cascade whose pre-selection principle is based on stress resistance (insensitivity to disturbance) and resilience (the rate of recovery after disturbance), competitiveness, and viability of the selected units (Parsons, 1997; 2005; 2007). As a corollary to the fact that most mutations are deleterious and that the gametes with the least vulnerability are selected, only the gametes survive that are the most robust to mutations. A huge body of literature shows that living systems on all levels of organization—from macromolecules to whole organisms—are to some extent robust to mutations (de Visser et al., 2003; Wilke and Adami, 2003; Kitano, 2004; Stelling et al., 2004; Wagner, 2005a; b; c; Kaneko, 2007; Mihaljev and Drossel, 2009; Draghi et al., 2010; Freilich et al., 2010). Mutationally robust systems are often also robust to environmental change (Ancel and Fontana, 2000; Meiklejohn and Hartl, 2002; de Visser et al., 2003; Milton et al., 2003; Wagner, 2005a; Cooper et al., 2006; Masel and Siegal, 2009; Szollosi and Derenyi, 2009; Lehner, 2010; Hayden et al., 2012; Stewart et al., 2012). Evidence suggests that insensitivity to environmental perturbations and robustness against mutations are generally correlated (Meiklejohn and Hartl, 2002; Remold and Lenski, 2004); hence, selection to promote survival under a large variety of environments might indirectly increase mutational resilience (Papp et al., 2009). Importantly, the ability to detoxify ROS, or resist oxidative stress, must be heritable (Olsson et al., 2008).

Stress tolerance determines competitive properties and outcome of biotic interactions (Liancourt et al., 2005). Julian Huxley (1942, 1947) and later JZ Young

(1951) advocated a concept of biological progress according to which broadly increasing is adaptation to life in general, rather than to any particular mode of life. One of the important features of this progress is increasing independence of the environment. This concept was derived from taking into account the characteristics distinguishing dominant groups from both their non-dominant contemporaries and their dominant predecessors. p53 is a key mediator of stress/oxidative stress resistance selection regimes (Derry et al., 2001). Importantly, the modulation of stress resistance by p53 is context-dependent, depending on the level of mitochondrial bioenergetics stress. The *C. elegans* p53 ortholog *cep-1* is required to extend longevity in response to mild suppression of mitochondrial proteins that are involved in electron transport chain-mediated energy production, and also mediates both the developmental arrest and life-shortening induced by severe mitochondrial stress (Ventura et al., 2009; Torgovnick et al., 2010). The context-dependence of p53 family proteins on stress resistance and longevity was shown in a variety of organisms ranging from *C. elegans* and *Drosophila* to humans (Feng et al., 2011). Involving p53 signaling pathways that effect mitochondrial homeostasis and function (Matoba et al., 2006; Liu B et al., 2008; Vaseva and Moll, 2009; Galluzzi et al., 2011; Maddocks and Vousden, 2011), the "Mitochondrial Threshold Effect Theory", holds that it depends on the severity of the mitochondrial dysfunction whether a mutation results in somatic and cellular life span elongation or reduction (Lee SS et al., 2003; Sampayo et al., 2003; Kondo et al., 2005; Ventura et al., 2006).

Stress resilience (i.e. oxidative stress resistance) and energetic efficiency are both key fitness components and pervasive selection criteria in resource-limited habitats (MacArthur and Wilson, 1967; Zotin, 1990; Parsons, 1997; 2005; 2007). Fitness can be approximated to energetic efficiency especially towards the limits of survival. Furthermore, fitness at the cellular level should correlate with fitness at the organismal level, especially for development time, survival and longevity; 'good genotypes' under stress should therefore be at a premium (Parsons, 2005). Asking which systems-level aspects of metabolism are likely to have adaptive utility and which could be better explained as by-products of other evolutionary forces, Papp et al. (2009) concluded that the global topological characteristics of metabolic networks and their mutational robustness are unlikely to be directly shaped by natural selection. Conversely, models of optimal design revealed that various aspects of individual pathways and the behavior of the whole network show signs of adaptations, even though the

exact selective forces often remain elusive (Papp et al., 2009).

The molecular processes associated with sexual reproduction reveal a complexity that goes far beyond the simple sexual reproduction = meiotic recombination scenario. Sexual reproduction had to integrate a host of different strategies into a single coherent process. I try to trace the evolutionary course of events that may have led to this complex process.

1. Shuffling genes to bring favorable alleles from different genomes together into one genome is a first approach. But, as countless theoretical models have shown, it appears to be not enough to give sexual reproduction a competitive advantage over asexual reproduction, particularly when recombination load (see chapter 18.1) threatens to offset this advantage. In addition, the advantage may disappear when asexual reproduction uses mitotic recombination (Mandegar and Otto, 2007).
2. To become an evolutionary success, sexual reproduction had to tap into another resource: mutagenesis. Theoretical modeling has delineated the basic conditions under which this innovation took place. Maynard Smith (1971b) showed that for larger populations, sex may accelerate evolution by a factor very approximately equal to the number of loci at which at any time favorable mutations are possible but have not yet occurred. Otto and Hastings (1998) demonstrated that pre-selection of gametes would have significant effects on the frequencies and types of mutations and alleles in a population. Homologous recombination requires DSBs and oxidative stress. And oxidative stress is the fuel that drives mutagenesis and delivers free of charge the process to select the pearls among the pebbles. In addition, oxidative stress fires the processes related to epimutagenesis and transgenerational inheritance (see chapter 16). Due to the unfavorable ratio between deleterious and beneficial (epi)mutations, a large number of gametes had to be produced to get a reasonable number of quality gametes. The metabolic investment further increased the oxidative stress, a runaway process that brought human spermatogenesis to the brink of error catastrophe.

Sexual reproduction generated a mechanism that, in its consequence, is a beneficial-mutation enrichment system. However, the quality check regime is far from optimal (Hartshorne et al., 2009). This may have several reasons: (i) the quality checks based on cellular stress-resistance cannot reflect the complexity of the environment and its manifold adaptive challenges; (ii) the system cannot check the proper functioning of differentiated cells in a multicellular organism with its division of labor; (iii) although the stochasticity of the gametic bottleneck is attenuated by the manifold quality checks, a residual stochastic, possibly fitness-eroding, element remains and (iv) the system relies on the bet-hedging strategy that must

allow for a less than optimal quality check to create e.g. “hopeful monsters” (Chouard, 2010).

11.1 Excursion: RNA virus quasispecies

A hallmark of RNA genome homeostasis is the error-prone nature of their replication and retrotranscription. Viral RNA polymerases exhibit characteristically low fidelity with measured mutation rates of roughly 10^{-4} mutations per nucleotide copied, which is orders of magnitude greater than those of nearly all DNA-based viruses and organisms (Batschelet et al., 1976; Holland et al., 1982; Steinhauer and Holland, 1987; Lauring and Andino, 2010). The major biochemical basis of the limited replication fidelity is the absence of proofreading/repair and postreplicative error correction mechanisms that normally operate during replication of cellular DNA. In spite of this unique feature of RNA replicons, the dynamics of viral populations seems to follow the same basic principles that classical population genetics has established for higher organisms (Domingo et al., 1996; 2012; Moya et al., 2000). The quasispecies concept was introduced by M. Eigen and co-workers as a formal mathematical model that was initially formulated to explain the evolution of life in the “precellular RNA world” (Eigen, 1971; Eigen and Schuster, 1977; Eigen et al., 1988). The quasispecies model can be viewed as a simple framework that contains all the basic ingredients of Darwinian evolution. In particular, it captures the critical relation between mutation rate and information transmission (Eigen, 1971; Eigen and Schuster, 1977). According to Jenkins et al. (2001) the quasispecies model is an equilibrium mutation-selection process and describes a heterogeneous distribution of whole genomes ordered around one or a degenerate set of fittest sequences known as “master” sequences (Eigen 1987, 1992; 1993, 1996; Nowak, 1992). Genomes are not independent entities due to mutational coupling among variants, and instead, the entire mutant distribution forms an organized cooperative structure which acts like (quasi) a single unit (species), hence its name. The quasispecies evolves to maximize the average rate of replication of the entire mutant distribution rather than the frequency of the single fittest sequence in the population, and thus the target of natural selection has been proposed to be ‘the mutant distribution as a whole,’ as opposed to individual variants (Eigen 1987, 1992; 1993, 1996). Wilke (2005) pointed out that quasispecies theory is simply a subset of theoretical population genetics, and it is mathematically equivalent to the theory of mutation-selection balance. Quasispecies theory treats multiple loci, whereas early work on

mutation-selection balance has focused on one- or two-locus models. On the other hand, most work on population genetics considers finite populations and includes stochastic effects, whereas quasispecies theory is first and foremost a deterministic description of infinite populations. Its basic equations are very similar in structure to mutation-selection equations that are studied in the population genetics literature (Baake and Gabriel, 2000; Bürger, 2000; Baake and Wagner, 2001). The level of genetic diversity in a viral population, termed the quasispecies cloud size, is an intrinsic property of the quasispecies. The theoretical advantage of maintaining a diverse quasispecies is that, when the virus is shifted to a new environmental niche or selective regimen, a variant may already be present in the population which will be more fit in the new environment (Schneider and Roossinck, 2001).

Eigen and Schuster (1977) investigated the relationship between the length of genetic sequences and the rate of error in replication. When the mutation rate is adjusted upwards, the rate of adaptation increases. A quantitative analysis revealed that evolution rates increase linearly with mutation rates for slowly mutating viruses. However, this relationship plateaus for fast mutating viruses (Sanjuán, 2012). But then, all of a sudden, at a critical mutation rate, the whole system collapses in what is referred to in the literature as an “error catastrophe.” This may be generally, but vaguely, circumscribed as a critical mutation rate beyond which mutation can no longer be controlled by selection and leads to genetic degeneration. More specifically, it was originally described for the sharply-peaked landscape and defined as a critical mutation rate above which the fittest genotype is lost from the population (Eigen et al., 1989; Biebricher and Eigen, 2005; Bull et al., 2005). What happens is that the system of short-term memory carriers can no longer maintain a long-term memory—not only can the system not adapt further, it also loses everything that it had previously gained (Andersson, 2011). Evolvable systems have to navigate the space defined by conservation and innovation.

RNA viruses typically have short generation times and large populations, both of which contribute to their observed quasispecies structure (Domingo and Holland, 1997; Duffy S et al., 2008). As RNA virus genetic replicative machinery is generally about a millionfold more error prone than that of organismal DNA, detailed analysis of RNA virus evolution over a 50-year period is essentially equivalent to study of an organismal system over a 50-million-year period (Holland et al., 1982). In different virus species there is

a wide range of intrahost quasispecies cloud size (Domingo et al., 1992; 1998; 2012; Plyusnin et al., 1996; Bonneau et al., 2001; Alves et al., 2002; Farci et al., 2002; Wang WK et al., 2002; Beasley et al., 2003; Biek et al., 2003; Davis et al., 2003; Lin SR et al., 2004; Jerzak et al., 2005; Ciota et al., 2009; Brackney et al., 2010). It may be much higher than interhost variation, reflecting the action of purifying selection (Holmes, 2003a; Chain and Myers, 2005; Jerzak et al., 2005; Edwards et al., 2006; Suzuki, 2006; Redd et al., 2012) that is determined by the extent of host-specific adaptation and other selection pressures (Nichol et al., 1993; Schneider and Roossinck, 2001). Since its introduction into the US in 1999, West Nile virus (WNV) remains a relatively homogeneous virus population, with the most divergent strains containing only a few nucleotide and/or amino acid substitutions (Anderson et al., 2001; Ebel et al., 2001; 2004; Lanciotti et al., 2002; Beasley et al., 2003; Davis et al., 2003). However, intrahost genetic diversity in naturally and experimentally infected mosquitoes and birds revealed that WNV populations are structured as quasispecies and documented strong purifying natural selection in WNV populations (Jerzak et al., 2005; 2008).

Quasispecies genetic variation can be reduced by purifying selection and by genetic bottlenecks (Yuste et al., 1999; Lázaro et al., 2003; Li and Roossinck, 2004; Davis CT et al., 2005; Chen and Holmes, 2006; Duffy S et al., 2008; Cuevas et al., 2009; Redd et al., 2012). Genetic bottlenecks are stochastic events that cause strong reductions in the effective population size and take place when only a few individuals of a population found a new one. Therefore, bottlenecks reduce the genetic diversity of a population. When a few, or even a single genome, of a viral quasispecies is randomly chosen to generate a new population, there is a high probability that it carries a deleterious mutation relative to fitter genomes of the parental population. This mutation will be transmitted to all the members of the new population (Manrubia et al., 2005). Bottleneck events are frequent in the course of the life cycles of viruses, not only in the most obvious case of host-to-host transmission (Artenstein and Miller, 1966; Couch et al., 1966; Ali et al., 2006; Chen and Holmes, 2006; Carrillo et al., 2007; Betancourt et al., 2008; Smith et al., 2008; Haaland et al., 2009; Redd et al., 2012), but also during the intrahost spread of virus (Foy et al., 2004; Li and Roossinck, 2004; Scholle et al., 2004; Quer et al., 2005; Ali et al., 2006; Pfeiffer and Kirkegaard, 2006; Betancourt et al., 2008; Smith et al., 2008; Haaland et al., 2009; Bull et al., 2011; Domingo et al., 2012). This balance between the continuous generation of new mutants and the action of positive and negative selective forces and

bottlenecks acting on complex ensembles of replicating units leads to a very dynamic, though highly organized population (Domingo et al., 1978, 2001). What is left by purifying selection and transmission bottlenecks to the action of natural selection is only the proverbial "tip of the iceberg" of quasispecies genetic variation (Clarke et al., 1994; Li and Roossinck, 2004; Chen and Holmes, 2006). Despite the fast sequence evolution that is characteristic of viruses, sets of genes are conserved in large groups of viruses (Argos et al., 1984; Kamer and Argos, 1984; Goldbach, 1987; Koonin and Dolja, 1993). Analytical and simulation methods demonstrated that severe bottlenecks of viral transmission are likely to drive down the virulence of a pathogen because of stochastic loss of the most virulent pathotypes, through a process analogous to Muller's ratchet. Patterns of accumulation of deleterious mutation may explain differing levels of virulence in vertically and horizontally transmitted viral diseases (Novella et al., 1995; 1999; Bergstrom et al., 1999; Lázaro et al., 2003; Novella, 2004; Cuevas et al., 2009).

Population bottlenecks are stochastic events that strongly condition the structure and evolution of natural populations. Considering that most mutations are deleterious, it was predicted that the frequent application of bottlenecks would yield a population unable to replicate. According to theory, in experiments with viruses experiencing a high replication error rate due to the action of mutagens, but in the absence of bottlenecks, real extinctions of infectivity are observed (Sierra et al., 2000; Crotty et al., 2001; Pariente et al., 2001; Grande-Pérez et al., 2002; Severson et al., 2003). However, *in vitro* as well as *in vivo* systems evolving through bottlenecks present a remarkable resistance to extinction (Manrubia et al., 2005; Cases-González et al., 2008). Therefore, it is reasonable to assume that there must be mechanisms able to counterbalance the negative effect of bottlenecks. In the case of vertically transmitted viruses, bottlenecks may be particularly severe, since only a small amount of viruses are able to cross the barriers to infect the embryo. Competition among genomes can only take place inside the infected host. Bottlenecks are also very frequent in horizontally transmitted viruses and during replication inside an infected organism (Gerone et al., 1966; Nowak et al., 1991; Pang et al., 1992; Quer et al., 2005; Ali et al., 2006; Pfeiffer and Kirkegaard, 2006; Roossinck and Schneider 2006; Carrillo et al., 2007; Betancourt et al., 2008; Smith et al., 2008; Haaland et al., 2009; Domingo et al., 2012). Under horizontal transfer, each virus can infect every susceptible individual of the host population, and competition can

also happen at the inter-host level (Wilson et al., 1992; Chao et al., 2000). The inter- and intra-host competition that takes place in horizontally transmitted viruses should mitigate the effect of bottlenecks (Bergstrom et al., 1999). This means that an intra- and inter-host competition among viruses selects the more virulent forms, which have greater chances of infecting a new host (Manrubia et al., 2005). These findings contain important messages:

(i) Both theoretical (Wagner and Gabriel, 1990; Kondrashov, 1994; Gordo and Charlesworth, 2000) and experimental (Chao, 1990; Coates, 1992; Duarte et al., 1992; 1993; Clarke et al., 1993; Escarmis et al., 1996; 2002; 2006; 2009; Yuste et al., 1999; de la Peña et al., 2000; Lázaro et al., 2003; Novella, 2004; Novella and Ebendick-Corpus, 2004; de la Iglesia and Elena, 2007; Weatherford et al., 2009; Jaramillo et al., 2013) work has shown that Muller's ratchet operates in stochastic bottlenecks resulting in fitness losses and, eventually, in the extinction of the population.

(ii) On the other hand, bottlenecks associated with selective events increase or at least do not attenuate the fitness of the transmitted viruses (Manrubia et al., 2005; Sagar, 2010; Blish, 2012) that present a remarkable resistance to extinction (Manrubia et al., 2005; Cases-González et al., 2008). Interestingly, several investigations have suggested that transmitted HIV-1 and/or early variants in the recipient are more closely related to the donor's ancestral sequences suggesting that variants with ancestral features were favored for transmission, with evolution starting all over in newly infected individuals (Zhu et al., 1993; Herbeck et al., 2006; Sagar et al., 2009; Blish, 2012).

The genetic diversity within an RNA virus quasispecies population facilitates adaptation to and improved fitness on existing or changing environments through natural selection, so long as population sizes are large (Holland et al., 1982; 1991; Kurath and Palukaitis, 1990; Fitch et al., 1991; Coffin, 1992; Gorman et al., 1992; Kinnunen et al., 1992; Martinez et al., 1992; Domingo and Holland, 1997; Duffy S et al., 2008). For example, the quasispecies structure has been identified as an important determinant in viral evasion of the host immune response and the development of resistance to antiviral drugs and therapies (Domingo et al., 1998; 2012; Essajee et al. 2000; Farci and Purcell, 2000; Farci et al., 2002). Therefore, the mutational diversity of RNA viruses facilitates their persistence at the cellular, organismal and population levels.

The quasispecies pattern of virus evolution is only recognized by looking at the mutational dynamics of virus replication within the cells (Batschelet et al., 1976; Holland et al., 1982; Steinhauer and Holland, 1987;

Fitch et al., 1991; Coffin, 1992; Gorman et al., 1992; Lauring and Andino, 2010). Countless mutations occur, but only a miniscule fraction can survive repeated passages from host to host (Clarke et al., 1994). A rapid intrahost evolution need not be reflected in rapid evolution at the interhost population level (the one resulting from multiple interhost transmissions) (Fryer et al., 2010; Domingo et al., 2012). For the same virus a higher rate of evolution is obtained when the compared sequences correspond to viruses isolated within a short time span than when they correspond to isolates separated by a long time interval (Sobrinho et al., 1986; Domingo, 2007). This dynamic could not have been recognized by investigating virus evolution only from transmission bottleneck to transmission bottleneck, treating intracellular virus replication as black box. So far, evolutionary theory approached the evolutionary dynamics of sexual reproduction exclusively from an outcome perspective focusing on recombination and gamete bottlenecks, treating the molecular processes of sexual reproduction within the gonads more or less as black box. And therefore missed its mutation-selection balance with its quasispecies dynamics. Importantly, the quasispecies cloud size in sexual reproduction encompasses both mutated (including recombined) and epimutated variants. The quasispecies theory explained quantitatively the boundaries, within which evolution works best (Eigen et al., 1988, Eigen, 1992). There should have been no evolutionary constraints that could have hindered higher taxa to tap into this evolutionary resource of quasispecies dynamics. Thus, populations of mutated gamete populations have a great deal in common with virus quasispecies: master sequence and cloud size, purifying selection due to sexual selection cascades, and gamete bottlenecks.

The quasispecies concept has also been applied to other biological systems such as prions, bacteria and tumor cells (Más et al., 2010; Ojosnegros et al., 2011; Domingo et al., 2012). In the following, I largely adhere to the excellent treatise of Más et al. (2010) on this topic. Cancer cells may show a mutator phenotype (Loeb, 1998; 2001; Bielas et al., 2006) that may increase the probability of achieving the most advantageous mutation combination for tumor growth. Every tumor harbors high-frequency mutations, usually those resulting in the gain of function of an oncogene or the loss of a tumor suppressor, accompanied by a complex combination of low-frequency mutations. These mutations are thought to drive the global cancer phenotype, and their characteristics resemble those of viral quasispecies with the presence of a dominant "master" clone accompanied by a "clan" of minor forms, the quasispecies cloud (Más et al., 2010). The mutant

“clan” generated during cancer cell replication allows the tumor to face diverse challenges, including the immune system and treatment (Más et al., 2010). Cancer can be considered as a complex biological system that evolves through mutations and epigenetic changes following Darwinian principles of competition and selection (Merlo et al., 2006). Theoretical studies have correlated cancer and genetic instability (Maley and Forrest, 2000; Gonzalez-Garcia et al., 2002) with quasispecies models of minimal replicators (Solé et al., 2003; Brumer et al., 2006; Tannenbaum et al., 2006) and even with incursions into error catastrophe (Solé and Deisboeck, 2004).

11.2 SMSC, bottlenecks and natural selection

The Neo-Darwinian idea that evolution is driven by purely random germline mutations followed by independent natural selection on the progeny has become a widely accepted dogma in biology. Moreover, it is conventional wisdom that natural selection is much more efficient in invertebrate species with large effective population sizes, such as *C. elegans*, than in those with relatively small effective population sizes, such as many vertebrates, as reflected in many aspects of genome evolution (Lynch and Conery, 2003; Denver et al., 2004). Species with small census population sizes routinely go through narrow gamete bottlenecks, i.e. from a large, sometimes huge, number of gametes only a small number of gametes succeed to become offspring. This gamete bottleneck is thought to be stochastic: since all cells within a multicellular individual are recently derived from a common single-celled ancestor (the zygote or spore) and are hence closely related, with little expected variation, it is thought that selection between gametes can be ignored (Maynard Smith and Szathmáry, 1995, p. 244; Otto and Hastings, 1998). Within this conceptual framework, the huge number of gametes, respectively the large number of cell divisions per generations necessary to produce this large number, is a definite burden. From zygote to zygote, the number of cell divisions has been estimated to be: 50 for maize (Otto and Walbot, 1990), 35 for *Drosophila* (at 18 days for males and at 25 days for females; Drost and Lee, 1998), 25 for female mice (Drost and Lee, 1998), 62 for 9-month-old male mice (Drost and Lee, 1998), 23 for human females (Vogel and Rathenberg, 1975), and 36 for human males at puberty plus 23 per year thereafter (Vogel and Rathenberg, 1975). The number of cell divisions per generation is strongly age dependent in *Drosophila* and in mammalian males, rising, for example, in human males from 36 for a 13-year-old to over 500 for a 35-year-old (Otto and Hastings, 1998). That the

large number of generations is a relevant factor with regard to mutation load is illustrated by the male mutation bias that, at least in part, is replication-dependent. If the gamete bottleneck is stochastic, sexually reproducing organisms are in trouble. Both theoretical (Wagner and Gabriel, 1990; Kondrashov, 1994; Gordo and Charlesworth, 2000) and experimental (Chao, 1990; Coates, 1992; Duarte et al., 1992; 1993; Clarke et al., 1993; Escarmís et al., 1996; 2002; 2006; 2009; Yuste et al., 1999; de la Peña et al., 2000; Lázaro et al., 2003; Novella, 2004; Novella and Eberhard-Corpus, 2004; de la Iglesia and Elena, 2007; Weatherford et al., 2009; Jaramillo et al., 2013) work has shown that Muller's ratchet operates in stochastic bottlenecks resulting in fitness losses and, eventually, in the extinction of the population. This would mean that sexually reproducing organisms, rather than asexually reproducing, have a huge risk to suffer from mutational meltdown. Estimates of human germline base substitution rates range from 0.97 to 3.8×10^{-8} per base per generation (Haldane, 1935; Kondrashov and Crow, 1993; Crow, 1993b; Nachman and Crowell, 2000; Kondrashov, 2003; Xue et al., 2009; Lynch, 2010b; Roach et al., 2010; The 1000 Genomes Project Consortium, 2010; Awadalla et al., 2011; Conrad et al., 2011; Kong et al., 2012; Sun et al., 2012). A human mutation rate of $\sim 2.5 \times 10^{-8}$ mutations per nucleotide site corresponds to 175 (range 91–238) mutations per diploid genome per generation (Nachman and Crowell, 2000). Assuming that (i) there is no selective bottleneck between gametogenesis and offspring and (ii) 95 to 100% of all mutations have either neutral ($\sim 30\%$ of amino-acid changing mutations in humans, $\sim 16\%$ in *Drosophila* [Eyre-Walker, 2002], and $\sim 2.8\%$ in enteric bacteria [Charlesworth and Eyre-Walker, 2006]) or deleterious effects on fitness (Eyre-Walker and Keightley, 2007) this ratio would mean that with each generation, fitness of human populations would erode. In addition, the degree of fidelity in epigenetic transmission is about three orders of magnitude lower than that of DNA sequence (an error rate of 1 in 10^6 and 1 in 10^3 for DNA sequences and DNA modification, respectively) (Ushijima et al., 2003; Laird et al., 2004; Riggs and Xiong, 2004; Genereux et al., 2005; Fu et al., 2010; Petronis, 2010). Thus, a huge number of (epi)mutations with possibly detrimental phenotypic effects may degenerate germline performance in each new generation, contributing to an almost certain (epi)mutational meltdown.

On the other hand, studies in RNA viruses have suggested that bottlenecks associated with selective events increase or at least do not attenuate the fitness of the transmitted viruses (Manrubia et al., 2005;

Sagar, 2010; Blish, 2012) that present a remarkable resistance to extinction (Manrubia et al., 2005; Cases-González et al., 2008). I have presented extensive evidence for the selectivity of the gamete/offspring bottleneck (see chapter 8). Assuming that bottlenecks are selective, the narrower the bottleneck the more stringent the underlying selection process can be expected to be.

Sexual mutagenesis and selection cascades and gamete bottlenecks are mutually interdependent. The one would not work without the other. Accordingly, they are finely tuned to each other and to the actions of natural selection that provides the environmental arena for the “struggle for survival” of the pre-selected offspring populations. A general pattern can be recognized that allows to distinguish between three broad categories of organisms (see figure 1):

Category 1 (Microorganisms): microscopic body size, large population size, condition-dependent sexual reproduction or asexual reproduction, stress-dependent mutagenesis, “pearls” are selected by natural selection

Category 2 (Invertebrates): intermediate body size and population size. Ectotherms. Sexual reproduction with moderate (epi)mutagenesis and less stringent gamete and offspring quality control resulting in relaxed gamete bottleneck. Intermediate fecundity. Moderate impact of SMSC on preselected variation. Moderate impact of natural selection.

Category 3 (Mammals and birds): large body size, small population size, endotherms. Sexual reproduction with strong (epi)mutagenesis and stringent quality control resulting in narrow gamete bottleneck. Low fecundity. High impact of SMSC on preselected variation. Lower impact of natural selection.

West and colleagues (West and Deering, 1995; Bickel and West, 1998; West and Bickel, 1998) studied the evolution rates of mammalian DNA, based on recent estimates of numbers of nonsynonymous substitutions in 49 genes of human, rodents, and artiodactyls. The rate variations are better described by lognormal statistics, as would be the case for a multiplicative process, than by Gaussian statistics, which would correspond to a linear, additive process. The theoretical explanation of these statistics requires the evolution of different substitution rates in different genes to be a multiplicative process in that each rate results from the interaction of a number of interdependent contingency processes. A multiplicative process is one that will only occur if a number of sub-events take place, so that the probability of the

grand event occurring equals the product of the probabilities of each of the sub-events occurring (West and Deering, 1995; Bickel and West, 1998; West and Bickel, 1998). The joint action of the SMSC-natural selection complex could provide the sub-events for this multiplicative process.

Depending on the distribution of fitness effects of new mutations, Gillespie defined three specific model-based domains of molecular evolution (Gillespie, 1999; Jensen and Bachtrog, 2011). In the Ohta domain (Ohta, 1973), patterns of molecular evolution are driven mainly by slightly deleterious mutations (Gillespie, 1999). In this domain, the rate of substitution decreases with increasing effective population size, due to an increase in the efficiency of purifying selection against deleterious mutations. In the Kimura domain (Kimura, 1968), molecular evolution is dominated by mutations with no effect on fitness, and the rate of substitution is independent of the effective population size but simply given by the neutral mutation rate (Gillespie, 1999). Finally, in the Darwin domain, molecular evolution is driven by beneficial mutations, and the rate of substitution is predicted to increase with effective population size (Gillespie, 1999; Jensen and Bachtrog, 2011). If beneficial mutations are independent, rates of adaptation increase linearly with increasing population size. However, if beneficial mutations are common and linked, the rate of substitution will be substantially reduced and eventually become independent of the effective population size of a species (Gillespie, 2000). Within the SMSC regime, a greater fraction of changes will be explored in the larger effective population size of gametes and the role of stochastic processes will be reduced. Thus, the role of the Ohta domain is greatly reduced, as has been suggested by Otto and Hastings (1998) and the Darwin domain is increased.

There is considerable controversy about the fitness effects of mutations in mutation accumulation (MA) studies (Bataillon, 2000; 2003; Keightley and Lynch, 2003; Shaw et al., 2003) and the power of MA studies to detect beneficial mutations (Bataillon, 2000; 2003). These studies involve the use of experiments where mutations are allowed to accumulate in replicate populations under laboratory conditions and in the relative absence of natural selection. At the end of these experiments, the replicate lineages are then assessed for a range of fitness measures against a control lineage and an estimate of the number of new deleterious mutations per zygote per generation is then made (Lynch et al., 1999). Spontaneous MA experiments in *Drosophila* (Mukai et al., 1972; Fry et al., 1999; Lynch et al., 1999; Chavarrias et al.,

2001), *Caenorhabditis elegans* (Vassilieva and Lynch, 1999; Vassilieva et al., 2000), *Daphnia* (Lynch et al., 1998), wheat (Bataillon et al., 2000), yeast (Wloch et al., 2001a; Zeyl and de Visser, 2001), *E. coli* (Kibota and Lynch, 1996), and *Arabidopsis* (Schultz et al., 1999; Wright et al., 2002) detected downward trends in the mean fitness of MA line populations relative to control populations as generations accrued. However, equivocal results were obtained in *Arabidopsis thaliana* (Shaw et al., 2000; Shaw et al., 2002), *Drosophila* (Gilligan et al., 1997), *C. elegans* (Keightley and Caballero, 1997), and yeast (Zeyl et al., 2001), although some of these data were questioned (Keightley and Lynch, 2003), [but see Shaw et al. (2003) and Bataillon (2003)]. In addition, many animal models are maintained under such unnaturally favorable conditions that accumulation of deleterious mutations and fitness decline is inherent (Bryant and Reed, 1999; Lynch and O'Hely, 2001; Araki et al., 2007; 2009; Hall and Colegrave, 2008), an effect that cannot be prevented by the SMSCs of sexual reproduction. Importantly these animal models and MA experiments were conducted in taxa corresponding to the invertebrate type of the SMSC-natural selection pattern (see figure 1B) with larger census population sizes and less rigorous sexual selection cascades in which natural selection still plays an important role in maintaining population fitness.

In *Drosophila*, gamete population size during SMSC is small in relation to the population size under natural selection. In humans, the SMSC selects from a much larger gamete population size than processes related to natural selection. Accordingly, in *Drosophila* species (where population size is about 10^6), the proportion of nonsynonymous substitutions that have been fixed by positive selection is about 50% while for hominids (with population size around 10,000), this proportion is close to zero. Similarly, the proportion of nonsynonymous mutations that are effectively neutral is less than 16% in *Drosophila*, whereas it is about 30% in hominids (Eyre-Walker and Keightley, 2007). When selection at the cell and individual levels act in a cooperative manner, increased rather than decreased opportunity for germline selection will be favored by evolution (Otto and Hastings, 1998).

A riddle first pointed out 40 years ago on the basis of comparative allozyme data is the mysteriously narrow range of genetic diversity levels seen across taxa that vary markedly in their census population sizes (Lewontin, 1974; Leffler et al., 2012). As discussed earlier, the effective size of a population (N_e) determines the probability of (and time to) fixation or removal of mutant alleles (Lynch, 2006; Charlesworth,

2009). Extensive information on absolute population sizes, recombination rates, and mutation rates strongly supports the view that eukaryotes have reduced genetic effective population sizes relative to prokaryotes, with especially extreme reductions being the rule in multicellular lineages (Lynch, 2006). According to Kimura (1962), a simple population genetic model relates the probability of fixation of a mutation to effective population size and strength of selection. However, molecular evolution studies showed no conspicuous footprints of population size (Lewontin, 1974; Kimura, 1983; Gillespie, 1991a; b; 1999; 2001). For example, estimates of silent (Nachman, 1997) or amino acid (Nevo et al., 1984) variation among species are distressingly similar, suggesting at face value that the effective sizes of most species—from bacteria to humans—are within one order magnitude of each other (Lewontin, 1974). Accordingly, mathematical models that attempted to correlate polymorphism/molecular substitution rates with effective population sizes (Nevo et al., 1997a; Huzurbazar et al., 2010) faced a problem. Higher taxa that invariably have lower N_e than lower taxa have higher polymorphism/molecular substitution rates than can be explained by their N_e . Thus at face value, with decreasing effective population size the strength of selection increased (Huzurbazar et al., 2010). Alternative explanations for the insensitivity of molecular evolution to population size included: that natural selection is challenged by genetic drift (Ellegren, 2009); that a combination of population bottlenecks and historical effects may blunt the effects of N on evolution (Nei and Graur, 1984); that hitchhiking is analogous to bottlenecks in its ability to reduce genetic variation and render it less sensitive to population size (Maynard Smith and Haigh, 1974); and that linkage can amplify the effects of selection in small effective population size species (Nevo et al., 1997a). Moreover, it was argued that similarity of obvious mutation rates among lineages with vastly different generation lengths and physiological attributes points to a much greater contribution of replication-independent mutational processes to the overall mutation rate (Kumar and Subramanian, 2002). With the insights gained from the eco-evo theory of sexual reproduction, it can be concluded that the riddle resulted from the perspective restricting evolutionary processes to postnatal populations exposed to natural selection. Relating evolutionary processes to the joint (but presumably not additive) germ cell and postnatal population sizes that are subjected to both SMSCs and natural selection (figure 1) can be expected to resolve the molecular evolution–population size conundrum. That evolutionary processes in

populations with vastly differing population sizes, generation lengths and SMSCs yielded surprisingly similar evolutionary rates (that are not dependent on mutation rate, Huang, 2008) points to a general evolutionary principle that may guide all of life.

12. Random trial or educated guess?

The organisms we see today are deeply marked by the selective action of two (now we know it's almost four, KH) thousand million years' attrition. Any form in any way defective in its power of survival has been eliminated; and today the features of almost every form bear the marks of being adapted to ensure survival rather than any other possible outcome. Eyes, roots, cilia, shells and claws are so fashioned as to maximize the chance of survival. And when we study the brain we are again studying a means to survival.

Ross W. Ashby (1956, p. 196) *An Introduction to Cybernetics*

Summary

Evolution is a cybernetic process that has all attributes of a learning automaton. The feedback that is essential for any learning process comes from the selective survival/death of organisms, bestowing "educated guess" characteristics upon evolutionary processes. Educated guess approaches limit the search space and increase the likelihood that some of the variations generated will be useful. The Baldwin effect states that the ability of individuals to learn can guide and accelerate the evolutionary process. Non-stochastic engineering tools are the evolutionary result of learning processes: stress-induced mutagenesis, non-random recombination, mutability of simple sequence repeats, activity of transposable elements, phenotypic plasticity, all of which can act as evolutionary tuning knobs when (epi)genetic innovation is needed. Sexual reproduction, combining these elements in a single process, is the commander in chief of transgenerational information transfer.

The Modern Synthesis holds that (i) mutations occur independently of the environment, (ii) mutations are due to replication errors, and (iii) mutation rates are constant (Lenski and Mittler, 1993; Brisson, 2003). Currently, biologists usually agree that all genetic mutations occur by "chance" or at "random" with respect to adaptation (Miller, 2005) and the novel

allele is subsequently selected for or against (Davis, 1989; Rosenberg, 1994). The claim dates back to Darwin's conception of "spontaneous," "accidental" or "chance" variation (Darwin, 1859; Darwin and Seward, 1903). The Modern Synthesis later redefined Darwin's idea as rooted in the phenomenon of genetic mutation following a long period of controversy over the "chance" vs "directed" character of variation (Merlin, 2010). It has been argued that mutations must be random because natural selection cannot "assist the process of evolutionary change," since "selection lacks foresight, and no one has described a plausible way to provide it" (Dickinson and Seger, 1999). Such an evolutionary strategy was called a raffle or lottery (Stockley et al., 1997; Parker et al., 2010) and would correspond to a "random trial" approach: genetic change would arise at random, independent of its functional consequences and natural selection would decide which lottery ticket wins. However, even in a raffle approach the number of lottery tickets, as in sperm competition games (Parker, 1990), would increase the chances of a win.

However, it would be highly adaptive for organisms inhabiting variable environments to modulate mutational dynamics in ways likely to produce necessary adaptive mutations in a timely fashion. Metzgar and Wills (2000) argued that adaptively tuned mutation rates do not require any special foresight. Instead, they must have been selected for repeatedly in the past for their ability to generate genetic change. Mutational tuning does not require the specific generation of adaptive mutations (nonrandomness with respect to function) but rather the concentration of mutations under specific environmental conditions or in particular regions of the genome (nonrandomness with respect to time or location) (Metzgar and Wills, 2000).

In 1966, mathematicians, physicists and engineers met in Philadelphia (Moorhead and Kaplan, 1967). The mathematicians argued that neo-Darwinism faced a formidable combinatorial problem. Murray Eden illustrated the issue with reference to an imaginary library evolving by random changes to a single phrase: "Begin with a meaningful phrase, retype it with a few mistakes, make it longer by adding letters, and rearrange subsequences in the string of letters; then examine the result to see if the new phrase is meaningful. Repeat until the library is complete" (Eden, 1967). Would such an exercise have a realistic chance of succeeding, even granting it billions of years? In the view of mathematicians, the ratio of the number of functional genes and proteins, on the one hand, to the enormous number of possible sequences

corresponding to a gene or protein of a given length, on the other, seemed so small as to preclude the origin of genetic information by a random mutational search. A functional protein one hundred amino acids in length represents an extremely unlikely occurrence. There are roughly 10^{130} possible amino acid sequences of this length, if one considers only the 20 protein-forming acids as possibilities. In human codes, M. P. Schützenberger argued, randomness is never the friend of function, much less of progress. When we make changes randomly to computer programs, “we find that we have no chance (i.e. less than $1/10^{1000}$) even to see what the modified program would compute: it just jams.” (Schützenberger, 1967). Not surprisingly, these arguments were grist to the mill of the advocates of Intelligent Design (e.g. Meyer, 2008).

The term cybernetics stems from the Greek κυβερνητης (kybernetes, steersman, governor, pilot, or rudder). Cybernetics concerns the functioning of self-regulatory systems (Wiener, 1948; Ashby, 1956). Cybernetics requires a closed signal loop: action by the system causes some change in its environment and that change is fed to the system via information (feedback) that enables the system to change its behavior. The “random trial” and “trial and error” approaches differ in an important variable: feedback of outcome. “Random trial” lacks the feedback loop: it either cannot find out whether the trial was a success or failure or it is completely unable to learn from this knowledge. The “trial and error” approach has this feedback loop that identifies “errors”. In evolution this is Charles Darwin’s natural selection (Ackley and Littman, 1991) and Alfred R. Wallace’s elimination of the unfit (Smith CH, 2012a; b). A learning system is able to draw its lesson from the error and make its next trial less random. Thus, in contrast to the “random trial” approach, the “educated guess” approach is less random-driven but uses past experience to navigate future direction: the system is able to learn. “Educated guess” approaches limit the search space and increase the likelihood that some of the variations generated will be useful (Jablonka and Lamb, 2007). There is no great mystery about their evolution: they arose through natural selection as a side-effect or modification of functions that evolved for other purposes (Ackley and Littman, 1991; Jablonka and Lamb, 1995; 2005; 2007; Caporale, 1999; 2003a; b; 2009; Radman et al., 1999; Shapiro, 2011; King, 2012).

Learning is defined as any relatively permanent change in behavior resulting from past experience, and a learning system is characterized by its ability to improve its behavior with time, in some sense tending

towards an ultimate goal (Narendra and Thathachar, 1974). A vital component of the learning process is the environment. If the environment were relatively static, there might be little need for learning to evolve. Systems could instead evolve to a state where they have innate mechanisms to handle that environment. But if the environment is diverse and unpredictable, innate environment-specific mechanisms are of little use. Instead, individuals need general adaptive mechanisms to cope with arbitrary environments. In this way, a diverse environment encourages the evolution of learning (Chalmers, 1990). A learning automaton is an adaptive decision-making device that learns the optimal action out of a set of actions through repeated interactions with a random environment. The two characteristic features of learning automaton are that the action choice is based on a probability distribution over the action-set and it is this probability distribution that is updated at each instant based on the reinforcement feedback from the environment (Thathachar and Sastry, 2002).

Often evolution is characterized as cybernetic (e.g. Ashby, 1954; 1956; Schmalhausen, 1960; Waddington, 1961a; Corning, 2005). In his 1858 essay, A.R. Wallace referred to the evolutionary principle “as exactly like that of the centrifugal governor of the steam engine, which checks and corrects any irregularities almost before they become evident...”. For Gregory Bateson (1972, p. 435) “the result will be...a self-corrective system. Wallace, in fact, proposed the first cybernetic model.” However, the first account of how a phenotypic change induced by a change in the environment could lead to a change in the inherited genome was provided by Spalding (1837). Spalding’s driver of evolution comprised a sequence of learning followed by differential survival of those individuals that expressed the phenotype more efficiently without learning (Bateson, 2012). Fitness-related differential reproduction is the feedback control that drives the cybernetic system. With this feedback control adaptation proceeds by trial and error (Ashby, 1954).

The Baldwin effect, independently forwarded by Baldwin (1896), Lloyd Morgan (1896), and Osborn (1896), but largely so called because of Baldwin’s influential book (Baldwin, 1902), states that the ability of individuals to learn can guide and accelerate the evolutionary process (Hinton and Nowlan, 1987; French and Messinger, 1994; Weber and Depew, 2003; Sznajder et al., 2012). Currently, this principle is widely used in evolutionary computing and evolutionary algorithms (Ackley and Littman, 1991; Bull, 1999; Eiben and Smith, 2008; Paenke et al.,

2009). The Baldwin effect consists of the following two steps (Turney et al., 1996): In the first step, lifetime learning gives individual agents chances to change their phenotypes. If the learned traits are useful to agents and result in increased fitness, they will spread in the next population. This step means the synergy between learning and evolution. In the second step, if the environment is sufficiently stable, the evolutionary path finds innate traits that can replace learned traits, because of the cost of learning. This step is known as genetic assimilation (Arita and Suzuki, 2000). Mathematical models suggest that learning would speed up the adaptation process by providing more explicit information about the environment in the genotype (Sendhoff and Kreutz, 1999; Arita and Suzuki, 2000). Learning alters the shape of the search space in which evolution operates and thereby provides good evolutionary paths towards sets of co-adapted alleles. Hinton and Nowlan (1987) demonstrated that this effect allows learning organisms to evolve much faster than their non-learning equivalents, even though the characteristics acquired by the phenotype are not communicated to the genotype. However, orthodox evolutionary biologists tend to dismiss the Baldwin Effect. The orthodoxy of evolutionary biologists is strongly reductionist, "which implies that the causes and basic mechanisms of evolution are only to be found at the level of genetics" (Parisi et al., 1992). As a consequence, behavior and learning, both being highly holistic processes, have been largely ignored in attempting to understand evolutionary processes. Another reason for the lack of attention is that evolutionary biologists feel "behavior and learning are the province not of biology but of psychology and ethology" (Parisi et al., 1992; French and Messinger, 1994).

The organization and evolution of molecular and organismal diversity in nature at global, regional, and local scales are nonrandom and structured; display regularities across life; and are positively correlated with, and partly predictable by, abiotic and biotic environmental heterogeneity and stress (Nevo, 2001). Hotspots (and, by implication, coldspots) exist for nucleotide mutation, recombination, insertion/deletion, duplication and chromosomal rearrangements and are hence consequential for evolvability (Maki, 2002; Chen B et al., 2007). As discussed in chapter 2, the stress response (a cascade of internal and external changes triggered by stress) is a component of the ecological stress definition (Parker et al., 1999; van Straalen, 2003). The coping with stress is inherent to cybernetic systems. The necessary information feedback loop for learning systems is provided by Alfred R. Wallace's

elimination of the unfit (Smith CH, 2012a; b) and Darwin's survival and reproduction of the more stress-resilient organisms. In the following, I will discuss a variety of stress-dependent genetic and epigenetic phenomena that are not stochastic and can be inferred of being selected for by cybernetic processes.

12.1 Stress-induced mutagenesis

Sturtevant (1937) introduced the idea that the mutation rate is an evolvable property, and thus subject to optimization by natural selection. A large body of subsequent theoretical work has delimited the broad parameters under which the mutation rate is expected to evolve (Kimura, 1960; 1967; Leigh, 1973; Holsinger and Feldman, 1983; Kondrashov, 1995b; Dawson, 1998; Drake et al., 1998; Johnson, 1999; Sniegowski et al., 2000; André and Godelle, 2006; Baer et al., 2007; Lynch, 2010a; Shaw and Baer, 2011).

Stress-induced mutation is a collection of molecular mechanisms in bacterial, yeast and animal cells that promote mutagenesis specifically when cells are maladapted to their environment, i.e. when they are stressed. In this sense, stress-induced bacterial and eukaryotic mutagenesis (Achilli et al., 2004; Tenailon et al., 2004; Galhardo et al., 2007; Robleto et al., 2007; Pybus et al., 2010; Rosenberg, 2011; Shee et al., 2011a; b) is a bet-hedging behavior.

The mechanism of stress-induced mutagenesis understood in greatest detail is classical SOS mutagenesis (Friedberg et al., 1995; 2006; Sutton et al., 2000; Schlacher and Goodman, 2007). Suboptimal environmental conditions can influence the small- and large-scale genomic changes that occur in evolving populations. For example, exposure of *E. coli* cells to starvation, crowding, or nonoptimal temperature activates the SOS response (Finkel and Kolter, 1999; Storz and Hengge-Aronis, 2000; Hastings et al., 2004). SOS elevates rates of homologous and nonhomologous recombination, interferes with DNA polymerase proofreading, and induces error-prone replication (Abbott, 1985; Humayun, 1998; Napolitano et al., 2000; Storz and Hengge-Aronis, 2000; Yeiser et al., 2002).

A phenomenon called adaptive mutation in microbes indicates that mutation rates can be elevated in response to stress, over an order of magnitude higher than extrapolations from fast-growing cells, producing both deleterious and rare beneficial mutations (Loewe et al., 2003; Sniegowski, 2004). Mutations can arise in apparently static bacterial populations when subjected to nonlethal selective pressures (Ryan, 1959; Ryan et al., 1961; 1963; Shapiro, 1984; Cairns et al., 1988).

"Adaptive" or "stationary-phase" mutation is a collection of apparent stress responses in which cells exposed to a growth-limiting environment generate genetic changes, some of which can allow resumption of rapid growth (Loewe et al., 2003; Sniegowski, 2004). A stationary-phase-specific process, the expression of the "growth advantage in stationary phase" (GASP) phenotype, depends on the appearance of new mutations in the population (Zambrano et al., 1993; Zambrano and Kolter, 1996; Yeiser et al., 2002; Corzett et al., 2013). The new mutations confer a competitive advantage to cells, allowing them to take over the population. In the well-characterized Lac system of *Escherichia coli*, reversions of a lac frameshift allele give rise to adaptive point mutations (Cairns and Foster, 1991; Hastings et al., 2004; Foster, 2005). The otherwise high-fidelity process of double-strand break repair by homologous recombination is switched to an error-prone mode under the control of the RpoS general stress response (Ponder et al., 2005; Gonzalez et al., 2008; Shee et al., 2011a). *E. coli* encodes five DNA polymerases (Goodman, 2002; Johnson and O'Donnell, 2005; Friedberg, 2006). High-fidelity DNA polymerase (Pol) III performs the majority of DNA replication under vegetative conditions, with Pol I contributing principally to maturation of Okazaki fragments (Kornberg and Baker, 1992; Friedberg, 2006). Three alternative DNA polymerases (Pol II, Pol IV, and Pol V) perform a vital physiological role by mediating translesion synthesis, enabling efficient replication past DNA damage that would otherwise halt replication, albeit with significantly reduced fidelity (Goodman, 2002; Fuchs et al., 2004; Tippin et al., 2004; Nohmi, 2006; Bichara et al., 2011; Corzett et al., 2013). These error-prone DNA polymerases can be induced under a variety of environmental stresses (Taddei et al., 1995; Yeiser et al., 2002; Layton and Foster, 2003; 2005; Stumpf and Foster, 2005; MacPhee and Ambrose, 2010) and have been characterized most extensively following induction of the SOS regulon in response to DNA damage, leading them to be referred to as SOS-induced polymerases (Courcelle et al., 2001; Goodman, 2002; Friedberg, 2006; Nohmi, 2006; Yang and Woodgate, 2007). These alterations increase the rates of point mutation and genome rearrangement, making it likely that SOS plays a role in evolutionary change (Echols, 1981; Radman et al., 1999).

Also in this system, adaptive gene amplification has been documented as a separate and parallel response that allows growth on lactose medium without acquisition of a compensatory frameshift mutation (Andersson et al., 1998; 2011; Hastings and

Rosenberg, 2002; Hastings et al., 2004; Hersh et al., 2004; Roth and Andersson, 2004; Kugelberg et al., 2006; Slack et al., 2006). There are two ways that mutations could be directed – selective generation or selective capture (Hall, 1998). In fact, later evidence revealed that stressed cells also accumulate nonadaptive mutations at a higher rate than nonstressed cells, indicating that cells experiencing stress have an increased mutation rate genome-wide, suggesting a transient, possibly epigenetically regulated, hypermutability in a small fraction of the population (Foster, 1997; Torkelson et al., 1997; Rosche et al., 1999; Godoy et al., 2000; Loewe et al., 2003; Bjedov et al., 2003; Gonzalez et al., 2008).

Hypermutators arise through several mechanisms. For instance, general and specific DNA repair systems, mismatch repair (MMR), and oxidative damage repair have been shown to be repressed or inefficient in cells under conditions of stress in eukaryotic and bacterial systems (Feng et al., 1996; Mihaylova et al., 2003; Pedraza-Reyes and Yasbin, 2004; Hara et al., 2005; Saint-Ruf and Matic, 2006; Robleto et al., 2007; Vidales et al., 2009; Debora et al., 2011) while error-prone polymerases are active in stressed cells (Pham et al., 2001; Yeiser et al., 2002; Kivisaar, 2003; Sung et al., 2003; Duigou et al., 2004; 2005; Tegova et al., 2004; Tippin et al., 2004; Hara et al., 2005; Saint-Ruf and Matic, 2006; Corzett et al., 2013).

The occurrence of stress-induced mutagenesis is now widely accepted (Torkelson et al., 1997; Rosche and Foster, 1999; Godoy et al., 2000; Velkov, 2002; Bjedov et al., 2003; Kivisaar, 2003; Rosenberg and Hastings, 2003; Tenaillon et al., 2004; Wright, 2004; Foster, 2005; 2007; Galhardo et al., 2007; 2009; Sundin and Weigand, 2007; Zhang and Saier, 2009; 2011; Cohen and Walker, 2010; Gibson et al., 2010; Heo and Shakhnovich, 2010; Jayaraman, 2011; Pybus et al., 2010; Quinto-Aleman et al., 2011; Shee et al., 2011a; b; Corzett et al., 2013; Mittelman, 2013; but see Hendrickson et al., 2002, Roth et al., 2006; Andersson et al., 2011; Roth, 2011). In populations under various environmental stresses—stationary phase, starvation or temperature-jump—adaptation most often occurs through transient fixation of a mutator phenotype, regardless of the nature of stress. By contrast, the fixation mechanism does depend on the nature of stress. In temperature jump stress, mutators take over the population due to loss of stability of MMR complexes. In starvation and stationary phase stresses, however, a small number of mutators are supplied to the population via epigenetic stochastic noise in production of MMR proteins (a pleiotropic effect), and their net supply is higher due to

reduced genetic drift in slowly growing populations under stressful environments (Heo and Shakhnovich, 2010).

Transcription and replication are associated with mutation bias. Interference between DNA replication and transcription have been suggested as source of genomic instability (Poveda et al., 2010; Lin and Pasero, 2012; Helmrich et al., 2013). Transient DSBs are continuously created during transcription and replication (Costanzo et al., 2001; Dmitrieva et al., 2003; Ohnishi et al., 2009). In bacteria and yeast, proportional to transcription rate, transcription-associated mutagenesis (TAM), including single-base substitutions and insertions/deletions, and transcription-associated recombination (TAR) were demonstrated (Herman and Dworkin, 1971; Savic and Kanazir, 1972; Ripley, 1982; de Boer and Ripley, 1984; Keil and Roeder, 1984; Voekel-Meiman et al., 1987; Davis, 1989; Datta and Jinks-Robertson, 1995; Beletskii and Bhagwat, 1996; 2001; Klapacz and Bhagwat, 2002; 2005; Mokkaapati and Bhagwat, 2002; Hudson et al., 2003; Reimers et al., 2004; Ross et al., 2006; Saxowsky and Doetsch, 2006; Kim et al., 2007; Fix et al., 2008; Kim H et al., 2010; Pybus et al., 2010; Lippert et al., 2011; Kim and Jinks-Robertson, 2012). Adaptive mutation during prolonged nutritional stress in cells that are not dividing and in genes whose functions are selected is associated with induction of several affected genes (Wright et al., 1999). Recently, TAM was demonstrated in an inducible allele in stationary cells under selective pressure (Pybus et al., 2010). This association could explain why adaptive mutations often appear directed and how cells under these conditions avoid the accumulation of lethal mutations (Davis, 1989). The expression level of a protein is one of the major determinants of molecular evolution (Sharp, 1991; Green et al., 1993; Duret and Mouchiroud, 2000; Pál et al., 2001; 2006; Krylov et al., 2003; Rocha and Danchin, 2004; Zhang and Li, 2004; Agrafioti et al., 2005; Drummond et al., 2005; 2006; Koonin and Wolf, 2006; Rocha, 2006; Drummond and Wilke, 2008). Studies on the yeast *Saccharomyces cerevisiae* indicate that the strongest predictor of evolutionary rate is expression level of a protein that explains 30–50% of the variation in the rate of protein evolution (Pál et al., 2001; Drummond et al., 2005; 2006), much more than any other known variable. Likewise, transcription enhances site-directed mutagenesis and recombination in mammalian cells (Nickoloff, 1992; Skandalis et al., 1994; Bachl et al., 2001; Aguilera, 2002; Green et al., 2003; Sohail et al., 2003; Saxowsky and Doetsch, 2006; Gottipati et al., 2008; Da Sylva et al., 2009; Mugal et al., 2009; Hendriks et al., 2010).

During transcription, the nontranscribed strand becomes single stranded and is much more vulnerable to most mutagens and oxidative stress than is the double-stranded DNA (Singer and Kusmierek, 1982; Fix and Glickman, 1987; Skandalis et al., 1994; Wright, 2000; Francino and Ochman, 2001) because it is not protected by pairing (Hoede et al., 2006). Thus, the nontranscribed strand has been found to have greater numbers of mutations than the transcribed strand in *E. coli* (Beletskii and Bhagwat, 1996; Klapacz and Bhagwat, 2005; Fix et al., 2008) and humans (Skandalis et al., 1994; Green et al., 2003; Mugal et al., 2009). On the other hand, preferential repair of DNA base lesions from transcriptionally active genes compared to inactive regions (Bohr et al., 1985; Tu et al., 1996) and transcribed strand-specific repair (Leadon and Cooper, 1993) have been observed. Stressors such as heat (Maresca and Schwartz, 2006), starvation (Hastings et al., 2004), inflammation (Blanco et al., 2007; Lavon et al., 2007), toxins (Salnikow and Zhitkovich, 2008), free radical injury (Cerdeira and Weitzman, 1997), or other sources of DNA damage (Ponder et al., 2005) can modify gene transcription and thus alter the rate of mutations affecting fitness (Galhardo et al., 2007). Transcription thus has the potential to modify the genetic landscape by locally altering mutation rates, by stimulating loss of heterozygosity and by generating diverse types of rearrangements that include deletions, duplications, inversions and translocations (Davis, 1989; Kim and Jinks-Robertson, 2012).

Bacteria have specific loci that are highly mutable (Moxon et al., 1994). The coexistence within bacterial genomes of such 'contingency' genes with high mutation rates, and 'housekeeping' genes with low mutation rates, is the result of adaptive evolution, and facilitates the efficient exploration of phenotypic solutions to unpredictable aspects of the host environment while minimizing deleterious effects on fitness (Moxon et al., 1994). Mutation bias is a direction-giving factor, invoking the effects of deletion:insertion bias (Petrov and Hartl, 1998), strand-specific nucleotide biases (Beletskii and Bhagwat, 1996), CpG bias (Fryxell and Zuckerkandl, 2000), GC-biased gene conversion (Marais, 2003; Berglund et al., 2009; Duret and Galtier, 2009; Romiguier et al., 2010; Capra and Pollard, 2011) and GC:AT bias (Lobry, 1997; Singer and Hickey, 2000).

Mutagenesis associated with transcription of simple sequence repeats (see chapter 12.3) and TEs (see chapter 12.4) are major sources of genetic variation. Studies on *E. coli* reveal a major contribution of transposons and insertion elements to mutagenesis

(Arber et al., 1994). Importantly, TAM is not dependent on efficient translation of mRNA (Mokkapati and Bhagwat, 2002). Evidence favoring the inducible (adaptive) evolutionary paradigm over neutrality has been accumulated for bacterial (Ponder et al., 2005; Cirz and Romesberg, 2007), plant (Galloway and Etersson, 2007) and metazoan genomes (Levasseur et al., 2007) and include faster-than-expected rates of phenotype acquisition, close temporal correlation with environmental changes and proof of improved fitness.

12.2 Non-random recombination

Increased recombination has been observed in response to stress (fitness-associated recombination) (Plough, 1917; Grell, 1971; Zhuchenko et al., 1986; Parsons, 1988; Gessler and Xu, 2000; Hadany and Beker, 2003a; b; Schoustra et al., 2010; Zhong and Priest, 2011), including genetic stress (Tedman-Aucoin and Agrawal, 2012; Stevison, 2012). Mitotic recombination might itself be mutagenic owing to errors introduced during double-strand break repair (Lercher and Hurst, 2002). Indeed, the rate of recombination and the rate of substitutions are positively correlated (Lercher and Hurst, 2002). A number of studies have observed that recombination rates are positively correlated with extant levels of genetic variation in a wide variety of organisms, including *Drosophila* and humans (Aguade et al., 1989; Begun and Aquadro, 1992; Nachman et al., 1998; Stephan and Langley, 1998; Hamblin and Aquadro, 1999; Hardison et al., 2003; Hellmann et al., 2003; Lercher and Hurst, 2003; Roselius et al., 2005; Shapiro et al., 2007; Noor, 2008). Recombination can also lead to gross chromosomal rearrangements (Lambert et al., 2005). Thus mutation and recombination rates involve different kinds of genetic alterations, with mutation conferring gene-level changes, and recombination generating genome-level alterations (Heng, 2009). The consequences of their effect on the genome are radically different, but the selective process acting on the genetic diversity that they generate is the same. Hence, the rate of genetic-variant generation was defined as the joint sum of mutation and recombination rates (Capp, 2010).

Meiotic recombination events are not randomly distributed along the chromosomes, but occur at specialized sites, 1-2 kb long, called hotspots (Steinmetz et al., 1982; Petes, 2001; Pevzner and Tesler, 2003a, b; Kent et al., 2003; Bourque et al., 2004; McVean et al., 2004; Myers et al., 2005; Arnheim et al., 2007). In the human genome there is evidence for extreme local recombination rate variation spanning four orders in magnitude, in which

60% of all recombination events take place in about 6% of the sequence (McVean et al., 2004; The International HapMap Consortium, 2007). Recombination hotspots are a ubiquitous feature of the human genome, occurring on average every 200 kilobases or less, but recombination occurs preferentially outside genes (McVean et al., 2004). Gene functions associated with cell surfaces and external functions tend to show higher recombination rates (immunity, cell adhesion, extracellular matrix, ion channels, signalling) whereas those with lower recombination rates are typically internal to cells (chaperones, ligase, isomerase, synthase) (The International HapMap Consortium, 2007). Human hotspots are enriched for a degenerate 13 base pair (bp) motif, suggesting that underlying DNA sequence is a major determinant in hotspot specification (Myers et al., 2008). In yeast and mice, meiosis requires topoisomerase (Spo11)-induced DSBs for initiation of genetic crossovers (Keeney, 2007). Histone methylation marks define the vast majority of mammalian recombination hotspots (Baudat et al., 2010; Grey et al., 2011; Ségurel et al., 2011; Smagulova et al., 2011). A zinc finger protein with histone H3 lysine 4 methyltransferase activity, PRDM9 (Hayashi et al., 2005), is thought to bind to hotspot recognition sites in DNA and trimethylate nearby histones (H3K4me3), thereby activating chromatin and attracting the topoisomerase SPO11, which then catalyzes the initial DSBs. H3K4me3 is a prominent and preexisting mark in budding yeast and mammals for formation of the programmed DSBs (Borde et al., 2009; Buard et al., 2009; Kniewel and Keeney, 2009). Allelic variants of PRDM9 zinc fingers are significantly associated with variability in genome-wide hotspot usage among mammals (Baudat et al., 2010; Myers et al., 2010; Parvanov et al., 2010). However, the spatial correlation between H3K4me3 and DSB hotspots may be attributable to coincident localization of both to gene promoters (Buard et al., 2009; Tischfield and Keeney, 2012). Hotspots are still observed in Prdm9 knockout mice, and as in wild type, these hotspots are found at H3K4 trimethylation marks. Prdm9 knockout mice are proficient at initiating recombination (Hayashi et al., 2005). However, in the absence of PRDM9, most recombination is initiated at promoters and at other sites of PRDM9-independent H3K4 trimethylation. Such sites are rarely targeted in wild-type mice, indicating a role of the PRDM9 protein in sequestering the recombination machinery away from gene-promoter regions and other functional genomic elements (Brick et al., 2012). Recently published surveys of the rapidly evolving sequences of PRDM9 zinc fingers from multiple species of mammals

and diverse metazoans (Oliver et al., 2009; Thomas et al., 2009) suggest that PRDM9 may have been involved in hybrid sterility and speciation (Mihola et al., 2009; Sandovici and Sapienza, 2010) in multiple lineages on many occasions. In human peripheral lymphocyte metaphase, chromosomal regions with a high density of 8-oxodG, i.e. a higher susceptibility to oxidative damage, coincide with regions exhibiting a high meiotic recombination rate as well as with those with a high density of SNPs (Ohno et al., 2006).

12.3 Mutability of simple sequence repeats

Genomic microsatellites (simple sequence repeats; SSRs), iterations of 1 to 6 bp nucleotide motifs, have been detected in the genomes of every organism analysed so far, and are often found at frequencies much higher than would be predicted purely on the grounds of base composition (Tautz and Renz, 1984; Epplen et al., 1993; Toth et al., 2000). The number of repeated units can range anywhere from a few to hundreds or even thousands of copies. Estimates from the human genome reference sequence indicate that microsatellites may account for ~3% of the genome. This contribution, however, is highly approximate and depends strongly on how repeat length and sequence purity thresholds are defined (Kozłowski et al., 2010). On the other hand, approximately 50% of the human genome is occupied by repetitive sequences, including TEs (Jasinska and Krzyzosiak, 2004; Richard et al., 2008). Numerous lines of evidence have demonstrated that genomic distribution of SSRs is nonrandom, presumably due to strong selective pressures because of their effects on chromatin organization, regulation of gene activity, recombination, DNA replication, cell cycle, translation, mismatch repair (MMR) system, etc. (Li YC et al., 2002; 2004). Evolutionarily conserved SSRs are abundant in promoters in both the yeast and human genome (Vinces et al., 2009; Sawaya et al., 2013). On the other hand, numerous lines of evidence show that SSRs located in promoter regions and intronic regions can affect gene activity (Hoffman et al., 1990; Punt et al., 1990; Lafyatis et al., 1991; Sandaltzopoulos et al., 1995; Chen and Roxby, 1997; Meloni et al., 1998; Gebhardt et al., 1999; 2000; Vinces et al., 2009; Sawaya et al., 2013). SSR repeat number appears to be a key factor for gene expression and expression level (Hamada et al. 1984; Chamberlain et al., 1994; Lanz et al., 1995; Miret et al., 1998; Okladnova et al., 1998; Xu and Goodridge, 1998; Gebhardt et al., 1999; 2000; Liu L et al., 2000b; Li YC et al., 2002; 2004).

An immanent feature of microsatellites is their high mutability, which leads to both sequence and length polymorphism (Kelkar et al., 2008; Madsen et al., 2008;

Pumpernik et al., 2008), the latter being at least one order of magnitude greater than the former (Borstnik and Pumpernik, 2002; Pumpernik et al., 2008). The SSR mutation rates (10^{-2} to 10^{-6} events per locus per generation) are very high, as compared with the rates of point mutation at coding gene loci (Li YC et al., 2002; Ellegren, 2004; Payseur et al., 2011; Sun et al., 2012). SSRs encode their own mutability through the unit size, length, and purity of the repeat tract (Ellegren, 2004; King and Kashi, 2007; Legendre et al., 2007). For example, repeats consisting of short units are much more common and less stable (Schug et al., 1998) than repeats of longer units. Mutational mechanisms include DNA slippage during DNA replication (Tachida and Iizuka, 1992), recombination between DNA strands (Harding et al., 1992), or an interaction of both (Li YC et al., 2002). Generally, all DNA metabolic processes leading to transient separation of DNA strands such as replication, recombination, repair and transcription have stimulatory effects on repeat instability (Pearson et al., 2005; Wells et al., 2005; Wells and Ashizawa, 2006; López Castel et al., 2010; Mclvor et al., 2010). Several lines of evidence, accumulated from prokaryotic, yeast, mammalian cell culture and animal model studies indicate that transcription through repeating sequences is an important factor promoting their instability (Wierdl et al., 1996; Bowater et al., 1997; Mangiarini et al., 1997; Mochmann and Wells, 2004; Lin et al., 2006; 2009; Lin and Wilson, 2007; Soragni et al., 2008; Ditch et al., 2009; Mclvor et al., 2010). The persistent interaction between transcription template DNA and nascent RNA (RNA•DNA hybrids, R loops) was shown to stimulate genomic instability, identifying R loops as a common mutagenic conformation (Lin Y et al., 2010; Mclvor et al., 2010). Although the mutation process seems to display distinct differences among species, repeat types, loci and alleles, age and sex (Brock et al., 1999; Hancock, 1999; Ellegren, 2000; 2004; Schlötterer, 2000), the instability manifests predominantly as changes in the number of SSR repeats. DNA damage caused by external stresses such as UV irradiation, gamma-irradiation, t-butyl hydrogen peroxide, oxidative damage, etc. can induce slippage mutations and increase genetic instability in SSR sequences (Jackson et al., 1998; Jackson and Loeb, 2000; Chang et al., 2002; Slebos et al., 2002; Fonville et al., 2011). Stress-dependent SSR instability may be modulated by Hsp90 (Mittelman et al., 2010; Mittelman and Wilson, 2010; Fonville et al., 2011). DNA methylation in mammals is associated with repeat stability: demethylation of minor satellites, subtelomeric satellites, microsatellites and selfish repeats appears

to lead to increased recombination and mutagenesis and may result in destabilisation of the chromosome on which they reside (Hansen et al., 1999; Okano et al., 1999; Xu et al., 1999; Bourc'his and Bestor, 2004; Guo G et al., 2004; Kazazian, 2004; Kim M et al., 2004; Wang D et al., 2004; Gonzalo et al., 2006; Lees-Murdock and Walsh, 2008). Assaying microsatellite instabilities, a common phenotype associated with mutations affecting DNA replication fidelity/processivity or the MMR functions (Sia et al., 1997; Prolla et al., 1998), in mouse embryonic stem cells with homozygous deletion of the Dnmt1 gene and consequently a hypomethylated genome, the Dnmt1 null embryonic stem cells exhibited high microsatellite instability frequencies (4 to 7-fold increase in the microsatellite slippage rate) in comparison to the wild-type embryonic stem cells (Guo G et al., 2004; Kim M et al., 2004; Wang and Shen, 2004).

Emerging evidence implicates coding and noncoding SSRs as important sources of common, subclinical genetic variation in morphological and behavioral traits in numerous species, including humans, dogs, and flies (Goodman et al., 1997; Sawyer et al., 1997; Fondon and Garner, 2004; Kashi and King, 2006; Mittelman and Wilson, 2010). Coding microsatellites are enriched in genes for transcription factors and other regulatory proteins, and changes in the length of these repeats exert incremental impacts on gene function (Gerber et al., 1994; Wren et al., 2000; Albrecht et al., 2004; Bacolla et al., 2008). Variations in the lengths of noncoding repeats in the promoters of genes have been shown to quantitatively affect transcription and have likely facilitated transcriptional evolution (Vinces et al., 2009). SSRs located in the promoter, intronic, untranslated and coding regions of stress response genes may modulate the evolvability of organisms. In 296 *Escherichia coli* genes related to repair, recombination and physiological adaptations to different stresses, Rocha et al. (2002) observed a significant high number of short close repeats capable of inducing phenotypic variability by slipped-mismatch during DNA, RNA or protein synthesis. The authors suggested that overrepresentation of repeats in stress response genes may be a bacterial strategy to increase versatility under stressful conditions. In *Haemophilus influenzae*, tandem oligonucleotide repeats are far from being randomly distributed in the genome but are substantially overrepresented in genes encoding virulence determinants (Hood et al., 1996) potentially conferring an adaptive advantage in changing host environments. SSRs in promoter regions may serve as transcriptional elements for heat-shock protein genes in *Drosophila* (Sandaltzopoulos et al., 1995), *Aspergillus* (Punt et al.,

1990), and *Phytophthora* (Chen and Roxby, 1997). Based on evidence in a variety of taxa from virus and yeast to humans (Trecó and Arnheim 1986; Wahls and Moore 1990a; b; Aharoni et al., 1993; Majewski and Ott, 2000; Templeton et al., 2000), SSRs have been proposed as hot spots for recombination (Jeffreys et al., 1998; Templeton et al., 2000). Thus, SSRs as evolutionary tuning knobs may provide an evolutionary advantage of fast adaptation to new environments (Kashi et al., 1997; King et al., 1997; Trifonov, 2003; Kashi and King, 2006; Schmidt and Anderson, 2006; Fondon et al., 2008; Vincés et al., 2009; Gemayel et al., 2010; King, 2012b).

The effectiveness of the MMR system is critical to SSR stability. DNA methylation appears to be closely linked to MMR to maintain SSR (Kim M et al., 2004; Wang and Shen, 2004). In prokaryotic and eukaryotic cells, impaired function of MMR enzymes increases the rate of SSR mutation rates by several orders of magnitude (Levinson and Gutman, 1987a; Strand et al., 1993; Jiricny, 1994; Richards and Sutherland, 1994; Tautz and Schlötterer, 1994; Sia et al., 1997; Strauss et al., 1997; Tran et al., 1997). It is a paradox that the MMR system, which limits mutation in SSR sequences, is particularly vulnerable to mutation by virtue of having SSRs in its own coding regions (Chang et al., 2001). All "minor" components of the human DNA MMR system—MSH3, MSH6, PMS2, and MLH3—contain mononucleotide microsatellites in their coding sequences. The loss of activity in any one of these minor proteins generates a weaker mutator phenotype than occurs with loss of the major MMR proteins, MSH2 and MLH1 (Chang et al., 2001). A study of 10,000 random primate (primarily human) coding sequences (8.6 million base pairs) showed that the average-sized sequence coding for a human gene is expected to contain approximately 0.1, 0.03, and 0.006 mononucleotide runs of length 7 bp or more, 8 bp or more, and 9 bp or more, respectively (Metzgar et al., 2000). Together, the four minor MMR genes contain three 7-bp runs, four 8-bp runs, and one 9-bp run. Controlling for gene length, the probability of finding this many mononucleotide microsatellites by chance in a group of four genes is 1.3×10^{-6} (Chang et al., 2001). The constellation of microsatellites in the coding regions of the minor MMR genes is a general feature among eukaryotes (Chang et al., 2001). SSR instability in humans is associated with such DNA MMR genes as MLH1 (Boyer et al., 1995), MSH2, MSH3, and MSH6 (Boyer et al., 1995; Clark et al., 1999). When these genes mutate or become defective, SSR instability consequently increases. Mononucleotide repeats have a strong influence on the local mutation rate (Levinson and Gutman, 1987b).

In yeast, extending a mononucleotide repeat (of length ≥ 4) by one nucleotide leads to an increase in the local mutation rate by about a factor of two (Tran et al., 1997). Nontriplet microsatellites, when located in coding sequences, are expected to introduce frameshift loss-of-function mutations at high frequency (Moxon et al. 1994). The authors hypothesized that the exceptional density of microsatellites in the minor MMR genes represents a genetic switch that allows the adaptive mutation rate to be modulated over evolutionary time (Chang et al., 2001).

Trinucleotide repeats (TNRs), whose numbers do not affect the reading frame, tend to be overrepresented in exons (Richard et al., 2008). The relative abundance of TNRs in coding regions and their selective enrichment in genes for transcription factors and other regulatory proteins suggest that TNRs provide a positive evolutionary benefit (Albrecht and Mundlos, 2005; Bacolla et al., 2008; Mittelman and Wilson, 2010). The features of TNRs that suggest their functionality include: (i) widespread occurrence in exons, (ii) formation of stable hairpin or quadruplex structures by some TNRs and (iii) coding for homo-amino acid tracts (Kozlowski et al., 2010). However, at more than 20 loci in the human genome, the lengthening of a TNR tract beyond some threshold causes a neurodegenerative or neuromuscular disorder (Albrecht and Mundlos 2005; Orr and Zoghbi, 2007; Bacolla and Wells, 2009; Orr, 2009; La Spada and Taylor, 2010; López Castel et al., 2010). More than 20 years ago, increase in length of TNRs was found to be a mutation responsible for spinobulbar muscular atrophy, fragile X syndrome and myotonic dystrophy type 1 (Fu et al., 1991; La Spada et al., 1991; Brook et al., 1991; Mahadevan et al., 1992; Tsilfidis et al., 1992). Since then, more than 20 human syndromes, including Huntington disease, many of the inherited ataxias, and the muscular dystrophies, as well as pathologies in plants and animals, have been attributed to repeat expansions (Wells and Ashizawa, 2006). These unusual mutations, termed dynamic mutations due to their unstable, progressive character and non-Mendelian inheritance occur predominantly at GC-rich repeat sequences (Pearson et al., 2005). Long TNRs tend to become unstable during their transmission to offspring, giving rise to progeny with longer repeat tracts (expansions) or shorter ones (contractions). The typical bias toward expansions leads to progressively more severe disease symptoms in the progeny in each subsequent generation. The extraordinarily high mutation frequency levels of Huntington's disease germline mutations are most consistent with a mutation process that occurs throughout germline mitotic divisions, rather than

resulting from a single meiotic event (Leeflang et al., 1999).

12.4 Activity of transposable elements

Barbara McClintock, who is best known for her discovery of transposable elements and their mobilization under stress, was later primarily interested in the sensory and decision-making (that is, cognitive) capacities of cells with damaged genomes (Shapiro, 2010) and concluded her Nobel Prize lecture (1984): "In the future, attention undoubtedly will be centred on the genome, with greater appreciation of its significance as a highly sensitive organ of the cell that monitors genomic activities and corrects common errors, senses unusual and unexpected events, and responds to them, often by restructuring the genome".

In species such as *Drosophila*, TEs comprise approximately 10% of heterochromatic (Bartolome et al., 2002) and only 2%–3% of euchromatic DNA (Bartolome et al., 2002; Kaminker et al., 2002) but cause over 50% of de novo mutations (Eickbush and Furano, 2002). While insertions of TEs are responsible for only ~0.1% of de novo mutations in humans, the figure is 100-fold higher in the laboratory mouse (Maksakova et al., 2006). The prevalence of mouse TE activity indicates that the genome of the laboratory mouse is presently behind in the "arms race" against invasion (Maksakova et al., 2006). Throughout phylogenesis, a multitude of abiotic and biotic stressors disrupt epigenetic regulation and mobilize TE (McClintock, 1984; Paquin and Williamson, 1984; Strand and McDonald, 1985; Rolfe and Banks, 1986; Bradshaw and McEntee, 1989; Ratner et al., 1992; Arnault and Dufournel, 1994; Pouteau et al., 1994; Wessler, 1996; Grandbastien, 1998; Capy et al., 2000; Morillon et al., 2000; Ikeda et al., 2001; Chen et al., 2003a; Daboussi and Capy, 2003; Lu and Ramos, 2003; Jorgensen, 2004; Pesheva et al., 2005; 2008; Todeschini et al., 2005; Farkash et al., 2006; Ilves, 2006; McGraw and Brookfield, 2006; de la Vega et al., 2007; Stoycheva et al., 2007b; 2010; Bouvet et al., 2008; Cam et al., 2008; Desalvo et al., 2008; Perez-Hormaeche et al., 2008; Oliver and Greene, 2009a; Zeh et al., 2009; Zhang and Saier, 2009; 2011; Rebollo et al., 2010; 2012; Casacuberta and González, 2013; Feng et al., 2013). Activation of TEs is not always directly triggered by a specific stress but the effects that such stress causes in other cellular mechanisms may allow a rapid activation of some particular TE copies (Dai et al., 2007; Coros et al., 2009). Noncoding and small interfering RNAs are another possible path by which TEs respond to stress (Hilbricht et al., 2008; Mariner et al., 2008; Lv et al., 2010; Yan et al., 2011; McCue et al., 2012). Alu

elements function as cell stress genes: different stress conditions cause an increase in the expression of Alu RNAs, which rapidly decreases upon recovery from stress (Häsler and Strub, 2006). Alu RNA has been implicated in regulating several aspects of gene expression such as alternative splicing, RNA editing, translation and miRNA expression and function (Häsler and Strub, 2006; Häsler et al., 2007). The evidence that only some specific TE families, and not all the TEs in the genome, are activated in response to stress and that these TEs respond to some specific stress conditions and not others, strongly suggest that activation of TEs by stress is not only a byproduct of genome deregulation. The consequences of TE activation in response to stress are diverse (Casacuberta and González, 2013). Stress-activated TEs: (i) contribute to major genomic rearrangements (Maumus et al., 2009), (ii) confer nearby genes the capacity to respond to stress (Guo and Levin, 2010; Servant et al., 2012), which may lead to the creation of new regulatory networks (Naito et al., 2009; Ito et al., 2011) and (iii) alter the genome randomly through insertion of the newly generated copies (Dai et al., 2007). Recently, it was found that Tf1, a long-terminal repeat retrotransposon in *Schizosaccharomyces pombe*, was activated by heat treatment and preferentially integrated into promoters and activated the expression of genes that themselves were induced by heat (Feng et al., 2013). The authors suggested that the integration preference of Tf1 for the promoters of stress response genes and the ability of Tf1 to enhance the expression of these genes co-evolved to promote the survival of cells under stress (Feng et al., 2013). Inserts of Tf1 can enhance the transcription of adjacent genes only if the genes have stress response promoters and are activated by the stressor and/or oxidative stress (Feng et al., 2013). These findings corroborate earlier evidence that TE insertion may be non-random and may be directed to target sites by various specific factors including transcription activators (Devine and Boeke, 1996; Singleton and Levin, 2002; Leem et al., 2008; Zhang and Saier, 2009; 2011; Majumdar et al., 2011; Mularoni et al., 2012).

Integration of TEs has the potential to wreak havoc by destroying coding sequences throughout the genome of the host cell. On the other hand, there is abundant evidence for the adaptive effects of TE activation events in bacteria (Schmidt and Anderson, 2006; Chou et al., 2009; Stoebel et al., 2009; Sun J et al., 2009b; Zhang and Saier, 2009; 2011; Stoebel and Dorman, 2010; Gaffé et al., 2011), plants (Yan L et al., 2006; Lin et al., 2007; Liu et al., 2008; Kanazawa et al., 2009; Chu et al., 2011), and animals (Schlenke and Begun, 2004; Aminetzach et al., 2005; Biemont

and Vieira, 2006; Darboux et al., 2007; Santangelo et al., 2007; González et al., 2008; 2009; 2010; González and Petrov, 2009; Naito et al., 2009; Schmidt et al., 2010; Franchini et al., 2011; Magwire et al., 2011; Casacuberta and González, 2013). The particular cases described may represent only the tip of the iceberg (Casacuberta and González, 2013). TEs can have a myriad of effects when they insert into new locations (Feschotte, 2008; Goodier and Kazazian, 2008; Gogvadze and Buzdin, 2009; Casacuberta and González, 2013) and can result in the acceleration of the evolution of genes in a myriad of ways providing a means for rapid species divergences in the affected lineages (Brookfield, 2004; Schmidt and Anderson, 2006; Böhne et al., 2008; Goodier and Kazazian, 2008; Oliver and Greene, 2009a; b; 2011; 2012; Rebollo et al., 2010; Hua-Van et al., 2011).

Some TEs display considerable target site selectivity while others display little obvious selectivity, although none appear to be truly "random." A variety of mechanisms for target site selection are used: (i) direct interactions between the recombinase and target DNA; (ii) interactions with accessory proteins that communicate both with the target DNA and the recombinase (Craig, 1997; Liao et al., 2000). TEs and host regulatory factors have coevolved in an arms race scenario (McDonald, 1998; Aravin et al., 2007b; Rebollo et al., 2012). A large body of evidence suggests that TEs play a significant role in the host response to an everchanging environment, both in prokaryote and in eukaryote organisms (Rebollo et al., 2010; 2012; Casacuberta and González, 2013). Bioinformatic surveys of TE-gene chimeric transcripts suggest that many gene promoters or alternative promoters are, in fact, derived from TEs (van de Lagemaat et al., 2003; Romanish et al., 2007; Conley et al., 2008; Feschotte, 2008; Faulkner et al., 2009; Rebollo et al., 2012). For example, in mouse and human, 18.1% and 31.4% of total transcription start sites, respectively, are located within TE sequences and are often found to be tissue specific (Faulkner et al., 2009). The preferential insertion of some TEs near genes may facilitate the exaptation of TE sequences as gene regulators (Feschotte and Pritham, 2007). It was postulated that a large fraction of gene promoters and enhancers were donated by ancient TEs, which may retain their cis-regulatory motifs but are so extensively degraded in overall structure that they are no longer recognizable as such (Rebollo et al., 2012). Domestication of TEs is also important in the evolution of genomes, such as the evolution of new protein-coding genes (including regulatory DNA binding factors), and regulatory small RNAs from TEs (Feschotte and Pritham, 2007; Sinzelle et al., 2009;

Werren, 2011). TEs are also passive generators of mutations. TEs that belong to the same family of elements and are located in different regions of the genome can act as substrates for ectopic recombination events generating rearrangements such as inversions, translocations or duplications (Schwartz et al., 1998; Hill et al., 2000; Bailey et al., 2003).

TEs can also act as vectors facilitating the horizontal transfer of new genetic content (HGT) (Ochman et al., 2000; Frost et al., 2005). This phenomenon has been extensively demonstrated in prokaryotes. As in prokaryotes, HGT has had an important role in eukaryote genome evolution (Keeling and Palmer, 2008; Syvanen, 2012). The evidence for HGT in diverse eukaryotes is expanding rapidly in organisms such as protists (Loftus et al., 2005), fungi (Fitzpatrick, 2012), nematodes (Haegeman et al., 2011) and in fish (Graham et al., 2008). Horizontal transfer of TEs has been reported in eukaryotic species as diverse as tetrapods, *Drosophila*, yeast and fungi (Anxolabéhère et al., 1988; Daniels et al., 1990; Maruyama and Hartl, 1991; Robertson and Lampe, 1995; Kordiš and Gubenšek, 1998; Gogolevsky et al., 2008; Lampe et al., 2003; Herédia et al., 2004; Hall et al., 2005; Pritham and Feschotte, 2007; Ray et al., 2007; Loreto et al., 2008; Pace et al., 2008; Gilbert et al., 2010; Schaack et al., 2010a). In eukaryotes, although TEs are capable of capturing and transferring genes at a high frequency within a species (Jiang et al., 2004; Morgante et al., 2005; Schaack et al., 2010a) they have not yet been found to transfer host genes between different species (Schaack et al., 2010a) although some authors predict that it will be soon discovered (Keeling and Palmer, 2008).

12.5 Phenotypic plasticity, genetic assimilation and accommodation

JM Baldwin (1896) noted: "The creatures which can stand the 'storm and stress' of the physical influences of the environment, and of the changes which occur in the environment, by undergoing modifications of their congenital functions or of the structures which they get congenitally—these creatures will live; while those which cannot, will not."

In nature, where environmental conditions are perpetually variable, organisms face the challenge of maximizing fitness under heterogeneous conditions. Selection has solved this problem in numerous ways including environmental canalization, which reduces environmental influence on trait expression (see chapter 10.4), and phenotypic plasticity, where a single genotype can produce multiple phenotypes under different environmental conditions. When a trait is canalized, it may be well-adapted to one

environment, but when a trait is plastic it may be well-adapted to many environments (Bradshaw, 1965; Pigliucci, 2001; Ghalambor et al., 2007).

Development is taken fairly broadly as the genotype-phenotype map (Lewontin, 1974; Wagner and Altenberg, 1996; Fontana and Schuster, 1998). Phenotypic plasticity is usually defined as a property of individual genotypes to produce different phenotypes when exposed to different environmental conditions (Pigliucci, 2001; West-Eberhard, 2003; Pigliucci et al., 2006). Phenotypic plasticity can be illustrated with the concept of a reaction norm, which is the representation of values that a trait takes across an environmental gradient (Woltereck, 1909; Waddington, 1942; de Jong, 1990; Weis and Gorman, 1990; Gomulkiewicz and Kirkpatrick, 1992; Via et al., 1995; Flatt, 2005; Aubin-Horth and Renn, 2009). Different genotypes may have different reaction norms, meaning that they respond differently to the same environmental conditions. Indeed, it is possible that one genotype responds to a change in an environmental variable while another does not change, or changes in another direction (Côté et al., 2007). The presence of genetic variation for a trait, along with the force of selection, determines whether selection acting on that trait will result in an evolutionary response. Therefore, if different genotypes in a population produce different reaction norms, and if the slope of the reaction norm is positively correlated with fitness, increased plasticity should evolve in that population for that particular trait (Schlichting and Pigliucci, 1998; Aubin-Horth and Renn, 2009).

Early on Wright (1931) pointed out that plasticity could also inhibit genetic divergence. If a species is plastic such that its phenotype matches the optimum in all environments, there would be no impetus for further evolution, an anti-Baldwin effect (Scheiner and Holt, 2012). Thus, the role of phenotypic plasticity in evolution has historically been a contentious issue because of debate over whether plasticity shields genotypes from selection (e.g. Grant, 1977; Levin, 1988; Falconer, 1989) or generates novel opportunities for selection to act (Robinson and Dukas, 1999; Pigliucci and Murren 2003; Price et al., 2003; West-Eberhard, 2003; Schlichting, 2004; Badyaev, 2005a; Ghalambor et al., 2007). Cumulative evidence suggests that both sides of the coin reflect evolutionary reality. Theoretical models for the evolution of adaptive phenotypic plasticity predict that given genetic variation, selection will favor adaptive plasticity when: (i) populations are exposed to variable environments, (ii) environments produce reliable cues, (iii) selection favors different phenotypes in each

environment, and (iv) no single phenotype exhibits superior fitness across all environments (Bradshaw, 1965; Levins, 1968; Via and Lande, 1985; Lively 1986; Gomulkiewicz and Kirkpatrick, 1992; Moran, 1992; Ghalambor et al., 2007). To a certain extent, phenotypic plasticity is at the level of phenotype—namely disturbance-related variation as bet-hedging strategy (Gabriel, 2005; Scheiner and Holt, 2012)—what stress-induced mutagenesis is at the level of genotype. This interpretation also implies that phenotypic plasticity is not necessarily adaptive (Padilla and Adolph, 1996; Ancel, 2000; Ghalambor et al., 2007) due to a considerable element of chance (Price et al., 2003) (like mutations that are rather deleterious than beneficial, see chapter 5.1). Moreover, adaptive plasticity or learning may allow genetically unfit individuals to compensate for the inadequacies of their genotypes and still attain high fitness. As a consequence, the genetic variation for fitness may become reduced and the response to selection may be slowed down (Johnston, 1982; Gordon, 1992; Papaj, 1994; Behera and Nanjundiah, 1995; Mayley, 1997; Ancel, 2000; Huey et al., 2003). However, in conjunction with natural selection in temporally and spatially heterogeneous environments, phenotypic plasticity is adaptive (Bradshaw, 1965; Levins, 1968; Provine, 1971; Schlichting, 1986; Scheiner and Lyman, 1989; de Jong, 1990; 1995; Brönmark and Miner, 1992; Newman, 1992; Scheiner, 1993; Day et al., 1994; Gotthard and Nylin, 1995; Robinson and Wilson, 1996; Blanckenhorn, 1998; Schlichting and Pigliucci, 1998; Agrawal AA, 2001; Pigliucci, 2001; Laurila et al., 2002; DeWitt and Scheiner, 2004; Laforsch and Tollrian 2004; Yeh and Price, 2004; Svanbäck and Eklöv, 2006; Latta et al., 2007; Rando and Verstrepen, 2007; Van Buskirk and Relyea, 2008; Beldade et al., 2011; Snell-Rood, 2012).

Like learning capacity and memory (Mery and Kawecki, 2002; 2003; 2005), phenotypic plasticity has its costs and limits (DeWitt et al., 1998; Reylea, 2002; Merilä et al., 2004; van Kleunen and Fischer, 2007; Van Buskirk and Steiner, 2009; Auld et al., 2010; Snell-Rood et al., 2010; Snell-Rood, 2012). In a meta-analysis of 27 studies (of 16 plant and 7 animal species) that measured selection on the degree of plasticity, plasticity tended to be more costly in treatments with greater stress but this was only true in studies of animals indicating that ecological costs increase in the context of competition, predation risk or resource limitation (Van Buskirk and Steiner, 2009). Because plasticity is a trait which is expressed across environments, hard and soft selection differentially favor plasticity and genetic specialization, respectively (Van Tienderen, 1991, 1997). If the environment

changes only very slowly relative to the generation time of the organism, then genetic specialization is favored over plasticity (Orzack, 1985). Obviously, for learning to be useful the environment must not change too fast relative to how fast the animal can learn (Dukas, 1998; Stomp et al., 2008). Since learning is expensive (Mery and Kawecki, 2002; 2003; 2005), in relatively stable environments there is rather a selective pressure for the evolution of instinctive behaviors (Turney, 1996).

Developmental plasticity is linked to epigenetic mechanisms (Bachmann, 1983; Aubin-Horth and Renn, 2009; Bonduriansky and Day, 2009; Beldade et al., 2011; Hallgrimsson and Hall, 2011; Valena and Moczek, 2012). A central question in considering evolutionary change in response to environmental change is whether the inherited epigenetic markers could facilitate genomic change (Johnson and Tricker, 2010; Bateson, 2012). Pál and Miklós (1999) and Price et al. (2003) modeled how phenotypic plasticity can allow for diversification by allowing for individuals to move among peaks on a fitness landscape. In a fitness landscape with multiple peaks and valleys, developmental variability can smooth the adaptive landscape to provide a directly increasing path of fitness to the highest peak. Thus, epigenetic inheritance and developmental variability allow initial survival of a genotype in response to novel or extreme environmental challenge, providing an opportunity for subsequent adaptation. This initial survival advantage arises from the way in which epigenetic inheritance and developmental variability smooth and broaden the landscape that relates genotype to fitness (Pál and Miklós, 1999; Frank, 2011).

The Baldwin effect, an interaction between non-heritable lifetime plasticity (e.g. learning) and evolution, has been shown to be able to guide evolutionary change and 'smooth out' abrupt fitness changes in fitness landscapes – thus enabling genetic evolution that would otherwise not occur (Borenstein et al., 2006; Mills and Watson, 2006; Frank, 2011). Phenotypic plasticity is an important mechanism by which populations can respond rapidly to changes in ecological conditions (Scheiner, 1993; Via et al., 1995; Pigliucci, 2001; Latta et al., 2007). Hinton and Nowlan (1987) demonstrated that phenotypic plasticity (specifically, lifetime learning by individuals) can enable an evolutionary system to find optima that would be very difficult to find without plasticity. Thus, lifetime learning in individuals can, in some situations, accelerate evolution by allowing individuals to exploit a novel environment if they possess the capacity to develop a new phenotype when faced with that novel

environment (Price et al., 2003; Yeh and Price, 2004). Thus, adaptive plasticity that places populations close enough to a new phenotypic optimum for directional selection to act can enhance fitness and is most likely to facilitate adaptive evolution in new and variable environments (Hinton and Nowlan, 1987; de Jong, 1995; Ancel, 1999; Robinson and Dukas, 1999; Pigliucci and Murren, 2003; Price et al., 2003; West-Eberhard, 2003; Behera and Nanjundiah, 2004; Schlichting, 2004; Yeh and Price, 2004; Badyaev, 2005a; 2009; Ghilambor et al., 2007; Moczek et al., 2011). Implicit in this hypothesis is the idea that genetic variation for plasticity exists (Khan et al., 1976; Jain, 1978; Newman, 1994; Stinchcombe et al., 2004) and plastic individuals will be favored over nonplastic ones in changing environments by natural selection (Nussey et al., 2005).

Lamm and Jablonka (2008) argued that the very same mechanisms may be involved in both plasticity and evolvability. Epigenetic inheritance leads to transgenerationally extended plasticity, and developmentally-induced heritable epigenetic variations provide additional foci for selection that can lead to evolutionary change. The epigenetic mechanisms involved in repatterning can be activated by both environmental and genomic stress, and lead to phylogenetic as well as ontogenetic changes. Hence, the effects and the mechanisms of plasticity directly contribute to evolvability (Lamm and Jablonka, 2008). Heritable plasticity can also respond to (1) artificial selection in which the experimenter selects on a focal trait or trait index, and (2) quasi-natural selection in which the experimenter establishes a set of environmental conditions and then allows the population to evolve (Scheiner, 1993; 2002). Rather than plasticity per se being adaptive, it acts as a form of bet-hedging by producing increased phenotypic variation among offspring (Scheiner and Holt, 2012). Species invading novel or extreme environments often, but not always, display increased plasticity compared to populations from the native range (Chapman et al., 2000; Lee CE et al., 2003; Dybdahl and Kane, 2005; Chun et al., 2007; Cano et al., 2008; Lardies and Bozinovic, 2008; Lombaert et al., 2008). Intriguingly, phenotypic plasticity evolved experimentally in *Pseudomonas fluorescens* cultures as bet-hedging strategy in a fluctuating environment (Beaumont et al., 2009).

12.5.1 Assimilation and accommodation

Eventually, the new phenotype may become fixed through genetic assimilation, or there may be an evolutionary shift in the elevation or the slope of the reaction norm, a process referred to as genetic

accommodation (West-Eberhard 2003; Pigliucci et al., 2006; Suzuki and Nijhout, 2006; Crispo 2007; Aubin-Horth and Renn, 2009). Both Waddington's assimilation (Waddington, 1953a; b) and genetic accommodation (West-Eberhard, 2003; Braendle and Flatt, 2006) are considered manifestations of the Baldwin effect (Robinson and Dukas, 1999; Crispo, 2007). Phenotypic accommodation is the first step in a process of Darwinian evolution by natural selection, where fitness differences among genetically variable developmental variants cause phenotype-frequency change due to gene frequency change (West-Eberhard, 2005). Given genetic variation in the phenotypic response of different individuals, the initial spread produces a population that is variable in its sensitivity to the new input, and in the form of its response. If the phenotypic variation is associated with variation in reproductive success, natural selection results; and to the degree that the variants acted upon by selection are genetically variable, selection will produce genetic accommodation, a change in gene frequencies under selection (West-Eberhard, 2003; 2005). Genetic assimilation ("phenotype precedes genotype") is a common mode of evolution (Waddington, 1961b; Pál and Miklós, 1999; Pigliucci and Murren, 2003; Palmer, 2004; West-Eberhard, 2005). Waddington (1961b) explicitly defined genetic assimilation as "a process by which characters which were originally 'acquired characters' may become converted, by a process of selection acting for several or many generations on the population concerned, into 'inherited characters.'" Waddington's concept of "acquired characters" is clearly equivalent to what we now consider phenotypically plastic traits (Pigliucci and Murren, 2003). During the initial spread, the novel phenotype may increase in frequency rapidly, within a single generation, if it is due to an environmental effect that happens to be common or ubiquitous. In the classical neo-Darwinian genotype-precedes-phenotype mode, mutations initially generate more extreme forms. Alternatively, if it is due to a positively selected mutation, or is a side effect of a trait under positive selection (Müller, 1990), the increase in frequency of the trait may require many generations (West-Eberhard, 2003; 2005). The transgenerational processes that effect assimilation and/or accommodation involve both epigenetic and genetic changes. Within any given individual, a new selective environment is likely to induce a variety of responses in different traits (e.g. Williams et al., 1995; Parsons and Robinson, 2006). Thus, individuals are likely to be made up of both canalized traits that do not respond to novel environmental stimuli (see chapter 10.4) as well as traits that differ in the type of plasticity

they exhibit (adaptive and non-adaptive), resulting in individuals that represent a mosaic of traits (Ghalambor et al., 2007).

12.6 Sexual reproduction

Genetic assimilation is the process whereby environmentally induced phenotypic variation becomes constitutively produced (i.e. no longer requires the environmental signal for expression) (Pigliucci et al., 2006). According to this definition, sexual reproduction transformed a process that evolved as a response to environmental disturbance into a proactive bet-hedging tool. Engaging cellular stress for the creation of genetic variability and its purifying selection as a **proactive** strategy in the face of pervasive environmental change, sexual reproduction can be regarded as the ultimate paragon of “educated guess”.

13. Sexual reproduction: evolvability and robustness

increase of fitness,..., must be brought about largely by changes which increase either genetic stability or variability without bringing about corresponding decrease in the other component. A progressive change is thus one that increases the sum of these components.

J.M. Thoday (1953)

Summary

Genotype (sequence) robustness and evolvability share an antagonistic relationship. On one hand, high robustness implies low production of heritable phenotypic variation. On the other hand, an organism’s capacity to generate heritable phenotypic variation relates to the intrinsic capacity of organisms to evolve. Yet, robustness generally confers evolvability to living systems because it allows them to undergo innovative modification without losing functionality. Estimates of the rates of evolution from contemporary studies range from four to seven orders of magnitude higher than those seen in the fossil record. In particular, there is a striking disparity between spontaneous mutation rates, measured over a small number of generations in studies of pedigrees and the much lower substitution rates measured over geological time frames. Sustained responses to artificial selection do not exhaust genetic variation. The ecological pattern of evolutionary rate supports the notion of a universal dependence of molecular evolution on

oxidative stress. A rich body of evidence clearly shows that sex allows for faster adaptation in dynamic environments. Degeneracy, the ability of elements that are structurally different to yield the same output, may act both as a source of robustness and evolvability in biological systems. Sexual reproduction uses several genetic and epigenetic tools that may yield functionally equivalent results. Sexual reproduction succeeded to promote both evolvability and robustness by a process based on oxidative stress: (epi)mutagenesis enhances evolvability while gamete quality control preselects for the most robust and stress resilient gametes.

The ability for an evolving population to adapt to a novel environment is achieved through a balance of robustness and evolvability. Robustness is the invariance of phenotype in the face of perturbation and evolvability is the capacity to adapt in response to selection (McBride et al., 2008). Wagner (2008a) wrote: “Mutational robustness and evolvability, a system’s ability to produce heritable variation, harbour a paradoxical tension. On one hand, high robustness implies low production of heritable phenotypic variation. On the other hand, both experimental and computational analyses of neutral networks indicate that robustness enhances evolvability... [G]enotype (sequence) robustness and evolvability share an antagonistic relationship. In stark contrast, phenotype (structure) robustness promotes structure evolvability. A consequence is that finite populations of sequences with a robust phenotype can access large amounts of phenotypic variation while spreading through a neutral network. Population-level processes and phenotypes rather than individual sequences are key to understand the relationship between robustness and evolvability.”

Degeneracy is the ability of elements that are structurally different to perform the same function or yield the same output. It is a prominent property of gene networks, neural networks, and evolution itself. Edelman and Gally (2001) were the first to propose that degeneracy may act both as a source of robustness and evolvability in biological systems (Whitacre and Bender, 2010). Sexual reproduction uses several genetic and epigenetic tools (see chapters 10 and 12) that may yield functionally equivalent results. Thus, sexual reproduction succeeded to promote both evolvability and robustness by the same process based on oxidative stress: (epi)mutagenesis enhances evolvability while gamete quality control selects for the most robust and stress resilient gametes.

13.1 Evolvability

According to Pigliucci (2008), Flatt (2005) defined evolvability as “the ability of a population to respond to selection,” whereas Griswold (2006) thought in terms of the rate of evolution of a given character (which depends on its heritability, among other things). Houle (1992), however, proposed that the genetic coefficient of variation, rather than heritability, is actually the appropriate quantification of evolvability. Quayle and Bullock (2006) operationally measure evolvability as the time that it takes for a population to hit a given phenotypic target (although this makes the simplifying assumption that the target itself doesn’t shift over time, as a result of environmental changes). Wagner and Altenberg (1996) moved significantly from this ‘classical’ concept of evolvability with their groundbreaking articulation of the distinction between variation and variability as determining evolvability (Pigliucci, 2008). Variation is a measure of the realized differences within a population, whereas variability is the propensity of characters to vary (whether or not they actually do) and depends on the input of new genetic variation through mutation or recombination. For Kirschner and Gerhart (1998) evolvability is an organism’s capacity to generate heritable phenotypic variation that relates to the intrinsic capacity of organisms to evolve (Sniegowski and Murphy, 2006; Pigliucci, 2008).

In her preface to Volume 870 of the *Annals of the New York Academy of Sciences: Molecular Strategies in Biological Evolution*, Lynn Caporale (1999) wrote: “Most descriptions of mutation have emphasized its negative consequences, and randomness with respect to biological function. This book seeks to balance the discussion by emphasizing mechanisms that both diversify the genome and increase the probability that a genome’s descendants will survive... Genomes that encode ‘better’ amino acid sequences are at a selective advantage. Genomes that generate diversity also are at an advantage to the extent that they can navigate efficiently through the space of possible sequence changes.” Volume 870 is a testimony to the manifold “ingenious” processes (e.g. Radman et al., 1999) that organisms evolved to generate genetic diversity as response to environmental challenge, having “learned” since eons that evolution favors the prepared genome.

In his 1905 paper, Einstein proposed that the same random forces that cause the erratic Brownian motion of a particle also underlie the resistance to the macroscopic motion of that particle when a force is applied (Kaneko, 2009; Lehner and Kaneko, 2011). This insight can be generalized to state that the

response of a variable to perturbation should be proportional to the fluctuation of that variable in the absence of an applied force (Kubo et al., 1985). In short, the more something varies, the more it will respond to perturbation, irrespective of the precise molecular details. A generalized version of the fluctuation–response relationship can be applied to evolved, dynamical systems (Sato et al., 2003; Kaneko and Furusawa, 2006; Kaneko, 2009). The concept has been confirmed experimentally in unicellular prokaryotes and eukaryotes (Sato et al., 2003; Yomo et al., 2006; Lehner, 2010; Park H et al., 2010). The literature reveals significant effects of genetic diversity on ecological processes such as primary productivity, population recovery from disturbance, interspecific competition, community structure, and fluxes of energy and nutrients. Thus, genetic diversity can have important ecological consequences at the population, community and ecosystem levels, and in some cases the effects are comparable in magnitude to the effects of species diversity (Gamfeldt et al., 2005; Fussmann et al., 2007; Gamfeldt and Kallstrom, 2007; Lankau and Strauss, 2007; Hughes et al., 2008). Moreover, theoretical and empirical studies suggest that diversity at one level may depend on the diversity at the other (Whitham et al., 2003; Abrams, 2006; Crutsinger et al., 2006; Johnson et al., 2006; Vellend, 2006; Lankau and Strauss, 2007).

Many modern theories that attempt to provide an explanation for the advantage of sex incorporate an idea originally proposed by Weismann more than 100 years ago: sex allows natural selection to proceed more effectively because it increases genetic variation through the shuffling of existing genetic material (Weismann, 1889; 1904; Barton and Charlesworth, 1998; Burt, 2000). Fisher’s (1930) fundamental theorem of natural selection holds that the rate of increase in fitness in a population at a time equals the additive genetic variance in fitness at that time.

Mutation is the ultimate source of genetic variation. A large fraction of mutations are deleterious and reduce the fitness of the individuals in which they occur. Thus, spontaneous mutagenesis is in general not adaptive, whereas the direction of evolution depends on natural selection exerted on populations of genetic variants (Arber, 1999). Natural selection reduces genetic variation in a population, eliminating the not-fit-enough. In asexual species, the mutation rate is the main parameter affecting evolvability. Mutation rates can evolve in asexual conditions because an allele that increases the mutation rate (mutator allele) is not eliminated from the population by recombination even

if it generates many deleterious mutations (Hurst, 2009). Bacterial mutator alleles provide good examples of systems in which the ability to evolve is selected because of its immediate beneficial consequences (Sniegowski et al., 1997).

Genotypic diversity enhances the evolutionary responsiveness and adaptability of populations (Ayala, 1968a; Abrams and Matsuda, 1997; Yoshida et al., 2003; Gamfeldt et al., 2005; Reusch et al., 2005; Gamfeldt and Kallstrom, 2007; Becks and Agrawal, 2012; Roze, 2012). Genotypic diversity of the seagrass *Zostera marina* enhances ecosystem stability and therefore buffers against biotic or abiotic disturbances (Hughes and Stachowicz, 2004; Reusch et al., 2005; Reusch and Hughes, 2006; Ehlers et al., 2008). Transects with high genotypic diversity recovered faster from grazing (Hughes and Stachowicz, 2004) and after a high temperature period compared with monoclonal transects (Reusch et al., 2005). Moreover, genotypic diversity increased resistance against parasites in leafcutting ants (Hughes and Boomsma, 2004). Genotypically diverse populations also bear a competitive advantage towards monoclonal populations in *Daphnia* (Tagg et al., 2005a; b). Genotypic diversity increases competitiveness in invading and resisting invasions of monoclonal populations (Tagg et al., 2005b). Conversely, erosion of genetic diversity impedes adaptive responses to stressful environments (Bijlsma and Loeschcke, 2012; Dierks et al., 2012). In summary, high genotypic diversity serves as a buffer against interfering biotic and abiotic disturbances.

Molecular biologists have long searched for molecular mechanisms responsible for tuning the rate of genetic-variant generation in fluctuating environments. In spite of several bacterial examples, no regulated variation in the genetic-variant generation has been identified in eukaryotic systems (Capp, 2010). Based notably on the example of industrial and pathogenic yeasts, Capp (2010) proposed a nonregulated molecular evolutionary mechanism for the appearance of the transient increase of the genetic-variant generation in eukaryotic cell populations facing challenging environments. The genetic-variant generation in the population was rapidly tuned as a result of a simple Darwinian process acting on the stochastic nature of gene expression (Capp, 2010).

The SMSC as introduced in this work represents the sought-after regulated genetic-variant generation. A faster response to selection is seen as an indicator for an increased genetic variance in fitness created by sex. Sex increases the rate of evolution (Kimura and Ohta, 1971; Kirkpatrick and Jenkins, 1989; Rice and

Chippindale, 2001; Butlin, 2002; Poon and Chao, 2004; Goddard et al., 2005; Cooper, 2007; Colegrave and Collins, 2008; Livnat et al., 2008), although evidence of sex constraining genomic and epigenetic variation and slowing down evolution also exists (Kondrashov and Kondrashov, 2001; Futuyama, 2010; Gorelick and Heng, 2011; Melián et al., 2012). There has been evidence that sex allows for faster adaptation in dynamic environments (Hamilton et al., 1990; Howard and Lively, 1994; Keightley and Otto, 2006; Goddard et al., 2005). Indications for faster adaptation has been shown for recombining regions/chromosomes compared with nonrecombining ones in several *Drosophila* species (McPhee and Robertson, 1970; Rice and Chippindale, 2001; Bachtrog and Charlesworth, 2002; Betancourt and Presgraves, 2002; Rice, 2002; Bachtrog, 2003; Presgraves, 2005). Adaptation to new evolutionary challenges should proceed faster in sexual populations than in asexual populations. Experiments with yeast and the green alga *Chlamydomonas reinhardtii* (Birdsell and Wills, 1996; Zeyl and Bell, 1997; Greig et al., 1998; Colegrave, 2002; Colegrave et al., 2002b; Kaltz and Bell, 2002; Goddard et al., 2005; Grimberg and Zeyl, 2005) along with work on other taxa (Rice, 2002; Rice and Chippindale, 2001), have largely supported the hypothesis (Albu et al., 2012). Accordingly, sexually reproducing populations are more likely to develop genetic resistance to pathogens, biocides or thermal stress than asexuals (Jaffe et al., 1997; Greig et al., 1998; Rispe and Pierre, 1998; Ooi and Yahara, 1999), at least in part by creating and maintaining genetic variability (Shufran et al., 1997; Bürger, 1999; Robson et al., 1999). Computer modeling indicates that the advantage of sexual reproduction can be substantial in conditions where the mutation rates are higher (Findlay and Rowe, 1990) as is achieved during responses to the selection pressure of a changing environment (Bürger, 1999; Waxman and Peck, 1999). Pre-selection of gametes has been predicted to have significant effects on the frequencies and types of mutations and alleles in a population (Otto and Hastings, 1998), substantially boosting evolvability. In both natural and artificial systems a picture is emerging of populations engaged not in hill-climbing (when they can be trapped on local hilltops) but rather drifting along connected networks of genotypes of equal fitness, with sporadic jumps between networks. These "neutral networks" are of particular significance if they have the "constant innovation" property for this raises the possibility that (given enough time) almost any possible fitness value can ultimately be attained by the population (Barnett, 1998).

Given that there is genetic variation in evolvability, it

can be selected for (Jones et al., 2007; Crombach and Hogeweg, 2008; Pigliucci, 2008; Salverda and de Visser, 2011). Turney (1999) suggested the following sufficient (but not necessary) condition for evolvability: If individuals A and B are equally fit but the fittest child of A is likely to be more fit than the fittest child of B, then A is more evolvable than B. The point of this condition is that evolution does not directly select for evolvability, since (by hypothesis) A and B are equally fit. In Turney's simple computational model, evolvability can increase indefinitely, even when there is no direct selection for evolvability (Turney, 1999). The model shows that increasing evolvability implies an accelerating evolutionary pace (Turney, 1999). For evolvability to increase, environmental change must occur within certain bounds. If there is too little change, there is no advantage to evolvability. If there is too much change, evolution cannot move fast enough to track the changes (Turney, 1999). RNA virus genotypes with similar fitness may differ in their evolvability (Burch and Chao, 2000; McBride et al., 2008). To understand what determines the long-term fate of different clones, each carrying a different set of beneficial mutations, Woods and co-workers (2011) "replayed" evolution by reviving an archived population of *Escherichia coli* from a long-term evolution experiment and compared the fitness and ultimate fates of four genetically distinct clones. The expected scenario was that eventual winners (EW) clones were already more fit than eventual losers (EL) clones at generation 500, but competition experiments showed that actually the opposite was the case. Surprisingly, two clones with beneficial mutations that would eventually take over the population after 1,500 generations had significantly lower competitive fitness after 500 generations than two clones with mutations that later went extinct. Replaying the experiment many times starting with the 500-generation EWs and ELs showed that the EWs indeed beat the ELs most of the time. Likewise, *E. coli* strains with larger fitness defects due to deleterious mutations are more evolvable than wild-type clones in terms of both the beneficial mutations accessible in their immediate mutational neighborhoods and integrated over evolutionary paths that traverse multiple beneficial mutations (Barrick et al., 2010).

Mammals, engaging an increased amount of oxidative stress during, particularly male, gametogenesis have evolved at more rapid rates than other organisms (Simpson, 1944; 1953; Romer, 1966; Van Valen, 1974; 1985; Cherry et al., 1982) and humans have evolved extremely rapidly relative to other mammals (Haldane, 1949a; Wyles et al., 1983; Zhang J et al., 2002; Clark et al., 2003; Pollard et al., 2006a; b; Prabhakar et al.,

2006; Bird et al., 2007; Hawks et al., 2007; Berglund et al., 2009).

Intriguingly, bet-hedging and evolvability have close links. Variation is the bet-hedging strategy to cover all bases in an often unpredictable environment (Cohen, 1966; Gillespie, 1973; 1974a; Slatkin, 1974; Tonegawa, 1983; Hairston and Munns, 1984; Seger and Brockmann, 1987; Moxon et al., 1994; Danforth, 1999; Meyers and Bull, 2002; Friedenberg, 2003; Balaban et al., 2004; Kussell and Leibler, 2005; Wolf et al., 2005; Venable, 2007; Acar et al., 2008; Ackermann et al., 2008; Beaumont et al., 2009; Olofsson et al., 2009; Childs et al., 2010; Gremer et al., 2012; Morrongiello et al., 2012; Starrfelt and Kokko, 2012). Importantly, variation on virtually every level of biological organization is both the bethedging strategy in variable environments and the firm basis of evolvability.

In evolutionary computation, the Genetic Algorithm (GA) is based on the "survival of the fittest" principle and simulates natural evolution on computer systems to solve complex problems. Individuals are selected and reproduced according to a fitness performance criterion. The fitter the individual, the higher are its chances to produce offspring. Since the process is biased towards the regions of the solution space which enclose the fittest individuals, the evolving population gradually loses diversity and converges. After a population has converged, it is very difficult to readapt to a new optimum when the environment changes (Cobb and Grefenstette, 1993; Simões and Costa, 2002; Bui et al., 2005). Thus, premature convergence is a problem for the GA as it gradually loses its exploratory ability during the evolutionary process under an oversimplified "survival of the fittest" principle. When used as a supplement to the "survival of the fittest" principle, evolvability is able to modify how selection proceeds in the GA and increase its exploratory capabilities (Wang and Wineberg, 2006). Thus, rather than the "survival of the fittest", the "survival of the more evolvable" is the organizing principle of a dynamic evolutionary process. Sexual reproduction is the fundamental strategy of evolvability set in action.

13.1.1 The ecological pattern of evolvability

Genetic diversity within populations and species diversity within communities are hypothesized to co-vary in space or time because of locality characteristics that influence the two levels of diversity via parallel processes, or because of direct effects of one level of diversity on the other via several different mechanisms (Vellend and Geber, 2005). The plausibility of genetic diversity–species diversity

relationships is supported by a variety of theoretical and empirical studies in ecology and evolution (Vellend and Geber, 2005).

Latitudinal gradients in species richness is one of the most universal and oldest known patterns in ecology and biogeography (Rohde, 1992; Brown and Lomolino, 1998; Hawkins et al., 2003a; Willig et al., 2003; Hillebrand, 2004a; b; Roy et al., 2004). Large data sets point towards climate as the major driving force of higher tropical species richness (Fischer, 1960; Stevens, 1989; Gaston, 1996; 2000; Cardillo, 1999; Hawkins and Porter, 2001; 2003; Francis and Currie, 2003; H-Acevedo and Currie, 2003; Hawkins BA et al., 2003a; b; 2007; Willig et al., 2003; Currie et al., 2004; Hawkins and Diniz-Filho, 2004; Cardillo et al., 2005). Faster tropical diversification has been implied by lower average taxon ages or higher rates of first appearances in the tropics (Stehli et al., 1969; Durazzi and Stehli, 1972; Hecht and Agan, 1972; Jablonski, 1993; Flessa and Jablonski, 1996; Allen A et al., 2006; Jablonski et al., 2006; Krug et al., 2007). At least 100 hypotheses have been proposed to explain this biogeographical pattern (e.g., Pianka, 1966; Rohde, 1978; 1992; Rahbek and Graves, 2001; Willig et al., 2003). There is little consensus as to which hypothesis (or combination of hypotheses) is the most likely explanation. Many hypotheses address how ecological processes might allow larger numbers of species to coexist in the tropics (e.g., productivity, energy, stability, spatial heterogeneity, predation, and competition hypotheses) (Pianka 1966; Willig et al., 2003). Several other hypotheses focus (explicitly or implicitly) on potential differences in rates of speciation and extinction between temperate and tropical regions (e.g., evolutionary rates hypothesis) (Willig et al., 2003; Mittelbach et al., 2007). A variety of correlations between, on the one hand, body size, metabolic rate, energy flux, ambient temperature and, on the other hand, variations in rates of nucleotide substitution, and tempo of macro- and micromolecular evolution have been recognized (Martin and Palumbi, 1993; Hawkins et al., 2003a; Pörtner, 2006; Kreft and Jetz, 2007; Welch et al., 2008; Sibly et al., 2012). Hypermutability is one of the most striking features of animal mitochondria: the mtDNA mutation rate is typically one order of magnitude higher than the nuclear one (Brown et al., 1979; Ballard and Whitlock, 2004; Lynch, 2006). This high mutation rate is one of the reasons why mtDNA is a very popular marker for biodiversity studies (Nabholz et al., 2009). There is a strong signal for the effects of metabolic rate on mitochondrial DNA evolution (Avise et al., 1992b; Adachi et al., 1993; Martin and Palumbi, 1993; Rand, 1994; Nunn and Stanley, 1998; Martin, 1999; Welch et al., 2008).

Cumulative evidence indicates that both mitochondrial ROS generation (Zar and Lancaster, 2000; Abele et al., 2002; Heise et al., 2003; 2006; Mujahid et al., 2005; 2007) and DNA damage by ROS (Eigner et al., 1961; Greer and Zamenhof, 1962; Lindahl and Nyberg, 1972; 1974; Frederico et al., 1990; Lindahl, 1993; Bruskov et al., 2002) are temperature-dependent. DNA repair capacity and net mutation rate are also temperature-dependent in a wide range of taxa (Muller, 1928; Lindgren, 1972 a; b; Savva, 1982; Raaphorst et al., 1999; Schmidt-Rose et al., 1999; El-Awadi et al., 2001; Lupu et al., 2004; 2006; Xu, 2004b). Thus, ambient temperature and energy flux drive molecular evolution in both plants, exo- and endothermic organisms (Currie, 1991; Bleiweiss, 1998; Abele et al., 2002; Allen A et al., 2002; 2006; Wright et al., 2003; 2006; 2010; 2011; Brown et al., 2004; Davies et al., 2004; Clarke and Gaston, 2006; Pörtner, 2006; Sanders et al., 2007; Hiddink and ter Hofstede, 2008; Jansson and Davies, 2008; Gillman et al., 2009; 2010; McCain, 2009; Stegen et al., 2009; Tittensor et al., 2010). On mountains, temperature decreases monotonically by an average of 0.6°C per 100-m elevational gain (Barry, 1992). Supporting the role of temperature, the diversity pattern is consistent both for temperature gradients due to latitude and elevation (Bleiweiss, 1998; Brown, 2001; Krömer et al., 2005; Kluge et al., 2006; Sanders et al., 2007; Gillman et al., 2009; McCain, 2009). The pattern of increased molecular evolution in species living in habitats with greater biologically available energy may also occur independently of latitudinal clines (Wright et al., 2003). These correlations led to the formulation of a metabolic eco-evolutionary model of biodiversity (Allen A et al., 2002; 2006; 2007; Brown et al., 2004; Stegen et al., 2009; 2012). Endothermic 'warmblooded' animals that use metabolism to maintain a constant body temperature (birds and mammals) have higher absolute rates of molecular evolution of mitochondrial and nuclear DNA than poikilothermic vertebrates with environmentally determined body temperatures, such as reptiles and fish (Martin et al., 1992; Adachi et al., 1993; Martin and Palumbi, 1993; Rand, 1994; Rico et al., 1996). The ecological pattern of evolutionary rate supports the notion of a universal dependence of molecular evolution on oxidative stress.

13.1.2 The tempo of evolution

For no bias can be more constricting than invisibility—and stasis, inevitably read as absence of evolution, had always been treated as a non-subject.

Gould and Eldredge, 1993

Mathematical models that mimic biological evolutionary processes have revealed that the

traditional view of Darwinian evolution, according to which the most fit of random mutants are selected, faces a major problem (Eden, 1967; Schützenberger, 1967; Bak et al., 1987; 1988; Bak, 1993; 1996; Fernández et al., 1998): It is much too slow to account for real evolution. Bak (1993, cited in Fernández et al., 1998) described the difficulty: "If, for the sake of argument, we imagine the outer world frozen (for a while) and try to construct from scratch an equally fit species by recourse to engineering techniques rather than by evolution, we will be forced to accept that eons are needed. By starting at a random configuration one certainly will reach a wrong and much less fit maximum. It would be necessary to systematically go through all configurations, involving exponentially large times." According to Kashtan et al. (2007), computer simulations that mimic natural evolution by incorporating replication, variation (e.g., mutation and recombination) and selection, typically observe a logarithmic slowdown in evolution: longer and longer periods are required for successive improvements in fitness (Lipson et al., 2002; Lenski et al., 2003; Kashtan and Alon, 2005). Simulations can take many thousands of generations to reach even relatively simple goals, such as Boolean functions of several variables (Lenski et al., 2003; Kashtan and Alon, 2005).

Both, coevolutionary systems and environmental variation may speed up the tempo of evolution. Both theoretical modeling and ecological evidence indicate that the rate of evolution is accelerated by coevolutionary patterns (Dieckmann and Law, 1996; Marrow et al., 1996; Fernández et al., 1998; Sorenson and Payne, 2001; Rice and Chippindale, 2002; Good-Avila et al., 2006). Likewise, temporally varying environments, particularly those that change over time in a modular fashion, such that each new environment shares some of the subproblems with the previous environment, can speed up evolution (Otto and Michalakis, 1998; Earl and Deem, 2004; Kashtan and Alon, 2005; Kashtan et al., 2007). By nature of the mathematical models, they could not identify the molecular processes that would be able to effect the evolutionary speedup.

Estimates of the rates of evolution from contemporary studies range from four to seven orders of magnitude higher than those seen in the fossil record (Gingerich, 1983; 2009; Reznick et al., 1997; Reznick and Ghalambor, 2001). Similarly, more than half a century ago, Kurtén (1959) found an inverse correlation between the rate of morphological evolution and the time interval over which the rate was measured. Specifically, the rate of morphological change between successive generations exceeded macroevolutionary

rates by several orders of magnitude. This time-dependent rate pattern was confirmed in a number of subsequent studies, which consistently showed that morphological evolutionary rates appeared faster when measured over shorter timescales (Gingerich, 1983; 2001; Roopnarine 2003). In the words of Gingerich (2009), "At... a rate found commonly in rate studies, a mammal could conceivably change from the size of a shrew to the size of a whale in 10^3 generations, and with suitable selection do this back and forth as many as $10^4 = 10,000$ times in the geological span of known insectivores and whales." Indeed, contemporary evolution can be very rapid (Ender, 1986; Thompson, 1998; Hendry and Kinnison, 1999; Yoshida et al., 2003; Reznick et al., 2004b; Hairston et al., 2005; Carroll et al., 2007; Latta et al., 2007; Schoener, 2011). Invasive species may be evolving with extraordinary rapidity in their new environments (Losos et al., 1997; Reznick et al., 1997; Diniz-Filho et al., 1999; Huey et al., 2000; 2005; Mooney and Cleland, 2001; Palumbi, 2001; Drummond et al., 2003; Blair and Wolfe, 2004; Schoener, 2011). A puzzling phenomenon has recently emerged in rates of molecular evolution estimated from DNA sequence data. In particular, there is a striking disparity between spontaneous mutation rates, measured over a small number of generations in studies of pedigrees and laboratory mutation-accumulation lines, and the much lower substitution rates measured over geological time frames (e.g., Parsons et al., 1997; Sigurdardóttir et al., 2000; Howell et al., 2003; Ho et al., 2005; 2008; 2011; Santos et al., 2005; Gibbs et al., 2009). Similarly, for the same virus a higher rate of evolution is obtained when the compared sequences correspond to viruses isolated within a short time span than when they correspond to isolates separated by a long time interval (Sobrino et al., 1986; Domingo, 2007). In a long-term evolution experiment of *D. melanogaster* over 600 generations, Burke et al. (2010) found little allele frequency differentiation between replicate populations. Adaptation was not associated with 'classic' sweeps whereby newly arising, unconditionally advantageous mutations become fixed (Burke et al., 2010). Thus, the substitution rate appears to be much lower than the mutation rate. This pattern is what can be expected from a model presented by Neher et al. (2010). In large populations, when the product of the population size N and the total beneficial mutation rate U_b is large, many new beneficial alleles can be segregating in the population simultaneously. The rate of adaptation in several models of such sexual populations increases linearly with NU_b only in sufficiently small populations. In large

populations, the rate of adaptation increases much more slowly as $\log NU_b$. This change from linear to logarithmic dependence on NU_b indicates that the rate of adaptation is limited by interference among multiple simultaneously segregating beneficial mutations rather than by the supply of beneficial mutations. As in the asexual case, because of interference between mutations, only a small fraction of the beneficial mutations fix—the rest are wasted. However, this fraction increases with increasing rate of recombination until it saturates at $NU_b s^2$, which is the limit of independently fixating mutations (Neher et al., 2010). Chevin and Hospital (2008) modeled the trajectory of an initially rare beneficial allele that does not reach fixation because its selective advantage is inversely proportional to the distance to a new phenotypic optimum, and that optimum is reached, because of other loci, before the variant fixes. This pattern resembles the situation in RNA viruses where evolution rates increase linearly with mutation rates for slowly mutating viruses. However, this relationship plateaus for fast mutating viruses (Sanjuán, 2012).

It is a long-standing issue whether this rapid evolution is based on standing genetic variation or is driven by *de novo* mutations. Understanding the source of variation for adaptation might tell us a great deal about the factors creating and maintaining genetic variation in natural populations (Hedrick, 1986; 2006; Lynch and Walsh, 1998; Barton and Keightley, 2002). The theory for standing variation assumes that newly beneficial alleles are neutral or deleterious prior to the change of environment and are maintained in the ancestral population through a balance of recurrent mutation, selection and drift (Orr and Betancourt, 2001; Hermisson and Pennings, 2005; Przeworski et al., 2005). Compared with new mutations, adaptation from standing genetic variation is thought to likely lead to faster evolution, the fixation of more alleles of small effect and the spread of more recessive alleles. There is potential to distinguish between adaptation from standing variation and that from new mutations by differences in the genomic signature of selection. Selection on standing genetic variation is ubiquitous in natural populations (Hill, 1982a; Hermisson and Pennings, 2005; Przeworski et al., 2005; Roff, 2007; Barrett and Schluter, 2008; Teotónio et al., 2010) and implicated in the rapid adaptive response to stressful environments (Jarosz and Lindquist, 2010). In artificial selection programs the time scale is usually considered too short for mutations to influence the rates or limits substantially, but this view has been questioned (Frankham, 1980). Hundreds of artificial selection experiments have generated changes in mean phenotypes well beyond the observed range in

the base population in just a few dozen generations (Falconer and Mackay, 1996), inspiring the view that quantitative variation is distributed over an effectively infinite number of loci with minuscule effects (Kimura, 1965; Lande, 1975; Bulmer, 1980). Much of the earliest work in theoretical population genetics downplayed the ability of mutation to overcome the force of selection (Fisher, 1930; Haldane, 1932). There have been continued responses over periods of 50 or more generations in some artificial selection experiments (Dudley, 1977; Enfield, 1980; Yoo, 1980a; b; c; Barton and Turelli, 1989; Falconer and Mackay, 1996; Weber, 1996; Weber et al., 1999; Barton and Keightley, 2002; Laurie et al., 2004). The record attained by artificial selection suggests that the response to selection is hardly limited to fine tuning (Reznick and Ghalambor, 2001), as has often been claimed (e.g., Gould and Eldredge, 1993). These sustained responses do not exhaust genetic variation (Frankham, 1980; Yoo, 1980b; Hill, 1982a; b; Dunnington and Siegel, 1996; Eitan and Soller, 2004; Laurie et al., 2004; Carlborg et al., 2006; Burke et al., 2010), arguing for a steady supply of new mutations. The increase in additive genetic variance due to mutation is $\sim 10^{-3}$ of the standing variation, which makes a significant contribution after ~ 50 generations of selection (Hill, 1982a; Lynch and Walsh, 1998). Genetic variation and, more specifically, lack of mutations should not and, it seems, does not limit at least straightforward selection response (Barton and Partridge, 2000).

Many aspects of reproduction are facilitated by proteins that control crucial cellular events such as mating type determination, spermatogenesis, gamete recognition, sperm-egg binding, etc. Contrary to their essential role, reproductive proteins are among the fastest evolving genes known to us (Civetta and Singh, 1995; Lee et al., 1995; Swanson and Vacquier, 1995; 1998; 2002; Metz and Palumbi, 1996; Ferris et al., 1997; Tsaur and Wu, 1997; Metz et al., 1998; Tsaur et al., 1998; Vacquier, 1998; Aguade, 1999; Hellberg and Vacquier, 1999; Gavrillets, 2000; Hellberg et al., 2000; Singh and Kulathinal, 2000; Wyckoff et al., 2000; Armbrust and Galindo, 2001; Swanson et al., 2001). For example, lysin, a sperm protein of marine invertebrates, evolves up to 50 times faster than the most rapidly evolving mammalian gene (Metz et al., 1998). Genome wide comparisons of some 1200 human-mouse orthologous genes have shown that many genes directly related to gamete adhesion rank in the top 5% of the most divergent genes (Makalowski et al., 1996). Likewise, accessory gland proteins, which are part of *Drosophila* seminal fluids, are twice as diverse between species as non-reproductive

Drosophila proteins (Civetta and Singh, 1995).

If evolution can be so fast, then why does it appear to be so slow in the genetic and geological fossil record? Stasis is a prevalent—perhaps the most prevalent—mode of evolution, especially pronounced on long timescales (Merilä et al., 2001; Gould 2002; Eldredge et al., 2005; Hairston et al., 2005; Estes and Arnold, 2007). Eldredge et al. (2005) reviewed how taxa can commonly exhibit both short-term evolutionary dynamics and long-term stasis and concluded that the complex pattern of selection imposed on geographically structured populations by heterogeneous environments and coevolution can paradoxically maintain stasis at the species level over long periods of time. Bell (2010) argued that selection fluctuates strongly over time with large changes in magnitude and frequent reversals in the direction of selection. This could retard the loss of genetic variation, with minimal long-term directional change. He supported this contention by estimates of selection coefficients, or other parameters directly related to selection coefficients, reported in contemporary population time-series (Bell, 2010). Carroll et al. (2007) explained the discrepancy between short-term fluctuating selection and long-term stasis: “Specifically, selection and evolution often fluctuate dramatically in direction through time, presumably tracking fluctuating environments, so that rapid short term changes rarely accumulate into long-term directional trends” (Gibbs and Grant, 1987; Hairston and Dillon, 1990; Ellner et al., 1999; Merilä et al., 2001; Grant and Grant, 2002; 2006; Calsbeek et al., 2012). Traits that are no longer under selective pressure degenerate or are fossilized to pseudogenes (Heininger, 2012). Inferential evidence that “stasis” is a highly dynamic process comes from the maintenance of a variety of processes that mediate adaptive plasticity (Masel et al., 2007). A coalescence of time scales on which ecological and evolutionary processes are acting has been proposed (Hairston et al., 2005; Carroll et al., 2007). For instance, in a prey-predator coevolutionary system (Abrams and Matsuda, 1997), the impact of prey evolution on predator per capita growth rate is 63% that of internal ecological dynamics (Hairston et al., 2005). For Darwin’s finches evolving in response to fluctuating rainfall (Grant and Grant, 2002) it has been estimated that evolutionary change has been more rapid than ecological change by a factor of 2.2 (Hairston et al., 2005). For a population of freshwater copepods whose life history evolves in response to fluctuating fish predation (Hairston and Dillon, 1990) evolutionary change has been estimated about one quarter the rate of ecological change – less than in the finch example, but nevertheless substantial (Hairston

et al., 2005).

On the other hand, it appears fairly generally accepted that stabilizing selection is an eminent cause of stasis (Vrba, 1980; Boucot, 1990; Gould, 2002, p. 880-5; Hansen and Houle, 2004; Estes and Arnold, 2007). Evolution is variously constrained on all levels of biological organization, from genome sequence to genome architecture, gene expression, molecular interactions and organismal phenotypes (Kimura, 1983; Clark, 1987; Loeschcke, 1987; Lynch, 2007a; Wolf et al., 2008; Koonin and Wolf, 2010). Viability and potential fitness gains, in a given genetic constraint, build a narrow evolutionary path (Tokuriki and Tawfik, 2009). Experiments showed that knockout of any essential gene confers a lethal phenotype to an organism (Fraser et al., 2000; Herring and Blattner, 2004). The number of such essential genes varies from organism to organism: all genes are essential in viruses, whereas in bacteria, essential genes can reach up to one-third of all genes (Zeldovich et al., 2007). Antagonistic pleiotropy (leading to negative genetic correlations), epistasis, and linkage disequilibrium can all constrain the generation of novel genotypes (Barton and Partridge, 2000). Pleiotropy is expected to constrain the rate of evolution (Otto, 2004), consistent with the observation that broadly expressed genes evolve more slowly (Hughes and Hughes, 1995; Hastings, 1996; Hurst and Smith, 1999; Duret and Mouchiroud, 2000; Hirsh and Fraser, 2001; Jordan et al., 2002; Subramanian and Kumar, 2004; Zhang and Li, 2004; Wall et al., 2005; Zhang and He, 2005; Liao and Zhang, 2006; Liao et al., 2006; Larracuenta et al., 2008). Long-term protein evolution is constrained by epistasis: substitutions that are accepted in one genotype are deleterious in another (Weinreich et al., 2005; Camps et al., 2007; Breen et al., 2012). Estimating the prevalence of epistasis in long-term protein evolution by relating data on amino-acid usage in 14 organelle proteins and 2 nuclear-encoded proteins to their rates of short-term evolution in at least 1,000 orthologues for each of these 16 proteins from species from a diverse phylogenetic background, Breen et al. (2012) found that the measured rate of amino-acid substitution in recent evolution is 20 times lower than the rate of neutral evolution and an order of magnitude lower than that expected in the absence of epistasis, indicating that epistasis is pervasive throughout protein evolution. The process of amino acid replacement in proteins is context-dependent, with substitution rates influenced by expression level, local structure, functional role, pleiotropic effects, and amino acids at other locations (Dayhoff et al., 1978; Jones DT et al., 1992; Overington et al., 1992; Koshi and Goldstein, 1995;

1998; Thorne et al., 1996; Jensen and Pedersen, 2000; Whelan and Goldman, 2001; Lartillot and Philippe, 2004; Pagel and Meade, 2004; Siepel and Haussler, 2004; Weinreich et al., 2005; 2006; Lovell and Robertson, 2010; Soskine and Tawfik, 2010; Salverda et al., 2011; Pollock et al., 2012). Often a limited number of trajectories might in fact be possible (Wood et al., 2005; Weinreich et al., 2006). Moreover, evolution in reverse is a widespread phenomenon in biology (Teotónio and Rose, 2000; 2001; 2002; Wiens, 2001; Porter and Crandall, 2003; Estes and Teotónio, 2009; Bell, 2010).

A mathematical model suggested a universal speed limit on the rate of molecular evolution by predicting that populations go extinct (via lethal mutagenesis) when mutation rate exceeds approximately six mutations per essential part of genome per replication for mesophilic organisms and one to two mutations per genome per replication for thermophilic ones (Zeldovich et al., 2007). There may be also upper limits imposed by functional or structural constraints; for example, excessive heterozygosity could interrupt chromosome pairing (Stephan and Langley, 1992) or lead to reproductive incompatibilities between individuals living in distant regions of the species' range (e.g. Seidel et al., 2008). For instance, MMR proteins actively inhibit recombination between diverged sequences (Chen and Jinks-Robertson, 1998; Kolodner and Marsischky, 1999), thus controlling rates of mutation and evolutionary adaptation.

The fossil record and molecular phylogenies indicate that evolutionary dynamics proceed by punctuational episodes rather than gradual change (Eldredge and Gould, 1972; Gould and Eldredge, 1977; 1993; Snieppen et al., 1995; Messier and Stewart, 1997; Cubo, 2003; Eldredge et al., 2005; Pagel et al., 2006; Hunt, 2007; Mattila and Bokma, 2008; Zeh et al., 2009; Venditti and Pagel, 2010; Laurin et al., 2012; Rabosky, 2012). Thereafter, pronounced decelerations in rates of phenotypic and genotypic evolution have been observed when populations are approaching a local adaptive peak (Lenski and Travisano 1994; Sniegowski et al., 1997; Cooper and Lenski, 2000; Elena and Lenski, 2003; Pagel et al., 2006). The exhaustion of beneficial variants—whether preexisting or potentially accessible by mutation, or the diminishing selective benefit of beneficial mutations may then slow the potential and speed of adaptation (de Visser et al., 1999; Chou et al., 2011) and increase the costs of mutagenesis. Starting from weak functional constraints near the time of origin of a gene there would be a gradual increase in selective pressures with time, resulting in fewer accepted

mutations in older versus more novel genes (Albà and Castresana, 2005). In well adapted populations living in stable habitats, conservation may become more important than innovation. Evolutionary models based on the asexual and sexual replication pathways in *Saccharomyces cerevisiae* suggested that sexual replication can eliminate genetic variation in a static environment, as well as lead to faster adaptation in a dynamic environment (Gorodetsky and Tannenbaum, 2008). But species-wide depletion of accessible beneficial mutations requires a degree of environmental constancy that is not typical of the earth's history (Lambeck and Chappell, 2001; Zachos et al., 2001; Eldredge et al., 2005).

Pronounced decelerations in rates of phenotypic evolution have been observed over thousands of generations in asexual populations of *E. coli* founded from a single cell (Cooper and Lenski, 2000). Stasis cannot derive from depletion of preexisting variation, nor from exhaustion of genetic variation more generally. In fact, the amount of genetic variation increased in these populations even as the rate of phenotypic evolution declined (Sniegowski et al., 1997). These populations evidently approached a local adaptive peak or plateau, at which point most potential (i.e., genetically accessible) beneficial mutations were fixed (Eldredge et al., 2005). Consistent with this explanation, the rate of adaptive evolution was re-accelerated by perturbing populations from their proximity to an adaptive peak, either by changing the environment (Travisano et al., 1995) or by introducing deleterious mutations (Moore FBG et al., 2000). In the framework of the fitness landscape described by Wright (1931), populations placed near the top of a fitness peak will experience less beneficial mutations than populations placed far from the adaptive optimum (Fisher, 1930; Lenski and Travisano, 1994; Elena and Lenski, 2003; Lázaro et al., 2003; Silander et al., 2007; Stich et al., 2010). Adaptation is therefore characterized by a pattern of diminishing returns — larger-effect mutations are typically substituted early on and smaller-effect ones later (Barton, 1998; Orr, 1998; 1999; 2005a; de Visser et al., 1999; Barton and Keightley, 2002; Barrick et al., 2009; Chou et al., 2011; Khan et al., 2011; Flynn et al., 2013). In genomes sampled through 40,000 generations from a laboratory population of *Escherichia coli*, although adaptation decelerated sharply, genomic evolution was nearly constant for 20,000 generations. Several lines of evidence indicate that almost all of these mutations were beneficial. This same population later evolved an elevated mutation rate and accumulated hundreds of additional mutations dominated by a neutral signature (Barrick et al., 2009). Complex species (those having

many characters) typically show slower increases in fitness during adaptation than do simple species (Orr, 2000b). Part of the reason is that the distance travelled to the optimum by a beneficial mutation is smaller in a complex than a simple species (this distance decreases with the square root of the number of characters) (Orr, 2000b). Recent work by Welch and Waxman (2003) indicates that this cost of complexity might be a general feature of adaptation (Orr, 2005a).

13.2 Robustness

Robustness can be defined as the tendency for a system to maintain functionality under perturbation. Mutational (or genetic) robustness is defined as the constancy of a phenotype in the face of deleterious mutations (Sanjuán et al., 2007). Waddington recognized decades ago that levels of phenotypic variation in natural populations tend to be small compared to what might be expected given typical levels of genetic and environmental variation (Waddington, 1957). Robustness seems to be the opposite of evolvability. If phenotypes are robust against mutation, it might be expected that a population will have difficulty adapting to an environmental change, as several studies have suggested (Ancel and Fontana, 2000; Carter et al., 2005; Sumedha et al. 2007; Cowperthwaite et al., 2008; Parter et al., 2008; Draghi et al., 2010). However, other studies contend that robust organisms are more adaptable (Bloom et al., 2006; Aldana et al., 2007; Elena and Sanjuán, 2008; McBride et al., 2008; Draghi et al., 2010; Wagner, 2012). Thus, robustness generally confers evolvability to living systems because it allows them to undergo innovative modification without losing functionality (Wagner, 2005a; Wagner, 2008a). High mutation rate is perhaps the most important prerequisite for adaptive genetic robustness (de Visser et al., 2003), so mutational robustness should be strongly selected in biological systems experiencing elevated mutation rates (Wagner et al., 1997; Montville et al., 2005). Evolution *in silico* demonstrated that faster replicating organisms can easily be out-competed at high mutation rates by slower replicators with greater mutational robustness (Wilke et al., 2001). The impact of deleterious mutations can be reduced when several genes contribute toward a single function, or when there are several copies of a single gene (Tautz, 1992; Wilkins, 1997). In both cases the consequence is genetic redundancy, also called genetic canalization (Gibson and Wagner, 2000). Phenotypic buffering of genomic mutations as provided by gene duplication and diploidy might have evolved to facilitate genetic

canalization in higher organisms (Krakauer and Plotkin, 2002; Gu et al., 2003). Biological systems are extraordinarily robust to perturbation by mutations, recombination and the environment. Intriguingly, populations evolved with higher mutation rates show a higher robustness under mutations (Mihaljev and Drossel, 2009). It has been proposed that this robustness might make them more evolvable. In fact, robustness is widely held to be a key factor advancing evolvability (Kirschner and Gerhart, 1998; Rutherford and Lindquist, 1998; Aharoni et al., 2005; Wagner, 2005a; b; 2008a; 2012; Masel and Siegal, 2009; Draghi et al., 2010; Masel and Trotter, 2010). Robustness to mutation allows genetic variation to accumulate in a cryptic state. Cryptic genetic variation is variation that is not normally seen by natural selection. A considerable amount of cryptic genetic variation may accumulate in the genomes of organisms, particularly when they are subjected to stabilizing selection (Hermisson and Wagner, 2004; Félix and Wagner, 2008; Le Rouzic and Carlborg, 2008; Masel and Siegal, 2009). Cryptic genetic variation is uncovered by environmental or genetic perturbations and might be an essential source of physiological and evolutionary potential (Gibson and Dworkin, 2004; Schlichting, 2008). Switching mechanisms known as evolutionary capacitors mean that the amount of heritable phenotypic variation available can be correlated to the degree of stress and hence to the novelty of the environment and remaining potential for adaptation. The best studied, but not only (Takahashi, 2012), putative evolutionary capacitor in a high recombination system is the heat shock protein Hsp90 (Rutherford and Lindquist, 1998; Queitsch et al., 2002; Rutherford, 2003; Debat et al., 2006; Kellermann et al., 2007; Rutherford et al., 2007a; b).

To my knowledge none of the theories attempting to explain the rationale for sexual reproduction acknowledged the implications that phenotypic robustness may have for the evolutionary benefits of sexual reproduction. Phenotypic robustness can be expected to attenuate and delay the immediate benefit of sexual reproduction-related genetic variation and hence, may be regarded as additional liability for the evolution of sexual reproduction.

14. Stress and sex: a double-edged relationship

Summary

The sex-stress/glucocorticoid relationship is

non-linear and is described by approximation as inverted “U”-shaped: sex is favored in intermediate stressful environments, while stable stressfree and extreme stressful environments favor asex. This modulation is mediated by a variety of endocrine, paracrine, and autocrine signals and intense cross talk between the hypothalamic–pituitary–adrenal (HPA) and hypothalamic–pituitary–gonadal (HPG) axes. Male reproductive performance is more susceptible to environmental stress, presumably due to the additive effects with endogenous gametogenetic stress. Additionally, in vertebrate males the HPG and HPA axes are linked in a double-negative feedback loop that toggles between sexual reproduction with functional males and asexual reproduction in response to trigger stimuli that impinge upon the feedback circuit. In contrast, the female vertebrate HPG axis is linked by a positive feedback to the HPA axis, while the HPA axis attenuates the HPG axis in a negative feedback loop, a pattern that can trigger oscillations which could explain the female menstrual cycles in vertebrates. There is evidence that the human spermatozoon is a cell in crisis, operating near the threshold of error catastrophe. Exemplarily, three hormonal systems, glucocorticoids, thyroid hormones and melatonin, are discussed that impinge upon the HPA and HPG axes and regulate reproductive activity and gonadal oxidative stress. Overall, HPA and HPG axes cross-talk on a multitude of levels to adapt sexual reproductive activity and (epi)mutagenesis as potential bet-hedging response to environmental conditions.

Sexual reproduction is intimately linked to ecological conditions (Lloyd, 1980). Sexual reproduction and stress are intimately related. Moderate levels of stress and stress mediators may have a positive effect on reproductive processes while greater stress has negative effects (Greenberg and Wingfield, 1987; Sapolsky et al., 2000; Moore and Jessop, 2003; Breuner et al., 2008; Milla et al., 2009; Schreck, 2010). Evolutionary theory predicts that stable environments to which organisms are well adapted would favor low mutation rates (anti-mutator genotypes), constrained only by the costs of error-repair mechanisms (Kimura, 1967; Drake, 1991). In contrast, environments subjected to frequent changes would select for increased mutation rates (mutator genotypes) that permit faster adaptation to the new conditions (de Visser, 2002; Travis and Travis, 2002; Denamur and Matic, 2006). Stressful environmental conditions elicit elevated (epi-)mutation and recombination rates and increased genetic and epigenetic diversity and

phenotypic variation. This occurs by at least two mechanisms: (i) the uncovering of pre-existing hidden variation or (ii) the generation of de novo variation, for example by increased (epi-)mutation, transposon activity, or sex/recombination (Plough, 1917; 1921; Neel, 1941; Grell, 1971; 1978; Nevo et al., 1979; 1997b; 1998; Balyaev and Borodin, 1982; Zhuchenko and Korol, 1983; Parsons, 1987; Hoffmann and Parsons, 1991; Hall, 1992; Steele and Jinks-Robertson, 1992; Korol et al., 1994; Abdullah and Borts, 2001; Finnegan, 2002; Lucht et al., 2002; Hadany and Beker, 2003a; b; Kovalchuck et al., 2003; Agrawal et al., 2005; Morgan, 2005; Molinier et al., 2006; Rando and Verstrepen, 2007; Baer, 2008; Boyko and Kovalchuk, 2011; Forche et al., 2011; Zhong and Priest, 2011; Grativol et al., 2012; Steinberg, 2012). Increased recombination in response to stress (fitness-associated recombination) (Plough, 1917; Grell, 1971; Zhuchenko et al., 1986; Gessler and Xu, 2000; Hadany and Beker, 2003a; Schoustra et al., 2010; Zhong and Priest, 2011) is thought to accelerate the rate of adaptation (Hadany and Beker, 2003b). In *Arabidopsis thaliana* plants treated with short wavelength radiation or flagellin (an elicitor of plant defences), somatic homologous recombination is increased in the treated population and these increased levels of homologous recombination persist in the subsequent, untreated generations (Molinier et al., 2006). In plants, animals, and fungi, TE activity increases in response to extrinsic stress and oxidative stress (McClintock, 1984; Arnault and Dufournel, 1994; Mhiri et al., 1997; Grandbastien, 1998; Capy et al., 2000; Ikeda et al., 2001; Chen et al., 2003a; Daboussi and Capy, 2003; Lu and Ramos, 2003; Jorgensen, 2004; McGraw and Brookfield, 2006; Bouvet et al., 2008; Cam et al., 2008; Perez-Hormaeche et al., 2008; Zeh et al., 2009; Rebollo et al., 2010; 2012; Stoycheva et al., 2010; Casacuberta and González, 2013).

A relationship between stressful conditions and elevated variance of physiological and phenotypic parameters has been documented in ecological studies (Møller and Swaddle, 1995; Orlando and Guillette, 2001; Joyner Matos, 2007; Fraterrigo and Rusak, 2008) that may even be useful as a biomarker (Callaghan and Holloway, 1999). Following environmental stress, both genetic and phenotypic variance of offspring increases (Balyaev and Borodin, 1982; Parsons, 1983; 1988; Nevo, 1988; 1998; 2001; 2011; Hoffmann and Parsons, 1991; 1997; Goho and Bell, 2000; Bublly and Loeschcke, 2002; Kis-Papo et al., 2003; Imasheva and Loeschcke, 2004; Badyaev, 2005a; b; Swindell and Bouzat, 2006; Theodorakis et al., 2006; Crean and Marshall, 2009) and heritability

decreases, at least for morphological traits (Charmantier and Garant, 2005; Wilson AJ et al., 2006). Environmental fluctuations are usually believed to play a "destructive role" in ecosystem dynamics and to act as a source of disturbance. However, noise is also known for its "constructive role", i.e., for the ability to create new ordered states in dynamical systems. Environmental noise may also enhance biodiversity (D'Odorico et al., 2008). An argument that has been repeatedly used to question the adaptive role of condition-dependent mutagenesis is that individuals in poor physiological condition have higher mutation rates for reasons having nothing to do with the possibility of generating a lucky beneficial mutation. Assuring the fidelity of DNA replication is metabolically costly and involves the products of many dozens to hundreds of genes (Wood et al., 2001). Individuals in poor condition will have fewer resources to devote to genomic surveillance, leading to the possibility that individuals in poor condition will suffer an increased mutation rate (Baer, 2008). Organisms apply two strategies to meet environmental challenges: resist or mutate (Heininger, 2001). To resist in periods of environmental harshness, highly efficient stress resilience mechanisms and states of metabolic dormancy (spores, diapause, hibernation) have evolved (Heininger, 2012). On the other hand, a generic thermodynamical analysis of genetic information storage yielded the insight that mutation rate depends on availability/utilization of metabolic resources. A lowered ability to employ metabolic resources in mutation suppression increase the minimum effective mutation rate. This predicts transient mutation rate increases as a response to stress (Hilbert, 2011).

Theoretical and experimental studies across a broad range of taxa demonstrate that sexual reproduction is favored in, and a response to, moderately stressful environments (Bell and Wolfe, 1985; Iglesias and Bell, 1989; Zeyl and Bell, 1997; Greig et al., 1998; Grishkan et al., 2003; Nedelcu and Michod, 2003; Eads et al., 2008; Martins et al., 2008; Denekamp et al., 2009; Steinberg, 2012). Likewise, oxidative stress as final common effector of stress signaling pathways is a general inducer of sexual reproductive activity (Bernstein and Johns, 1989; Heininger, 2001; Nedelcu and Michod, 2003; Nedelcu et al., 2004; Nedelcu, 2005; McInnis et al., 2006). In fungi, deletion or mutagenesis of NADPH oxidases that are used deliberately to produce ROS, specifically block differentiation of sexual fruit bodies, without affecting asexual development (Lara-Ortiz et al., 2003; Malagnac et al., 2004; Takemoto et al., 2007).

Gene swapping evolved as response to environmental variability. Facultatively sexual organisms often engage in sex more often when in poor condition. Aply, the term condition-dependent sex was coined (Hadany and Otto, 2007; 2009). Like condition-dependent mutagenesis (Baer, 2008) sexual reproduction is fitness-dependent in these organisms. Intriguingly, as a legacy to these shared evolutionary roots, similar neurotransmitters and highly connected nuclei within the hypothalamus of mammals control stress and reproduction (Dobson et al., 2003). Sexual reproduction "institutionalized" the generation of genetic variation as proactive coping strategy to biotic and abiotic variability and unpredictability. Ingeniously, applying a harsh stress-related gamete quality assurance, sexual reproduction introduced increasingly sophisticated selection regimes that selected gametes for their stress resistance, viability and metabolic efficiency.

The coin, however, has its flip side. Requiring a substantial amount of physiological and oxidative stress for its basic functions (Riley and Behrman, 1991; Heininger, 2001; Agarwal et al., 2003; 2005; Lue et al., 2003; Nedelcu, 2005; Aitken and Roman, 2008; Metcalfe and Alonso-Alvarez, 2010), the reproductive system, and particularly gametogenesis, is highly sensitive to additional abiotic and biotic stress. The double-edged relationship between sexual reproduction and stress is epitomized by evidence that pro-inflammatory cytokines both can stimulate (Verhoeven et al., 1988; Warren et al., 1990; Svechnikov et al., 2001) and inhibit (Lin et al., 1991; Hales, 1992; Mauduit et al., 1992; 1998; Xiong and Hales, 1994; Lister and Van Der Kraak, 2002; Diemer et al., 2003b; Bornstein et al., 2004) gonadal hormone biosynthesis in vertebrate testes and ovary cells. NF-kappaB, the target of cytokines, has been implicated both in the activation (Delfino et al., 2003; Zhang L et al., 2004) and repression of the androgen receptor promoter (Supakar et al., 1995; Nakajima et al., 1996). The ambivalent role of stress is also reflected by evidence that, dose-dependently, oxidative and nitrosative stress can both enhance (Peltola et al., 1996; Zirkin et al., 1997; Valenti et al., 1999; Andric et al., 2007; Hwang et al., 2007; 2009; Faes et al., 2009) and impair (Behrman and Aten, 1991; Endo et al., 1993; Del Punta et al., 1996; Hales, 2002; Tsai et al., 2003; Ducsay and Myers, 2011) vertebrate male and female gonadal steroidogenesis. Vertebrate male gonadal hormone synthesis is acutely reduced in a number of conditions associated with ROS production and oxidative/nitrosative stress in the testis (Del Punta et al., 1996; Kostic et al., 1998; Hales, 2002; Allen et al., 2004; Chaki et al., 2005; Murugesan

et al, 2005; Hanukoglu, 2006; Luo L et al, 2006; Turner and Lysiak, 2008). Examples are cryptorchidism (Chaki et al., 2005), aging (Zirkin and Chen, 2000; Luo L et al, 2006), and ischemia-reperfusion injury (Turner TT et al., 2005).

There is intense cross-talk between the vertebrate hypothalamic–pituitary–adrenal (HPA) axis response to stressors and the hypothalamic–pituitary–gonadal (HPG) axis that controls reproductive activity (Rivier and Rivest, 1991; Rivest and Rivier, 1995; Viau, 2002; Wingfield and Sapolsky, 2003; Mastorakos et al., 2006; Chand and Lovejoy, 2011). Stress- and/or corticosteroid-induced suppression of reproductive functions has been observed in mammals (Stephens, 1980; Moberg, 1985; Armstrong, 1986; Orr et al., 1994; Tilbrook et al., 2000; Manna et al., 2003; Dhanabalan and Mathur, 2009; Hansen, 2009; Chand and Lovejoy, 2011; Nirupama et al., 2013), including humans (Collu et al., 1984; Rabin et al., 1988; Tremellen, 2008), birds (Siegel, 1980), reptiles (Lance and Elsey, 1986; Elsey et al., 1990; 1991; Moore et al., 1991), amphibians (Licht et al., 1983, Moore and Zoeller, 1985; Zerani et al., 1991) and fishes (Pickering et al., 1987; Campbell et al., 1992; Haddy and Pankhurst, 1999; Pankhurst and Van Der Kraak, 2000; Dufour et al., 2005).

Corticosteroids have been found to have effects at every level of the HPG axis (Thibier and Rolland, 1976; Bambino and Hsueh, 1981; Welsh and Johnson, 1981; Mann et al., 1982; Sapolsky, 1985; Wingfield and Sapolsky, 2003). In general, the effect of corticosteroid is to suppress the secretion or action of the various releasing factors or hormones. Considerable evidence demonstrates the importance of sympathetic nervous, catecholaminergic and glucocorticoid control of Leydig cell function and development (Mayerhofer et al., 1990; Mayerhofer, 1996; Hardy et al., 2005). The deleterious effect of corticosteroid administration on reproductive parameters and functions has been described in mammals (Thibier and Rolland, 1976; Bambino and Hsueh, 1981; Welsh and Johnson, 1981; Mann et al., 1982; Sapolsky, 1985), birds (Wilson and Follett, 1976; Petite and Etches, 1988; 1991), reptiles (Guillette et al., 1995; Knapp and Moore, 1997; Moore and Jessop, 2003), amphibians (Moore and Zoeller, 1985; Kupwaide and Saidapur, 1987; Moore and Jessop, 2003) and fishes (Carragher et al., 1989).

Particularly well studied are the adverse effects of starvation and caloric restriction on reproduction (Heininger, 2012). Metabolic stress induced by caloric restriction reduces gonadal hormones, delays sexual maturation or inhibits reproductive phases in a variety of multicellular organisms from polychaetes to mammals (Schneider and Wade, 1990, Elman and

Breier, 1997).

At the cellular level, there is intense cross-talk between activated nuclear receptors, especially the glucocorticoid receptor, the estrogen receptor and the androgen receptor, and the activity of NF-kappaB (De Bosscher et al., 2006), which plays a key role in the control of genes involved in cellular stress responses.

14.1 Male reproduction is more susceptible to a variety of stressors

In both plants, invertebrates and vertebrates, compared to female, male gametogenesis and fertility are more sensitive to a variety of stressors, including temperature, radiation, and toxicants, but also immune and psychosocial stress (Gomes, 1970; Le Grande, 1970; David et al., 1971; 2005; Ash, 1980; McGrady, 1984; Orr et al., 1994; Saini, 1997; Rockett et al., 2001; Sikka, 2001; Chakir et al., 2002; Rivier, 2002; Araripe et al., 2004; Rohmer et al., 2004; Vollmer et al., 2004; Jensen et al., 2006; Jørgensen et al., 2006; Gupta et al., 2007; Podrabsky et al., 2008; Sakata and Higashitani, 2008; Hansen, 2009; Crespo and Shivaprasad, 2010; Hales and Robaire, 2010; Prasad et al., 2011; Nirupama et al., 2013). Already Cowles (1965) noted that excessively high but individually non-lethal temperatures may induce total aspermia or a heightened mutation rate. No observations indicate a similar susceptibility in female gamete formation. Somewhat similar susceptibility appears to occur in plants and animals other than the scrotal mammals. High but non-sterilizing heat may induce mutation rates 5 times for every 10°C rise in temperature. The narrow margin between gametogenic heat damage and optimal somatic temperatures is such that local gonadal and total somatic thermoregulation becomes critical in terms of normal numerical and qualitative multigeneration success (Cowles, 1965).

At least in some insects, there is evidence that spermatogenesis is less developmentally stable than oogenesis (Chung, 1962; Temin, 1966; Lindsley and Tokuyasu, 1980; Saccheri et al., 2005). Mutagenesis experiments in *Drosophila* suggest a 50% greater potential for mutations affecting male than female fertility (Lindsley and Tokuyasu, 1980). Chung (1962) and Temin (1966) showed that, in *D. melanogaster*, chromosome II homozygotes causing complete sterility were two to three times as common for males as for females. *Wolbachia* is a maternally transmitted intracellular symbiont that is mainly localized in the reproductive tissues of arthropods and it is responsible for the induction of feminization, parthenogenesis, male-killing and cytoplasmic incompatibility (Saridaki and Bourtzis, 2010). Intriguingly, *Wolbachia* infection may increase oxidative stress in infected arthropods

thus mimicking the environmental stress-induced, oxidative stress-mediated, male infertility (see chapter 15.1).

Small, marginal or colonizing populations go through periods of inbreeding. Inbreeding has adverse effects primarily on male fertility in many animals, including insects and mammals (Saccheri et al., 2005; Asa et al., 2007; Fitzpatrick and Evans, 2009; Zajitschek et al., 2009; Malo et al., 2010; Okada et al., 2011). *Drosophila* lines homozygous for the second chromosome displayed a significant reduction in male mating ability as a result of inbreeding (Miller et al., 1993; Miller and Hedrick, 1993; Enders and Nunney, 2010). Moreover, inbreeding generally increases the sensitivity of a population to stress, thereby increasing the amount of inbreeding depression (Miller, 1994; Pedersen et al., 2011; Bijlsma and Loeschcke, 2012). The joint effect of inbreeding and stress was more pronounced for male than for female reproductive performance (Enders and Nunney, 2010; Pedersen et al., 2011).

Intriguingly, disruption of a variety of genes involved in stress responses impairs male more than female fertility (Dix et al., 1996; Yue et al., 1999; Nakai et al., 2000; Celeste et al., 2002; Ng et al., 2002; Hsia et al., 2003; Held et al., 2006; 2011; Wright et al., 2007; Coussens et al., 2008; Burnicka-Turek et al., 2009; Grad et al., 2010). As further evidence that the increased stressor vulnerability is restricted to testicular germ cells, Sertoli cells are extremely resistant to many harsh treatments, often surviving well exposure to treatments causing the complete obliteration of male germ cells (e.g., Oakberg, 1959; Clegg, 1963; Bergh, 1981). Oxidative stress is required for sperm motility and viability, capacitation, acrosome reaction, hyperactivation and the fusion of spermatozoa with the oocyte (Aitken et al., 1995; 1998b; Griveau and Le Lannou, 1997; Rivlin et al., 2004; Kothari et al., 2010) but may, on the other hand, be detrimental for these functions and spermatozoan viability (Fujihara and Howarth, 1978; Wishart, 1984; Mammoto et al., 1996; Griveau and Le Lannou, 1997; Sikka, 2001). Even in birds where egg production appears to be more temperature sensitive than semen production, the male bird appears to contribute more to heat stress infertility than the female due to impaired fertilization success of sperm (McDaniel et al., 1995). In plants, the geographic distribution of sexual and asexual species suggests that more harsh environmental conditions favor asexuals (Peck et al., 1998; Eckert et al., 1999; Dorken and Eckert, 2001). Consistent with these observations, environmental stress, particularly cold and water stress, induces male

sterility in a multitude of plants (Sawhney and Shukla, 1994; Sheoran and Saini, 1996; Saini, 1997; Sakata and Higashitani, 2008; Zinn et al., 2010) (see chapter 15.2).

Gonadal activity in the male is subject to variation, as evidenced by marked changes in testosterone release as a function of social and reproductive status and in response to stress. Through a glucocorticoid receptor-mediated process, physiological levels of corticosteroids exert a number of deleterious effects on Leydig cells, including inhibition of testosterone biosynthesis, suppression of luteinizing hormone receptor expression and induction of Leydig cell apoptosis (Bambino and Hsueh 1981; Welsh et al., 1982; Cumming et al., 1983; Stalker et al., 1989; Cooke et al., 1992; Orr and Mann, 1992; Monder et al., 1994a; b; c; Gao et al., 1997; Sharp et al., 2007). On the other hand, males typically show reduced adrenocorticotrophic hormone (ACTH) and corticosterone responses to stress (Kitay, 1961; Critchlow et al., 1963; Lescoat et al., 1970; Le Mevel et al., 1978, 1979; Kant et al., 1983) compared with that shown in females, an effect that is attributed in part to the central inhibitory effects of testosterone. Gonadectomized males show increased plasma ACTH and corticosterone responses to several forms of stress (Viau and Meaney, 1991; 1996; Handa et al., 1994; Seale et al., 2004). This effect is reversed with testosterone or dihydrotestosterone (DHT), the reduced nonaromatizable form of testosterone, indicating an androgen receptor-mediated effect (Viau and Meaney, 1991; 1996; Handa et al., 1994). Corticotrophs express few if any androgen receptors (Dubois et al., 1978; Thieulant and Duvall, 1985; Viau and Meaney, 1996) and minimal aromatase activity (McEwen, 1980). Thus, the inhibition of stress-induced ACTH release by androgens is unlikely to be explained by direct actions of testosterone or its estrogen byproducts at the level of the pituitary. Evidence suggests central effects of gonadal steroids on HPA activity; females show higher levels of hypothalamic corticotropin-releasing hormone (CRH) (Hiroshige et al., 1973) and increased levels of CRH mRNA in the paraventricular nucleus (PVN) (Watts and Swanson, 1989). This sex difference reflects a stimulatory effect of estrogen on CRH synthesis and release; acute elevations in plasma estrogen levels in females increase CRH mRNA and content in the hypothalamus (Bohler, 1990; Viau and Meaney, 1992; Seale et al., 2004). The demonstration of increased CRH immunoreactivity (Bingaman et al., 1994) in castrated compared to sham male rats suggests testosterone modulates corticosterone release via HPA axis inhibition.

Positive feedback amplifies a signal, whereas negative feedback attenuates it. The male vertebrate HPG and HPA axes are linked in a double-negative feedback loop (Ferrell, 2002). In this circuit, testosterone (A) inhibits or represses the HPA axis (B) and B inhibits or represses A. Thus, there could be a stable steady state with A on and B off, or one with B on and A off, but there cannot be a stable steady state with both A and B on or both A and B off. Such a circuit could toggle between an A-on state (sexual reproduction with functional males) and a B-on state (asexual reproduction) in response to trigger stimuli that impinge upon the feedback circuit (Ferrell, 2002). Once either state has been established, it could persist indefinitely, being reinforced by the double-negative feedback loop, until some trigger stimulus forces the system to the other state. Positive feedback amplifies the signal, whereas negative feedback attenuates it. The female vertebrate HPG axis is linked by a positive feedback to the HPA axis (Bohler, 1990; Viau and Meaney, 1992; Seale et al., 2004), while the latter attenuates the former in a negative feedback loop (see above). Positive feedback in combination with negative feedback can trigger oscillations (Kholodenko, 2006), which could explain the female menstrual cycles in vertebrates. Due to this gender-differential susceptibility, sexual reproduction has a more narrow ecological distribution than asexual reproduction (geographical parthenogenesis, see chapter 15.3.3).

The poor quality of the human ejaculate sets it apart from that of most, if not all, other mammalian species. There is evidence that the human spermatozoon is a cell in crisis (Aitken, 1999; Aitken and Sawyer, 2003; Joffe, 2007; 2010) and is operating near the threshold of error catastrophe as defined in RNA viruses (Holmes, 2003b; Biebricher and Eigen, 2005; Luring and Andino, 2010; Christophersen, 2013). Thus, several epidemiological studies show that certain paternal occupations, for example, as a welder, painter, auto mechanic, greenhouse worker, or fireman, involving exposure to metals, combustion products, solvents, or pesticides, are associated with altered sperm quality, and an increase in time to pregnancy, spontaneous abortions, birth defects, or childhood cancer (Savitz et al., 1994; Olshan and van Wijngaarden, 2003; Hales and Robaire, 2010). Even in normal fertile specimens, as much as 50% of the ejaculated sperm population may be abnormally formed and a similar proportion may lack motility (Aitken, 1999). In clinical terms, the impoverished nature of human ejaculate is reflected in the dominant role played by the male factor in the etiology of human infertility, defective semen quality being the most

frequently defined cause of this condition in humans (Hull et al., 1985; Irvine, 1998). Not only is human semen quality poor, but there is a growing body of evidence that it is getting poorer. The first indication of this came from the meta-analysis of 14,947 normal men from 61 independent centers (Carlsen et al., 1992). This study revealed an approximate halving of ejaculate sperm concentrations (from 113 to $66 \times 10^6 \times \text{ml}^{-1}$) from 1938 to 1990. This general trend has been independently confirmed in a number of separate data sets (Multigner and Spira, 1997).

14.2 Hormonal modulation of oxidative stress as evolutionary tuning knobs of reproductive activity and genetic variation

As final common effector of a variety of stress signaling pathways, oxidative stress modulates the cellular DNA damage/repair/mutagenesis balance and (epi)genetic variation. Environmental stress has to be relayed to the gonads via a variety of neuroendocrine signals, establishing a soma-germline cross-talk. Here exemplarily three hormonal systems, glucocorticoids, thyroid hormones and melatonin, are discussed that impinge upon the HPA and HPG axes and regulate reproductive activity and gonadal oxidative stress. The focus is here on male reproductive activity since it is more dependent on stress and oxidative stress signaling pathways.

14.2.1 Glucocorticoids

Corticotropin-releasing hormone (CRH) and glucocorticoids (GCs) potentially affect vertebrate gonadal function by acting at any one or more of the following levels within the HPG axis: (i) the hypothalamus (to decrease the synthesis and release of GnRH); (ii) the anterior pituitary gland (to decrease the synthesis and release of LH and/or FSH); (iii) the gonads (to modulate steroidogenesis and/or gametogenesis directly) (Michael and Cooke, 1994; Goos and Consten, 2002). The sex-stress/glucocorticoid relationship is non-linear and is described by approximation as inverted "U"-shaped: sex is favored in intermediate stressful environments, while stable stressfree and extreme stressful environments favor asex (Moore and Jessop, 2003). Intriguingly, the same inverted "U"-shaped relationship has been described for glucocorticoids and cognitive performance and neuronal long-term potentiation and primed burst potentiation (Du et al., 2009). Furthermore, considerable data have shown that low doses of glucocorticoids have trophic actions on neuronal branching and survival (Gould et al., 1990), whereas higher doses are detrimental to neuronal survival (Sapolsky, 1992).

CRH is a 41-amino acid straight-chain peptide (Vale et al., 1981) that, during stress, is released from neurons in the paraventricular nucleus and regulates pituitary secretion of ACTH and pro-opiomelanocortin-derived peptides (Plotsky and Vale, 1984; Antoni, 1986). CRH has an antireproductive action in the brain (Sirinathsinghji et al., 1983; Rivier et al., 1986; Petraglia et al., 1987). Moreover, CRH has also been found in the testis of several mammalian species (Yoon et al., 1988; Audhya et al., 1989) and exerts a major regulatory influence on testicular function (Ulisse et al., 1989; 1990; Fabbri et al., 1990; Tinajero et al., 1992; Huang et al., 1995; 1997). Both stimulatory (Huang et al., 1995; 1997) and inhibitory (Ulisse et al., 1989; 1990; Fabbri et al., 1990; Tinajero et al., 1992; Dufau et al., 1993; Frungieri et al., 2002) actions of CRH on Leydig cell steroidogenesis have been reported, consistent with the inverted "U"-shaped stress-sexual reproduction relationship.

Moreover, studies have identified GC receptors in a range of ovarian and testicular cell types and have clearly shown that GCs can exert direct effects on gonadal steroidogenesis, both in vivo and in vitro (Michael and Cooke, 1994). The increased susceptibility of male reproductive activity seems to have both cellular, peripheral and central HPG and HPA components. GCs target a multitude of genes whose products have manifold effects on mitochondrial function and redox balance. GCs interact with intracellular receptors expressed in almost every tissue. In the absence of related ligands, glucocorticoid receptor (GR) α is cytoplasmic and transcriptionally inactive, because it is associated with several proteins (Pratt, 1992; Pratt et al., 1996). Binding of GCs to their receptor induces dissociation of receptor-associated proteins, with subsequent GR α activation and translocation into the cell nucleus (Bamberger et al., 1996). Homodimers of the activated receptor modulate the transcription of various (one to two hundred) responsive genes by binding to specific DNA-associated glucocorticoid responsive elements (GREs). The genomic actions also critically depend on recruitment of coactivators and corepressors that may account for many ligand- and cell-specific effects of GCs (van der Laan and Meijer, 2008). Moreover, the cellular redox state regulates GR ligand affinity, nuclear import of the GR and intracellular hormone potency (Makino et al., 1996; Okamoto et al., 1999; Tanaka et al., 1999; Tomlinson et al., 2004; Agarwal and Auchus, 2005; Kitagawa et al., 2007; Sherbet et al., 2007). GREs mediate tissue-specific pleiotropic actions on redox balance by affecting mitochondrial functions (Sionov et al., 2006; Amat et al., 2007; Bjelakovic et al., 2007), a variety of

anti-oxidant enzymes (Pereira et al., 1995; José et al., 1997; Lim and Kim, 2009) and oxidases, such as NADPH oxidases (Marumo et al., 1998; Girod and Brotman, 2004; Hsu et al., 2005; Mitchell et al., 2007; Tobias, 2012), cytochrome P450 mono-oxygenases (Pereira et al., 1998; Honkakoski and Negishi, 2000), and monoamine oxidases (Chen, 2004; Shih and Chen, 2004; Manoli et al., 2005; Ou et al., 2006; Chen K et al., 2011; Grunewald et al., 2012).

Modulation of mitochondrial redox and metabolic activities by GCs is biphasic. Short-term exposure to stress concentrations of GCs is associated with induction of mitochondrial biogenesis and enzymatic activity of selected subunits of the respiratory chain complexes, whereas prolonged exposure to GCs causes respiratory chain dysfunction, increased ROS generation, mitochondrial structural abnormalities, apoptosis and cell death, depending on the target tissue energy requirements and developmental stage of the organism (Orzechowski et al., 2002; Duclos et al., 2004; Lin H et al., 2004; Manoli et al., 2005; Alesci et al., 2006; Halliwell and Gutteridge, 2007). Thus, in a variety of tissues GCs have both anti- and pro-oxidant and anti- and proinflammatory actions. At low to moderate doses GCs stimulate spermatogonial proliferation (Milla et al., 2009) and decrease germ cell apoptosis (Yazawa et al., 2001; Mogilner et al., 2006), but at higher levels can inhibit both spermatogenesis and gonadal steroid production (Milla et al., 2009) and induce apoptosis of germ cells, particularly spermatogonia (Yazawa H et al., 1999; 2000; Sasagawa et al., 2001b; Orazizadeh et al., 2010).

Depending on the cellular milieu, heme oxygenase (HO) activity can be considered as an ambiguous redox modulator with both pro-oxidant and anti-oxidant activities (see chapter 7.2.6). The glucocorticoid element is the only demonstrated functional response element in the promoter sequence of HO-2 (McCoubrey and Maines, 1994; Weber et al., 1994; Raju et al., 1997). Intriguingly, HO-2 levels in the testis are controlled by GCs and developmental and tissue-specific factor(s) determine generation of transcripts unique to the organ (Liu N et al., 2000).

Cytochrome P450 aromatase is a key enzyme in the hormonal pathway catalysing the irreversible conversion of sex steroids, androgens to estrogens, and thus is highly relevant to the process of sex change (Gardner et al., 2005; Kroon et al., 2005). In a variety of vertebrates, including fishes, reptiles and birds, estradiol supplements during early development can result in feminization, whereas the inhibition of estradiol synthesis using aromatase inhibitors can result in masculinization (Yu et al., 1993; Lance, 1997;

Chardard and Dournon, 1999; Pieau et al., 1999; Crews et al., 2001; Bruggeman et al., 2002; Devlin and Nagahama, 2002; Crews, 2003). Therefore, it is commonly assumed that the regulation of estradiol synthesis by aromatase plays a key role in the sexual development and differentiation of these vertebrates (Lange et al., 2002). Analysis of the regulatory sequences of the aromatase isoform CYP19A1 from the teleost species *Gobiodon histrio*, a bi-directional sex changer, revealed a number of cis-acting GREs (Gardner et al., 2003; 2005). Experimental exposure to the unfavorable mating scenario of two males only, usually resulted in the smaller male reverting to the female state (Munday et al., 1998). It was suggested that the mechanism by which this operates involves a positive relationship between increased GC concentration (response to stress) and estrogen (required for sex reversal to female) (Gardner et al., 2005). A similar mechanism may operate in reptile temperature-dependent sex determination (Lance, 2009). GCs have been postulated to be critical regulators of the sex change process (Perry and Grober, 2003). This model is based on the link between GCs and social status in many vertebrates, the frequent suppression of reproductive function in subordinate animals, and GC regulation of steroid synthesis (Perry and Grober, 2003).

14.2.2 Thyroid hormones

In almost all taxa, reproductive activity is timed to optimize the chances of survival for the offspring. Seasons with their variable resource availability exert strong selective pressure for this timing. Evidence from different vertebrate groups strongly suggests that thyroid hormone (TH) is crucially required for the expression of seasonal rhythms, with changes in TH signaling being a key element of circannual timing mechanisms (Hazlerigg and Loudon, 2008). TH is an ancient signalling molecule whose function probably originated well before the divergence between the vertebrate and other deuterostome lineages (Hazlerigg and Loudon, 2008). Evidence linking TH to the control of breeding activity can be found in Echinoderms, as well as in the primitive chordate, *Amphioxus* (Heyland et al., 2005). Seasonally reproductive birds and mammals engage the TH system in the regulation of the seasonal response. Removal of the thyroid gland dramatically altered the seasonal changes in gonadal growth. Thyroidectomy blocked many of the seasonal responses to photoperiod in a variety of bird species (Benoit, 1936; Woitkevitch, 1940; Nicholls et al., 1988a; Dawson et al., 2001), that remarkably could be restored by a single injection of thyroxine (T_4). Subsequent studies in sheep showed that

thyroidectomy overcomes the seasonal (or photorefractory) inhibition of reproductive activity in rams in the spring and supports a concept of a key role for thyroid hormones in the expression of seasonal patterns of breeding activity (Nicholls et al., 1988b; Anderson and Barrell, 1998). THs regulate the duration of Sertoli cell proliferation, stimulate their functional maturation, affecting adult Sertoli cell number, and hence the capacity of the testis to produce sperm (Francavilla et al., 1991; Van Haaster et al., 1992; 1993; Buzzard et al., 2000; Holsberger and Cooke, 2005). TH receptors are located on the Sertoli cells in the seminiferous tubules, and possibly Leydig cells, and it is believed that triiodothyronine (T_3) binds directly to these receptors (Singh et al., 2011).

The pro-oxidant action of THs may play an essential role in the induction of seasonal reproductive activity. THs increase the metabolic rate, calorogenesis, and exacerbate oxidative stress due to the acceleration of aerobic metabolism (Wilson et al., 1989; Oppenheimer et al., 1996; Venditti et al., 2003; Fernandez et al., 2005). T_4 directly stimulates the production of superoxide anion in neutrophils and alveolar macrophages (Kanazawa et al., 1992; Nishizawa et al., 1998). THs have been associated with mitochondrial ROS generation and the induction of oxidative stress in various tissues such as brain, heart, blood, muscle, kidney and liver (Fernandez et al., 1985; Asayama et al., 1987; Zaiton et al., 1993; Venditti et al., 1997; Huh et al., 1998; Sewerynek et al., 1999; Tapia et al., 1999; Shinohara et al., 2000; Karbownik and Lewinski, 2003; Bednarek et al., 2004; Das and Chainy, 2004; Mogulkoc et al., 2005; Venditti and Di Meo, 2006). The THs triiodothyronine (T_3) and L-thyroxine sodium salt (T_4) produced DNA damage in human sperm mainly via the production of ROS but retained good cell viability (Dobrzynska et al., 2004). Altered thyroid status has been shown to influence several oxidative stress and enzymatic antioxidant defense parameters in rat testis (Choudhury et al., 2003; Mogulkoc et al., 2005; 2006). For example, hyperthyroidism was associated in the rat testis with increased lipid peroxidation, indicative of oxidative stress, increased levels of reduced glutathione (GSH) and increased levels of mitochondrial hydrogen peroxide (Sahoo et al., 2005; 2008; Mogulkoc et al., 2005; 2006). Increased activity levels of most antioxidant defense enzymes have also been demonstrated (Zamoner et al., 2007). These results indicate that TH treatment caused a high oxidative insult to the testis (Dobrzynska et al., 2004; Mogulkoc et al., 2005; 2006; Wagner et al., 2008; 2009) and are consistent with data showing that hyperthyroid tissues exhibit increased ROS production (Venditti and Di Meo,

2006). Conversely, transient hypothyroidism seems to induce oxidative stress in testis by reducing the levels of testicular enzymatic and nonenzymatic antioxidant defenses (Sahoo et al., 2007; Zamoner et al., 2008).

14.2.3 Melatonin

In vertebrates, primary photoreception is by nonvisual irradiance detectors in the retina, pineal, or hypothalamus (Bradshaw and Holzapfel, 2007). In seasonally breeding mammals changes in the photoperiod are used to time their reproductive cycles; temporal signals to the reproductive system are controlled by the circadian rhythm of pineal melatonin secretion with high levels in the dark period (Tamarkin et al., 1985; Pang et al., 1998; Bromage et al., 2001; Malpoux et al., 2001). Melatonin has a well known function in the regulation of circadian and seasonal rhythms (Cassone, 1990; Gwinner et al., 1997). Melatonin release from brain mediates the influence of environmental photoperiods on planarian asexual reproduction (Morita and Best, 1984; Morita et al., 1987), demonstrating that the melatonin signal is evolutionary old and not necessarily associated with sexual reproduction. In fact, melatonin is one of the phylogenetically oldest biological molecules and ubiquitous in microbes, plants and animals (Hardeland and Fuhrberg, 1996; Roopin and Levy, 2012). Numerous extrapineal sites of melatonin synthesis exist, and in some of them, quantities or concentrations considerably exceed those in pineal and blood plasma (Pandi-Perumal et al., 2006; Hardeland and Poeggeler, 2007). In extrapineal sites, with exception of the retina and, where present, the parietal organ, circadian rhythms may exhibit low amplitudes or even be virtually absent, and the transmission of dark signals seems to be rather unlikely in organs like bone marrow or gastrointestinal tract. The conclusion has to be that melatonin plays a number of different roles (Pandi-Perumal et al., 2006; Hardeland and Poeggeler, 2008), roles that have been changing during evolution (Tan et al., 2010).

Whether the day-light signal is interpreted as anti- or progonadotropic will depend on the species (long-day seasonal breeders including the hamsters, short-day seasonal breeders such as sheep, or nonseasonal breeders like humans), the duration of night melatonin peak (the duration hypothesis), the magnitude of the night melatonin peak (the amplitude hypothesis), and/or the window of sensitivity to melatonin (the internal coincidence hypothesis) (Arendt, 1988; Stankov and Reiter, 1990; Reiter, 1991; Lincoln, 2002). The hypothalamic-pituitary axis plays a key role in the regulation of reproduction by melatonin. In addition to the hypothalamus and pituitary, melatonin

receptors in the testis, epididymis, vas deferens, prostate, ovary and mammary gland suggest the concept of multiple sites of melatonin action on the reproductive system (Pang et al., 1998). Melatonin is synthesized in the testes (Tijmes et al., 1996; Kato et al., 1999; Fu et al., 2001; Stefulj et al., 2001) and melatonin receptors are expressed in rodent and avian testes (Ayre and Pang, 1994; Vera et al., 1997; Valenti et al., 2001; Frungieri et al., 2005; Izzo et al., 2010), but both testicular melatonin receptor expression and melatonin synthesis decline during rat aging (Sánchez-Hidalgo et al., 2009a; b).

Melatonin has been shown to alleviate oxidative stress in the testes following the experimental induction of unilateral varicocele and torsion-detorsion (Semercioz et al., 2003; Abasiyanik and Dagdönderen, 2004; Yurtçu et al., 2008) and other stressors (Gavazza and Catala, 2003; Bustos-Obregón et al., 2005; Armagan et al., 2006; Atessahin et al., 2006; Kara et al., 2007; Sönmez et al., 2007; Guneli et al., 2008; Rao and Gangadharan, 2008; Huang et al., 2009; Sarabia et al., 2009a; b; Espino et al., 2010). Pinealectomy aggravates the testicular oxidative damage as a consequence of induced hyperthyroidism (Mogulkoc et al., 2006). Importantly, melatonin may protect germ cells against DNA damage (Sarabia et al., 2009a) as is also indicated by the finding that high endogenous melatonin concentrations enhance sperm quality (Ortiz et al., 2011). Melatonin levels in seminal plasma are depressed in infertile patients exhibiting poor motility, leukocytospermia, varicocele and non-obstructive azoospermia, all of which are conditions associated with oxidative stress in the male tract (Awad et al., 2006).

Melatonin and its metabolites reduce oxidative stress in vitro and in vivo (Tan et al., 1993; 2003; Reiter et al., 2000; 2001; 2009; Rodriguez et al., 2004; Hardeland, 2005). Melatonin has two major attributes that set it apart from most other antioxidants. Firstly, it undergoes a two electron oxidation when acting as antioxidant, rather than the one electron oxidation favored by many free radical scavengers. As a result, melatonin cannot redox cycle and inadvertently generate free radicals (Hardeland, 2005; Aitken and Roman, 2008). Melatonin has been shown to both scavenge free radicals (Tan et al., 1993; 2002), to improve mitochondrial malfunction and H₂O₂ generation (Hardeland, 2005; Leon et al., 2005), to stimulate a number of antioxidant enzymes including superoxide dismutase, glutathione peroxidase and glutathione reductase and to down-regulate prooxidant enzymes, such as nitric oxide synthases and lipoxygenases (Reiter et al., 2000; Anisimov, 2003;

Semercioz et al., 2003; Rodriguez et al., 2004; Hardeland, 2005).

The hormone is important for the synchronization of reproductive response to appropriate environmental conditions in animals. In general, the annual changes in pineal melatonin secretion drive the reproductive responses of photoperiodic mammals (Bronson, 1989). In birds, the data on the photoperiodic action of melatonin are not so clear-cut (Tsutsui et al., 2013), possibly because there has been evidence that the avian hypothalamus can synthesize melatonin de novo (Kang et al., 2007). Yet, there are data available on regulation of seasonal processes by melatonin, including but not limited to that of gonadal activity and gonadotropin secretion (Ohta et al., 1989; Bentley et al., 1999; Bentley and Ball, 2000; Guyomarc'h et al., 2001; Rozenboim et al., 2002). In birds, mammals and other vertebrates, gonadotropin-inhibitory hormone (GnIH) is a neuropeptide that inhibits gonadotropin synthesis and release, indicating a conserved role for this neuropeptide in the control of the HPG axis across species. In birds, melatonin appears to act on GnIH neurons in stimulating not only GnIH synthesis but also its release, thus inhibiting plasma LH concentration (Chowdhury et al., 2013; Tsutsui et al., 2013). Recently, a similar, but opposite, action of melatonin on the inhibition of expression of mammalian GnIH was shown in hamsters and sheep, photoperiodic mammals. These results in photoperiodic animals demonstrate that GnIH expression is photoperiodically modulated via a melatonin-dependent process. Recent findings indicate that GnIH may also be a mediator of stress-induced reproductive disruption in birds and mammals (Tsutsui et al., 2013). Melatonin implants have been shown to delay the onset of clutch initiation in female great tits but without affecting clutch size, body mass, or timing of onset of activity (Greives et al., 2012). In other species, GnIH and GnRH expression are positively correlated (Bentley et al., 2003; Calisi and Bentley, 2009). In some species, GnIH may act to induce a temporary pause in reproductive effort without full HPG axis suppression and regression, which would cause the individual to miss the opportunity to breed in that year. In their natural environments, this temporary cessation of reproduction occurs in response to unpredictable environmental cues, such as stress, or mate/nest availability (Calisi et al., 2011). Thus, hypothalamic GnIH may serve as a short-term modulator of reproductive behaviors in response to social environment (Calisi et al., 2011).

Melatonin up-regulates the expression of GnIH mRNA

in starling gonads before breeding. In vitro, melatonin significantly decreases testosterone secretion from LH/FSH-stimulated testes before, but not during, breeding (McGuire et al., 2011). In the frog *Rana esculenta*, melatonin severely inhibits both control and GnRH-induced Leydig cell testosterone secretion in vitro (d'Istria et al., 2004) and has a direct inhibitory effect on the mitotic activity of primary spermatogonia in the testis (d'Istria et al., 2003). Physiological crosstalk between melatonin and glucocorticoid receptor is of high adaptive significance in wild animals for balancing immunity and oxidative stress during ecologically stressful conditions (Nelson and Drazen, 1999; Gupta and Haldar, 2013). Seasonal changes in plasma melatonin and glucocorticoids modulate the effect of glucocorticoids in the testis of anuran *Rhinella arenarum* (Regueira et al., 2013).

Overall, HPA and HPG axes cross-talk on a multitude of levels to adapt sexual reproductive activity and (epi)mutagenesis as potential bet-hedging responses to environmental conditions.

15. Asexual reproduction

...there are regimes where the advantages for sex are outweighed by its disadvantages. A complete theory for the existence of sex must be able to identify the regimes where either sexual or asexual replication are respectively dominant, in a manner that is consistent with observation.

E. Tannenbaum, 2008

Summary

Ecological conditions largely determine the evolutionary benefits of asexual and sexual reproduction. Populations of clonal organisms are often represented as being evolutionary inert with persistent genetic fidelity. However, molecular data from viruses, prokaryotes and eukaryotes support the argument that asexual taxa can maintain significant levels of genetic diversity and adaptability and can create increased genetic variation in response to stress. Asexuals have a variety of tools that can, often stress-dependently, generate genetic and phenotypic variation without the use of meiotic recombination: transposon activation, mutability of simple sequence repeats, prions, polyploidy, epigenetic modulation, automixis and mitotic recombination. Large population sizes and seed/egg banks facilitate bet-hedging strategies both within and between generations.

Modular organisms have an arsenal of strategies with which they can create non-sexual genotypic/phenotypic plasticity: somatic mutagenesis, polyploidy, seed banks, and epigenetic variation. Importantly, somatic mutations may be transmitted to the offspring both sexually and asexually. As result, plants and sessile aquatic animals often exhibit labile asex/sex expression and rather exhibit a near-continuum between sexuality and asexuality. Environmental stress, particularly cold and water stress, induces male sterility in a variety of plants. Clonal reproduction appears to offer a safe escape route for many plant species under suboptimal environmental conditions. Ancient asexuals violate the expectation that sex and recombination are necessary for long-term survival. The microscopic size and resource-rich habitats of bdelloid rotifers, Darwinulid ostracods and oribatid mites keeps the relative investment in new organisms low and allows genetic exploration of fitness landscapes by trial-and-error expeditions at the population level. Cyclical parthenogens alternate phases of asexual propagation with bouts of sexual reproduction and are of special interest because they allow a direct assessment of the ecological conditions, costs and benefits of sex versus asex. Generally, seasonal and food stress induce sexual reproduction. The phenomenon that parthenogenesis, and not outcrossed sexuality, prevails in harsh, uncertain, disturbed and novel conditions has been termed geographical parthenogenesis. As discussed in chapter 14.1 male reproduction is more susceptible to environmental disturbance and together with the superior colonizing ability of asexuals this explains the ecological distribution of sex/asex.

Traditionally, benefits of sex have been grouped into ecological and genetic explanations (Kondrashov, 1993; West et al., 1999; Hörandl, 2009; Otto, 2009; Hartfield and Keightley, 2012). If the prevalence of sex means it is so beneficial, how can asexuals — provided they are real — survive? By extension it must mean that the selective pressures that cause sex to persist and prevail are somehow less powerful or counteracted by even larger benefits of asexuality in these organisms. So, in an ideal world, a comparison of the genetics and ecology between asexual and sexual species could be expected to yield some hints as to what needs to change within the organism or in its environment to make either asexuality or sexuality the more successful strategy (Maderspacher, 2011; Neiman and Schwander, 2011).

Hereafter, like Vrijenhoek and Parker (2009), I use the term parthenogenesis in a broad sense for all-female clonal reproduction while, in the strict sense, it is the development of an egg without fertilization. The origin of parthenogenesis is polyphyletic in many taxa, suggesting that genetic systems maintaining sexuality are often labile. Asexual lineages are known to arise not infrequently within species, but most of the time perish quite quickly (Simon JC et al., 2003). Strict asexuality is thought to be an evolutionary dead-end in 'higher' organisms and that most asexual metazoans only form twigs on the tree of life (Schwander and Crespi, 2009). Evolutionary theory predicts that obligate asexuals have a long-term evolutionary disadvantage, compared with sexuals, owing to a more pronounced 'Hill-Robertson effect', a reduction in the efficacy of natural selection that occurs because finite populations accumulate associations of linked genes (haplotypes) that interfere with selection (Hill and Robertson, 1966; Felsenstein, 1974). Absent or very infrequent recombination reduces N_e , and thus the efficacy of selection against deleterious mutations (Ohta and Kimura, 1971), by increasing selective interference from linked loci (Hill and Robertson, 1966; Birky and Walsh, 1988; McVean and Charlesworth, 2000; Marais and Charlesworth, 2003; Charlesworth, 2012). Empirical evidences for such mechanisms were higher rates of non-synonymous mutation accumulation in asexual strains of *Daphnia* water fleas (Paland and Lynch, 2006) and *Potamopyrgus* snails (Neiman et al., 2010) compared to their sexual counterparts. This indeed demonstrated inefficient purifying selection associated with clonal reproduction. Thus, it is generally assumed that the higher mutation load in the mitochondrial genome and in the asexual nuclear genomes results from a lack of recombination (e.g. Bell, 1988b; Jansen and de Boer, 1998; Stewart et al., 2008b). A second problem is that the genetic uniformity of the offspring leads to a much lower genetic diversity, which is likely to make it much more difficult to adapt, for example, to changing environments or to parasites; consequently, classical theory holds that asexual species should be slow to evolve (Maynard Smith, 1978a; Bell, 1982).

15.1 Non-sexual ways to increase evolvability

In the framework of the fitness landscape described by Wright (1931), populations placed near the top of a fitness peak will experience less beneficial mutations than populations placed far from the adaptive optimum (Fisher, 1930; Lenski and Travisano, 1994; Elena and Lenski, 2003; Lázaro et al., 2003; Silander et al., 2007; Stich et al., 2010). This dependence of mutation effects on the degree of adaptation of populations led

to the theoretical prediction that mutation rates would be reduced in constant environments, in which the population has had enough time to adapt. Once the optimum has been attained, a homogeneous population of individuals with the optimal phenotype is the best adaptive solution, so the generation of further diversity is not necessary. Thus, stable environments would favor low mutation rates (anti-mutator genotypes), constrained only by the costs of error-repair mechanisms (Kimura, 1967; Drake, 1991).

Populations of clonal organisms are often represented as being evolutionary inert with persistent genetic fidelity. If such a biological entity as a 'clone' really did exist, it would be a fantastic entity, differing from everything else known in biology, i.e. it would possess a population mean but no variance for any particular trait. It would not be amenable to selection and adaptive variation and would thus be unchanging in time and space (Loxdale and Lushai, 2003) – and due to this evolutionary inertness highly susceptible to extinction. Reproductively favored clones should rapidly eliminate clones with lower fitness, leading to the erosion of genetic (i.e., clonal) diversity (Vrijenhoek, 1978; Fox et al., 1996; Weeks and Hoffmann, 1998). However, natural selection in temporally and spatially heterogeneous environments is a strong force that shapes dynamics of genotypic diversity (Herbert and Crease, 1980; Harshman and Futuyma, 1985; Browne and Hoopes, 1990; Geedey et al., 1996; Weeks and Hoffmann, 1998; 2008; Niklasson et al., 2004; Vorburger, 2005a). Molecular data from viruses, prokaryotes and eukaryotes support the argument that clones can possess a highly dynamic and adaptive genome (Parker, 1979a; b; Vrijenhoek, 1979; Herbert and Crease, 1980; Ochman et al., 1980; Bell, 1982; Hughes, 1989; Moritz et al., 1989; Browne and Hoopes, 1990; Widén et al., 1994; Fox et al., 1996; Lushai et al., 1998; 2000; 2003; Weeks and Hoffmann, 1998; Wilson et al., 1999; 2003; Kawamura and Fujiwara, 2000; Wolf AT et al., 2000; Delmotte et al., 2002; Lushai and Loxdale, 2002; Loxdale and Lushai, 2003; Schön et al., 2003; Niklasson et al., 2004; Baali-Cherif and Besnard, 2005; Vorburger, 2005a; Castagnone-Sereno, 2006; Terhivuo and Saura, 2006; Hörandl and Paun, 2007; Charaabi et al., 2008; Heathoff et al., 2009; Birky et al., 2010; Bode et al., 2010; Danchin et al., 2011b; Johnson MT et al., 2011; Monti et al., 2012). Thus, asexual organisms can maintain significant levels of genetic diversity and adaptability (White, 1970; Angus and Schultz, 1979; Turner et al., 1983; Good and Wright, 1984; Densmore et al., 1989; Hedges et al., 1992; Quattro et al., 1992; Haddal et al., 1994; Tinti and Scali, 1996; Vrijenhoek,

1998; Johnson et al., 1999; Halkett et al., 2005; Loxdale, 2008; 2010; Janko et al., 2011; Johnson MT et al., 2011). A group of asexual animals, the bdelloid rotifers, has diversified into distinct species broadly equivalent to those found in sexual groups and displays two fundamental properties of species, independent evolution and ecological divergence by natural selection. Thus, sex is not a necessary condition for creating phenotypic and genetic diversity and speciation (Oliver and Herrin, 1976; Atchley, 1977a; b; 1978; Parker, 1979a; b; Ellstrand and Roose, 1987; Fox et al., 1996; Mitton and Grant, 1996; Gorokhova et al., 2002; Barraclough et al., 2003; González et al., 2003; Birky et al., 2005; 2010; Fontaneto et al., 2007; 2009; Heathoff et al., 2007; Hillis, 2007; Strasburg et al., 2007; Kaya et al., 2009). Like sexually reproducing organisms, asexual taxa can create increased genetic variation in response to stress (Goho and Bell, 2000; Doroszuk et al., 2006; van Oppen et al., 2011; Berman and Hadany, 2012). A wide range of asexual taxa have been shown to undergo rapid genetic changes, including root-knot nematodes (Castagnone-Sereno, 2006), crustaceans (Schön et al., 2003) and insects (Wilson et al., 2003). In obligate parthenogenetic New Zealand *Sitobion* spp. aphid populations, genotypes were found highly heterozygous, whilst there was extensive turnover of genotypes, such that 36% were not sampled again but 42% were new after two years, suggesting clonal selective sweeps to be operative with some local persistence (Wilson et al., 1999).

In genetically clonal populations, phenotypic diversity in fluctuating environments is generated by stochastic phenotype-switching mechanisms (Soll and Kraft, 1988; Moxon et al., 1994; Pérez-Martín et al., 1999; Bayliss et al., 2001; Lachke et al., 2002; Bonifield and Hughes, 2003; Balaban et al., 2004; Kearns et al., 2004; van der Woude and Bäuml, 2004; Kussell and Leibler, 2005). There are a variety of tools that can, often stress-dependently, generate genetic and phenotypic variation without the use of meiotic recombination, such as transposons (Nevers and Saedler, 1977; Biel and Hartl, 1983; Chao et al., 1983; Modi et al., 1992; Wilke and Adams, 1992; Bowen and Jordan, 2002; Lankenau and Volf, 2009; Maumus et al., 2009; Oliver and Greene, 2009a; Zhang and Saier, 2009; Upton et al., 2011), simple sequence repeats, also called microsatellites and minisatellites (Kashi et al., 1997; von Sternberg, 2002; Kashi and King, 2006; King and Kashi, 2007; King, 2012a; b), and prions (True and Lindquist, 2000; Masel and Bergman, 2003; Tyedmers et al., 2008; Halfmann and Lindquist, 2010; Lancaster et al., 2010). Evolutionary theory predicts that ancient asexuals should contain fewer functional

retrotransposons than sexuals or even none at all, because sex is thought to be necessary to spread these transposons within populations (Hickey, 1982; Schön and Martens, 2000; Arkhipova and Meselson, 2005; Schön et al., 2009). Except for bdelloid rotifers (Arkhipova and Meselson, 2000) and yeast (Zeyl et al., 1996), however, this pattern could not be confirmed. Schön and Arkhipova (2006) found one group of degenerated retrotransposons, Daphne, in *Darwinula stevensoni*, and a second transposon group, Syrinx, that was still functional and had obviously recently been active. Other asexuals such as the fungi *Candida albicans* (Matthews et al., 1997; Goodwin and Poulter, 2000), Entamoeban protozoans (Pritham et al., 2005) and Foraminifera (Maumus et al., 2009) have also been shown to harbor functional retrotransposons in high numbers.

At the edge of life the adaptive road is becoming increasingly narrower. Thus, while moderate stress increases genetic diversity, extreme stressful environments decrease genetic diversity (Kis-Papo et al., 2003; Sonjak et al., 2007; de los Ríos et al., 2010; Vinogradova et al., 2011). Likewise, spontaneous mutation rates in extremophiles (Battista, 1997; Grogan et al., 2001; Grogan, 2004; Mackwan et al., 2007) and sexual reproduction of fungi (Kis-Papo et al., 2003) are reduced in extremely stressful habitats. In *H. volcanii* and the polyploid methanogenic archaeon *M. maripaludis*, gene conversion leads to a fast and efficient equalization of genome copies (Hildenbrand et al., 2011; Lange et al., 2011; Soppa, 2011).

Different ways have been described, in which parthenogenetic lineages may originate from sexual species (Simon JC et al., 2003). The majority of the cases of parthenogenesis studied today are associated with bacterial infections (Lorenzo-Carballa and Cordero-Rivera, 2009). Three different microorganisms have been found associated with parthenogenesis in arthropods: *Wolbachia* (Stouthamer and Werren, 1993; Stouthamer et al., 1993; 2010; Werren, 1997; Arakaki et al., 2001; Weeks and Breeuwer, 2001) and *Rickettsia* (Hagimori et al., 2006), both members of the α -proteobacteria group; and *Cardinium*, a member of the Cytophaga–Flexibacter–Bacteroides group (Zchori-Fein et al., 2001; Weeks et al., 2003; Zchori-Fein and Perlman, 2004; Provencher et al., 2005). In addition, an endosymbiont from the Verrucomicrobia group has been found associated with parthenogenesis in a nematode species (Vandekerckhove et al., 2000). Most of the cases of *Wolbachia*-induced parthenogenesis in haplodiploid

Hymenoptera cause diploidization of unfertilized haploid eggs, which develop into females. This occurs through different forms of gamete duplication, which result in the production of fully homozygous progeny (Suomalainen et al., 1987; Stouthamer and Kazmer, 1994; Gottlieb et al., 2002; Pannebakker et al., 2004). Intracellular *Wolbachia* induces oxidative stress in insect cell lines and in vivo (Brennan et al., 2008; Pan et al., 2012). *Wolbachia* may have a key role in the infected insect's ferritin expression and iron metabolism modulating their regulation of oxidative stress (Kremer et al., 2009; Saridaki and Bourtzis, 2010). Intriguingly, *Wolbachia* infection is associated with a higher amount of the base 8-oxo-deoxyguanosine in DNA and strand breaks in meiotic spermatocytes suggesting that ROS-induced DNA damage in sperm nuclei may contribute to the modification characteristic of cytoplasmic incompatibility, a form of male-derived zygotic lethality (Brennan et al., 2012). Thus, *Wolbachia* infection may mimic the environmental stress-induced, oxidative stress-mediated, male infertility (see chapter 14.1). On the other hand, the increased oxidative stress may increase oocyte genetic variation or expose otherwise cryptic genetic variation due to the concomitant downregulation of heat shock proteins (Xi et al., 2008). This increased genetic variation may make asexual reproduction in infected insects a viable strategy.

15.1.1 Large population size

In large populations, Muller's ratchet occurs more slowly, and even lower rates of recombination will effectively arrest mutation accumulation (Charlesworth et al., 1993). Obviously, a risk spreading, bet-hedging strategy is more promising in larger populations: the more lottery tickets are "bought" the higher are the chances to have a "winner". That's why unicellular organisms with their large population sizes are the ideal players for these evolutionary games (see chapter 4.2). For multicellular organisms, the large investment of scarce resources into mature organisms limits population sizes and makes this approach only feasible for microscopic multicellular organisms, e.g. Bdelloid rotifers, Darwinulid ostracods, oribatid mites, in less resource limited habitats. On the other hand, large populations of extremely old clonal plants have been reported (Steinger et al., 1996; Lynch AJJ et al., 1998; Reusch et al., 1999; Arnaud-Haond et al., 2012).

For small asexual populations and low mutation rates, the speed of adaptation is primarily limited by the availability of beneficial mutations: a mutation has the time to reach fixation before the next mutation occurs. Therefore, in this case the speed of adaptation

increases linearly with population size and mutation rate. By contrast, for large asexual populations or high mutation rates, beneficial mutations are abundant. In this case, the main limit to adaptation is that many beneficial mutations are wasted: when arising on different genetic backgrounds, they cannot recombine and thus are in competition with each other. The recent works can be broadly categorized into two classes: (i) so-called “clonal interference models” and (ii) models in which all mutations have the same effects. The clonal interference models (Gerrish and Lenski 1998; Orr, 2000a; Campos and de Oliveira, 2004; Campos et al., 2004, 2008; Wilke, 2004; Rosas et al., 2005; de Visser and Rozen, 2006; Park and Krug, 2007; Campos and Wahl, 2010; Sniegowski and Gerrish, 2010; Good et al., 2012) emphasize that different beneficial mutations have different-sized effects and that mutations with large beneficial effects tend to outcompete mutations with small beneficial effects. In the clonal interference models (Gerrish and Lenski, 1998; Wilke, 2004), the fixation probability of a beneficial mutation decreases monotonically with increasing N as a result of competition among beneficial mutations leading to an everincreasing advantage of sex. Clonal interference also drags out fixation events, providing time for further beneficial variants to arise from competitors before any of them have fixed (Desai et al., 2007). There is a small conceptual flaw in this derivation which is that the possibility that other beneficial mutations were segregating before the initial appearance of the focal individual was neglected (Patwa and Wahl, 2008). If many mutations are segregating simultaneously, the focal beneficial mutation is likely to have arisen on the background of a previously segregating beneficial mutation. Thus mutations may sweep in groups, the ‘multiple mutation’ regime (Tsimring et al., 1996; Kessler et al., 1997; Rouzine et al., 2003, 2008; Beerwinkel et al., 2007; Desai and Fisher, 2007; Desai et al., 2007; Zeyl, 2007; Brunet et al., 2008; Park SC et al., 2010). The latter type of models, also dubbed traveling-wave theory, emphasizes that in large populations, multiple beneficial mutations frequently occur in quick succession on the same genetic background. The speed of adaptation in these asexual populations is determined by the emergence and subsequent establishment of mutants that exceed the fitness of all sequences currently present in the population. Rather than approaching a limit for large N , the speed grows as $\ln N$ in the regime of practical interest, reflecting the increasing spread of the population distribution along the fitness axis (Park SC et al., 2010). The models can be tuned to account for finite population sizes and determine how quickly

populations adapt as a function of population size and mutation rates (Hallatschek, 2011). Conceptually, the multiple mutation regime lies on a continuum between clonal interference and quasispecies dynamics. The “clonal interference models” that focused on two loci only were implicitly assuming monomorphism at all the other loci in the genome. The calculation of the waiting time until the occurrence of a second mutation at a second locus, considered possible beneficial mutations only at a given second locus (Christiansen et al., 1998), whereas it would be more reasonable to think of the chance of a second mutation at any one of thousands of other loci. This would increase by several orders of magnitude the probability that beneficial mutations would be selected concurrently, making the conditions for an advantage of recombination much less stringent than is often assumed (Albu et al., 2012). Although there will still be rapid changes in allele frequencies as expected for periodic selection, now there will be many lineages transiently rising and falling as they continue to mutate and compete. There is growing evidence from multiple experimental approaches for exactly these sorts of ‘multiple mutation’ dynamics (Rozen et al., 2002; Desai et al., 2007; Kao and Sherlock, 2008; Barrick and Lenski, 2009; Betancourt, 2009; Kvitek and Sherlock, 2011; Lang et al., 2011; Herron and Doebeli, 2013; Lee and Marx, 2013; Marx, 2013). On the other hand, the clonal interference model has also experimental support (Atwood et al., 1951; de Visser et al., 1999; Miralles et al., 1999; Shaver et al., 2002; de Visser and Rozen, 2005; Hegreness et al., 2006; Cooper, 2007; Kao and Sherlock, 2008; Lee and Marx, 2013). Possibly, both models can predict the evolutionary dynamics in asexual populations dependent on the mutation rate, population size and the mutation’s selection coefficient (Bollback and Huelsenbeck, 2007; Kao and Sherlock, 2008; Sniegowski and Gerrish, 2010). Kim and Orr (2005) modeled the dynamics of adaptation in sexuals versus asexuals at 2 beneficial sites to determine the effect of recombination on the rate of adaptation. Importantly, (i) the relative difference in fixation time of the second beneficial mutation, between sexuals and asexuals, is small when populations are large with a high mutation supply; and (ii) as the mutation rate increases asexual populations behave progressively more like sexual populations. Consequently, there is no advantage to sex in an infinite population (assuming no epistatic fitness interaction between loci) (Maynard Smith, 1968; Eshel and Feldman, 1970) or small populations; instead, sex should have the greatest effect in populations of intermediate size (Otto and Barton, 2001; Kim and Orr, 2005).

15.1.2 Polyploidy

Genome doubling, or polyploidy, is a major factor accounting for duplicate genes found in eukaryotic genomes. Polyploidy can be regarded as another mechanism to increase both evolvability and robustness (see chapter 13). Polyploid giant cells can be formed by parasexual behavior in bacteria, algae, yeasts and other protozoans under various stress conditions (Rink and Partke, 1975; Urushihara, 1992; Mares et al., 1993; Akerlund et al., 1995; Pecoraro et al., 2011). Polyploidy is another source of genetic novelty that doesn't depend upon sex, although when it is passed on sexually it can create new organisms that are much more genetically unique, than after regular recombination alone (Niklas, 1997). Polyploidy can create organisms that are so genetically different from their parents that they are unable to breed with organisms from their parent species (Clarke, 2012). Polyploids often show novel phenotypes that are not present in their diploid progenitors or exceed the range of the contributing species (Ehrendorfer, 1980; Levin, 1983; Ramsey and Schemske, 2002). Polyploids exhibit progressive heterosis. Hybrid vigor or heterosis is evolutionarily defined as that the heterozygotes have a higher fitness in a population than the homozygotes and refers to the phenomenon that progeny of diverse varieties of a species or crosses between species exhibit greater biomass, speed of development, and fertility than both parents (Tunner and Nopp, 1979; Wetherington et al., 1987; Comai, 2005; Birchler et al., 2010; Chen, 2010). Genome polyploidization may result in unique gene combinations, genome rearrangements, altered gene expression patterns (including silencing and up- or downregulation of one of the duplicated genes), enlarged body, or cell size and elevated levels of heterozygosity and genetic diversity (Song et al., 1995; Parker and Niklasson, 2000; Wendel, 2000; Soltis and Soltis, 2000; Osborn et al., 2003; Soltis et al. 2004; Luttikhuisen et al., 2007; Leitch and Leitch, 2008). Genetic and epigenetic changes such as sequence loss, methylation-dependent regulation of duplicated genes and re-activation of epigenetically silenced transposons, are common consequences of polyploidization across a wide range of species (Comai et al., 2000; Wendel, 2000; Lee and Chen, 2001; Shaked et al., 2001; Kashkush et al., 2002; Madlung et al., 2002; 2005; Osborn et al., 2003; Wang J et al., 2004; Wang YM et al., 2004; Lukens et al., 2006; Chen, 2007; Paun et al., 2007; Doyle et al., 2008; Hegarty and Hiscock, 2008; Leitch and Leitch, 2008; Soltis and Soltis, 2009; Verhoeven et al., 2010b; Xiong et al., 2011).

Estimates are that at least 50%, and perhaps even 90%, of flowering plants have undergone one or more episodes of chromosomal doubling in their evolutionary history (Masterson, 1994; Otto and Whitton, 2000; Cui et al., 2006; Jiao et al., 2011). Gene duplication events were intensely concentrated around 319 and 192 million years ago, implicating two polyploidization events in ancestral lineages shortly before the diversification of extant seed plants and extant angiosperms, respectively. Significantly, these ancestral whole-genome duplications resulted in the diversification of regulatory genes important to seed and flower development, suggesting that they were involved in major innovations that ultimately contributed to the rise and eventual dominance of seed plants and angiosperms (Jiao et al., 2011). Especially harsh conditions or periods of climatic change might affect the rate of formation, establishment, persistence and long-term evolutionary success of polyploids in angiosperms (Fawcett and Van de Peer, 2010). Hybridization and polyploidization can trigger DNA methylation changes in plants (Adams and Wendel, 2005; Dong et al., 2006; Chen, 2007; Paun et al., 2007). Epigenetic mechanisms may play a key role for gene expression, phenotypic variation and instability in plant polyploids (Comai, 2005; Chen, 2007).

The impact of deleterious mutations can be reduced when there are several copies of a single gene (Tautz, 1992; Wilkins, 1997; Vorburger, 2001; Krakauer and Plotkin, 2002). Masking of deleterious mutations provides an immediate advantage to higher ploidy levels (Mable and Otto, 2001; Vorburger, 2001; Gerstein and Otto, 2009). Moreover, deleterious mutations can be eliminated in a genome copy number-dependent manner by gene conversion that is biased for the wild type (Khakhlova and Bock, 2006; Gaeta and Pires, 2010; Soppa, 2011). At higher male to female mutation ratios, and sufficiently large population sizes, hybridogenetic populations can carry a lower mutation load than sexual species. In smaller populations, the same mechanism reduces the speed of Muller's ratchet. Schultz (1969) proposed that hybridogenesis may act as a transition state in the formation of new species, and Vrijenhoek et al. (1989) found some evidence for such an event in a sexual species of *Poeciliopsis* with supposed hybridogenetic ancestry. Lower mutation accumulation in hybridogenetic populations opens the possibility that hybridogenetic species can develop into new sexual species once recombination is re-established and reproductive isolation from sexual ancestors has occurred (Som and Reyer, 2007; Som et al., 2007).

The emergence of new phenotypic and molecular variation shortly after polyploid formation has been documented, offering unique avenues for phenotypic response to selection (Orr and Otto, 1994; Song et al., 1995; Jiang et al., 1998; Soltis and Soltis, 1999; Osborn et al., 2003). It has been argued that polyploidy makes clones more tolerant to abiotic stress and gives them wider ecological tolerances and higher fitness than their sexual ancestors possess (Lewis, 1980; Weider, 1993a; Kearney et al., 2005), i.e. as general-purpose genotypes (Lynch, 1984; Weider, 1993a). Likewise, theory suggests that ploidy level can profoundly influence parasite resistance and host–parasite coevolution (Nuismer and Otto, 2004; Oswald and Nuismer, 2007). Host–parasite interactions have also been shown to exert strong selection on the underlying genes that modulate species interactions, e.g. favoring changes in ploidy level (Oswald and Nuismer, 2007). However, empirical data to support theory are scarce (Stover, 1986; Nuismer and Thompson, 2001; King et al., 2012). Higher ploidy may even be harmful (D'Souza et al., 2005).

In natural strains of *Saccharomyces cerevisiae* isolated from several natural populations at the “Evolution Canyon” microsite (Nahal Oren, Mt. Carmel, Israel), tetraploid strains were more tolerant to all DNA-damaging agents than their neighboring diploid strains (Lidzbarsky et al., 2009). Wider ecological tolerances also allow wider geographic distribution of polyploids (Adolffson et al., 2010) and invasion and occupation of new and harsh environments (Stebbins, 1950; Levin, 1983). In line with this hypothesis, examples of ploidy elevation along a south–north cline are common (e.g., Beaton and Hebert, 1988; Ward et al. 1994; Little and Hebert 1997; Luttikhuisen et al. 2007) supporting the view that polyploidy is selected for in extreme environments (Beaton and Hebert, 1988; Ward et al., 1994). In the diploid–tetraploid species pair of gray treefrogs, *Hyla chrysoscelis* and *H. versicolor* (Anura: Hylidae), the tetraploid species almost exclusively occupied areas of higher elevation, where climatic conditions were relatively severe (colder, drier, greater annual variation). In contrast, the diploid species was restricted to lower elevations, where climatic conditions were warmer, wetter and exhibited less annual variation (Otto et al., 2007).

However, an unequivocal test of the direct advantage of polyploidy in harsh environments has proven difficult to produce because of other factors that are closely associated with polyploidy. For example, polyploids often originate through hybridization, which may lead to ecological differences between ancestral

and derived lineages (Avisé et al., 1992a). Hence, alternative explanations for the dominance of elevated ploidy in high latitudes include: (1) asexual polyploids simply colonize northern habitats more efficiently than sexual diploids, as discussed by Kearney (2005) and Thompson and Whitton (2006), or (2) polyploids are ecologically different from their ancestral lineages and are therefore found in the high-latitude habitats.

One important confounding factor of asexuality and geographical distribution is the frequent association of apomixis and polyploidy (Vandel 1928; Suomalainen et al., 1987). All apomictic angiosperms are polyploid (Asker and Jerling, 1992) but not all polyploid plants are asexual. In the animal kingdom, the association between polyploidy and parthenogenesis is present in two-thirds of taxa, mostly insects and reptiles (Suomalainen et al., 1987; Otto and Whitton, 2000). There is an almost perfect match between the geographic distribution of reproductive modes and the geographic distribution of ploidy levels (Bierzychudek, 1987; Suomalainen et al., 1987; Jokela et al., 2003; Stenberg et al., 2003). Previous attempts to contrast the importance of asexual reproduction and elevated ploidy as explanations for geographic parthenogenesis have been complicated by this almost perfect match (Suomalainen et al., 1987; Jokela et al., 2003; Stenberg et al., 2003). Whereas most polyploid animals are parthenogenetic, only a small fraction of the polyploid plants are apomictic. In fact, more than 99% of the polyploid plants are sexual. In all unisexual vertebrates (some 90 species) (Vrijenhoek et al., 1989; Vrijenhoek, 1989) that have been carefully examined parthenogenesis arose in association with hybridization (Dawley, 1989; Avisé et al., 1992a; Avisé, 2008). According to Arnold (2007), hybridization underlies the origin of many parthenogenetic fish taxa. “Geographical polyploidy” has been coined by zoologists to emphasize the role played by polyploidy in geographical parthenogenesis (Little et al. 1997; Stenberg et al., 2003). It has been argued that elevated polyploidy alone may be a sufficient explanation for geographical parthenogenesis (Vandel, 1940; Lundmark and Saura, 2006) even though asexuality and polyploidy need not be directly related to each other (Lundmark and Saura, 2006). As an example of the latter, the wider geographic distribution of asexual triploids compared to asexual diploids of *Eucypris virens* ostracods is due to elevated ploidy rather than to asexuality (Adolffson et al., 2010).

Endothermic animals such as mammals and birds are particularly sensitive to polyploidy (Lampert and Schartl, 2008). Even partial aberrations from the regular diploid cell stage usually result in severe

developmental defects (FitzPatrick et al., 2002) and are an important factor in cancer formation (Krämer and Ho, 2001). Fishes, amphibians and reptiles on the other hand cope very well with polyploidy (Pandian and Koteeswaran, 1998). In this group polyploidy is considered an important driving force in evolution as it increases the genetic material on which mutation and selection can act (Ohno, 1970). Transitions to higher ploidy often require special cytogenetic processes that circumvent the problems occurring during normal meiosis when uneven number of chromosomes attempt to pair. It is therefore not surprising that the great majority of uneven ploidy groups lack meiosis and reproduce asexually (Otto and Whitton, 2000). In addition to merely having more DNA, advantages of polyploidy may result from frequent genome rearrangements (Soltis et al., 2004) and alteration of gene expression. In microorganisms, more DNA buffers against the adverse sequelae of mutagenesis and enables a bet-hedging evolutionary lifestyle. In adverse ecological habitats that constrains sexual reproduction, multicellular organisms may resort to DNA buffering by polyploidy. More DNA, however, has its resource costs (Neiman et al., 2013), particularly with regard to the limited resource phosphorus (Heininger, 2012). Asexual *Potamopyrgus antipodarum*, a New Zealand snail, have markedly higher bodily phosphorus and nucleic acid content per unit mass than sexual counterparts. These differences coincide with and are almost certainly linked to the higher ploidy of the asexuals (Neiman et al., 2009b; 2013).

15.1.3 Automixis and mitotic recombination

A whole array of processes intermediate between mitosis and meiosis are known. Some of these are grouped under the term automixis. Some automictic processes lead to homozygosity in offspring, others retain heterozygosity (Asher, 1970; Birky, 1996). Most thelytokous hymenopterans reproduce by some form of automixis. Early stages of meiosis to form a haploid ovum are normal. Diploidy is restored by fusion of two haploid nuclei from a single dividing oogonium. The restoration of diploidy may occur in different ways, each with different consequences for genetic variation among offspring (Lamb and Wiley, 1987; Suomalainen et al., 1987; Haccou and Schneider, 2004; Beukeboom and Zwaan, 2005; Mateo Leach et al., 2009). Importantly, the strength of Muller's ratchet is reduced considerably for several forms of automictic thelytoky (Haccou and Schneider, 2004).

Parasex can produce genetic diversity via independent chromosomal assortment, mitotic recombination, and the ability of the diploid state to act as a capacitor for

evolution by enabling the accumulation of recessive mutations that are deleterious individually but beneficial in combination (so-called reciprocal sign epistasis) (Pontecorvo, 1956; Schoustra et al., 2007; Calo et al., 2013). Mitotic recombination significantly hastens the spread of beneficial mutations in asexual populations. Indeed, given empirical data on mitotic recombination, adaptation in asexual populations proceeds as fast as that in sexual populations, especially when beneficial alleles are partially recessive (Mandegar and Otto, 2007). *Candida albicans*, the most prevalent pathogen of humans, has no known meiotic cycle but undergoes mitotic recombination during somatic growth. *C. albicans* undergoes a parasexual cycle wherein two diploid cells mate, resulting in cell fusion and a ploidy increase (2N to 4N), and the tetraploid cells then undergo mitosis and random chromosome loss to return to the diploid state with no recognized meiosis (Noble and Johnson, 2007; Forche et al., 2008; 2011). *C. albicans* generates increased amounts and different types of genetic diversity in response to a range of stress conditions that arises either by elevating rates of recombination and/or by increasing rates of chromosome missegregation (Forche et al., 2011). Likewise, biotic and abiotic stress increased plant somatic homologous recombination (Filkowski et al., 2004; Molinier et al., 2006; Boyko et al., 2010). Schoustra et al. (2007) examined the growth fitnesses of both haploid and diploid *Aspergillus nidulans* strains, and they found that diploid strains attained higher fitnesses than isogenic haploid strains (i.e., the diploid strains' progenitors) after ~3,000 mitotic generations, and invariably, these faster-growing isolates evolved from a diploid progenitor that had undergone a parasexual reduction to return to the haploid state. Thus, mitotic recombination occurring during the parasexual cycle can accelerate adaptation under laboratory conditions (Schoustra et al., 2007). The higher fitness obtained is due to "sign epistasis" effects (see chapter 18.1.1), where mutations occurring in diploid nuclei could be neutral or deleterious on their own in a haploid but are instead advantageous when combined. This study revealed that the parasexual cycle can serve as a capacitor for evolution and might generate genotypic diversity de novo rather than admixing genetic differences from two divergent parental isolates (Lee SC et al., 2010).

Gene conversion and mitotic crossing-over have the potential to both purge the genome of mutations and increase allelic richness of the species by bringing together advantageous mutations (between alleles within individuals or lineages) (Gandolfi et al., 2001) and escape 'Muller's ratchet' (Lehman, 2003). In

mutation-accumulation lines of asexual *Daphnia* it was shown that the rate of loss of nucleotide heterozygosity by ameiotic recombination is substantially greater than the rate of introduction of new variation by mutation (Omilian et al., 2006). But also gene conversion between different genomes within one cell of an oligoploid or polyploid microorganism would be a mechanism to escape 'Muller's ratchet' (Khakhlova and Bock, 2006). In *H. volcanii* and the polyploid methanogenic archaeon *M. maripaludis*, gene conversion indeed operates and leads to a fast and efficient equalization of genome copies (Hildenbrand et al., 2011; Lange et al., 2011; Soppa, 2011). Predicting the occurrence of recombination events by analyzing aligned sequences of a given region of DNA that all originate from one species, some evidence for recombination was found particularly in arbuscular mycorrhizal fungi, and less in *Darwinula stevensoni* and the bdelloid rotifers (Gandolfi et al., 2003), although the method could not resolve the question whether recombination was mitotic or meiotic. Another possible mechanism to escape Muller's ratchet is horizontal gene transfer in the population, and for several natural populations it has indeed been found that recombination is so frequent that it resembles sexual reproduction (Papke et al., 2004).

Many asexual taxa are thought to be particularly efficient in DNA repair, which would allow them to reduce the accumulation of deleterious mutations (Castonguay and Angers, 2012). There is evidence for this in asexual taxa such as asexual weevils (Tomiuk and Loeschcke, 1992), aphids (Normark, 1999), darwinulid ostracods (Schön et al., 1998), *Daphnia* (Omilian et al., 2006), and oribatid mites (Schaefer et al., 2006). This led Schaefer et al. (2006) to ask "why not more taxa are ancient asexuals if the long-term disadvantages of parthenogenetic reproduction can be defeated."

15.1.4 Phenotypic plasticity

In addition to their versatile genome, asexually reproducing organisms may display a high degree of phenotypic plasticity (Stibor, 1992; Bruno and Edmunds, 1997; Scheiner and Yampolsky, 1998; Hollingsworth, 2000; Amsellem et al., 2001; De Waal, 2001; Negovetic and Jokela, 2001; Mitchell and Read, 2005; Stelzer, 2005; Geng et al., 2007; Hoogenboom et al., 2008; Tully and Ferrière, 2008; Svanbäck et al., 2009; Gorelick et al., 2011; Castonguay and Angers, 2012; Massicotte and Angers, 2012). Bet-hedging, indicating phenotypic plasticity in varying environments, has been observed in various asexual taxa (Ricci, 1991; Gilbert and Schreiber, 1995; 1998;

Gilbert, 1998; Orsenigo et al., 1998; Altiero et al., 2006; Pinto et al., 2007; Rossi and Menozzi, 2012). Based on epigenetic mechanisms (Verhoeven et al., 2010a; Gorelick et al., 2011; Castonguay and Angers, 2012; Harris et al., 2012; Massicotte and Angers, 2012; Robichaud et al., 2012) this phenotypic plasticity is triggered particularly by environmental stress (Finnegan, 2002; Boyko and Kovalchuk, 2011; Grativol et al., 2012). Epigenetic variation could be particularly important to the evolutionary potential of asexual species that harbor little genetic variation (e.g. Wilson et al., 2003; Richards et al., 2008; Vogt et al., 2008; Verhoeven et al., 2010a).

15.1.5 Seed/egg banks and dormancy as bet-hedging strategies

Sexual reproduction relies on an "educated guess" bet-hedging strategy both within and between generations. Dormancy is a bet-hedging strategy used by a wide range of taxa, including microorganisms. It refers to an organism's ability to enter a reversible state of low metabolic activity when faced with unfavorable environmental conditions (Lennon and Jones, 2011). Soil and sediment banks of dormant propagules are a means to conserve genetic variation between generations and rely on temporal bet-hedging (Ellner, 1985; Gómez and Carvalho, 2000; Evans and Dennehy, 2005; Simons and Johnston, 2006; Evans et al., 2007; Gremer et al., 2012). These resting stages accumulate in the sediments of their habitats forming resting propagule banks (Hairston, 1996; Thompson K et al., 1997; Cáceres and Hairston, 1998; Gómez and Carvalho, 2000; De Meester et al., 2002; Brendonck and De Meester, 2003; Evans and Dennehy, 2005; Simons and Johnston, 2006; Evans et al., 2007; Gremer et al., 2012). Plants, rotifers, daphnids, copepods and *Artemia* are well known examples where dormancy is developmentally programmed in the form of seeds, resting eggs, ephippia or cysts (Gómez and Carvalho, 2000; Brock et al., 2003; Gyllström and Hansson, 2004; Denekamp et al., 2010; Clark MS et al., 2012). So far, at least to my knowledge, none of the treatises on the relationship between sexual and asexual reproduction appreciated the role of seed/egg banking. But I think that it is no freak of nature that organisms that set seed/egg banks are also particularly prone to indulge in asexual reproduction.

A seed/egg bank has the effect of overlapping the generations of the population, integrating the effects of selection and genetic variation over long periods of time (Templeton and Levin, 1979; Eriksson, 1996; Cáceres, 1997; Ehrlén and Lehtilä, 2002; Nunney, 2002; Brendonck and De Meester, 2003; Gyllström

and Hansson, 2004; Honnay et al., 2008). When a population goes through a genetic bottleneck, recruitment of below-ground/sediment genotypes conserved in the soil can quickly restore above-ground genetic diversity as soon as the habitat conditions become suitable again (McCue and Holtsford 1998, Brendonck and De Meester, 2003; Uesugi et al. 2007, Honnay et al., 2008). The costs and benefits of prolonged dormancy are context dependent. Forgoing one or more seasons of growth and reproduction in favor of remaining dormant can confer fitness advantages in a variable environment (Gremer et al., 2012).

The below-ground genetic reservoir is not limited to propagules. Many widespread ecosystems of temperate, arid and polar regions such as grassland, steppe, desert and tundra have >50% of plant production or biomass below-ground (Jackson et al., 1997; Steinaker and Wilson, 2005; Mokany et al., 2006; Pärtel et al., 2012; Poorter et al., 2012). Below-ground richness generally exceeds that above-ground, because of greater dispersion of plant parts below- than above-ground in both time and space. Most perennial plants have persistent below-ground storage organs and meristems that can survive during unfavorable seasons and years in the absence of above-ground biomass (Eissenstat and Yanai, 1997; Wells and Eissenstat, 2001) and allow short- or long-term dormancy for up to decades in the absence of above-ground biomass (Klimesova and Klimes, 2007; Reintal et al., 2010).

15.2 Asexual reproduction in sessile organisms

So far, at least to my knowledge, scientific treatises on the evolutionary rationale of sexual reproduction took no account of the fundamentally different mode of inheritance between modular and unitary organisms (see Heininger, 2012). Their different lifestyles, sessile vs. mobile, shaped their competitive selection pressures resulting in different germline segregation strategies and bauplans (Heininger, 2012). Sessile, modular organisms, plants and benthic aquatic animals, violate Weismann's doctrine (Weismann, 1892), lacking germ-soma sequestration (Jerling 1985; Sutherland and Watkinson, 1986; Buss, 1983; 1987; Hughes, 1989). Although genetic variants commonly arise within somatic genomes, organelles and cells, such a variant will not be heritable if it is (i) denied access to the formation of gametes or (ii) denied the capacity to asexually form an independent new organism capable of further propagation, or denied both (Buss, 1983). In modular organisms, the adult body is itself a reproductive unit thanks to the presence of totipotent somatic cells (e.g. meristems,

interstitial cells) that can form both gametes and somatic tissues and allow for variants arising in clonal growth to contribute to heritable evolutionary change (Monro and Poore, 2004; 2009). Thus, the ease of switching between sexual and asexual reproduction and the genetic and epigenetic consequences of this switch should be fundamentally different for modular and unitary organisms.

Asexual reproduction is common in plants. Harper (1977) estimated that over 80% of perennial plants have some form of clonal reproduction. A later survey of plant species from Central Europe estimated that close to 67% of the species considered could potentially reproduce clonally (Klimes et al., 1997). Clonal reproduction can be considered as an alternative life cycle loop that allows persistence of a species in the absence of the ability to complete the normal life cycle (i.e. seed production, germination and recruitment). Clonal reproduction appears to offer a safe escape route for many plant species under suboptimal environmental conditions (Kudoh et al., 1999; Erikson and Ehrlén, 2001; Honnay and Bossuyt, 2005). Population dynamics of perennial forest herbs, for example, are strongly influenced by successional stage through the degree of canopy closure: low light conditions can suppress sexual recruitment and trigger clonal growth (Verburg and Grava, 1998; Kudoh et al., 1999; Lezberg et al., 2001). Apomixis in plants may take two general forms: the seeds or spores may be derived from altered developmental sequences that bypass normal meiotic divisions and omit syngamy, or apomixis may be based upon vegetative reproduction (Klekowski, 2003). Stolons, runners, rhizomes, tubers, bulbils, corms, layering, fragmentation, and apomixis are among the myriad alternative modes of asexual reproduction exhibited among angiosperms (Richards, 1997). Morphological plasticity on an ecological time scale is common in forms with somatic embryogenesis. Three general types of shoot apical meristems occur in vascular plants: single tetrahedral apical initial in pteridophytes, unstratified with impermanent initials in gymnosperms and stratified with impermanent initials in angiosperms and some gymnosperms (Klekowski, 2003). Many plants are constructed by iteration at both modular and clonal scales, which produces a hierarchical organization. Each level of the hierarchy is a level at which replication or copying occurs, at which births and deaths can be counted. The units at each level can carry mutations and transmit them to future generations (Clarke, 2012). As a plant ages, the number of mutations per apical initial increases (Klekowski, 1988; Klekowski and Godfrey, 1989). Thus, long-lived plants accumulate somatic mutations and become genetic mosaics as they grow. Moreover,

under abiotic or biotic stress increased mutagenic changes in plant genomes have been identified (McClintock, 1984; Cullis, 1987; 2005; Ries et al., 2000; Lucht et al., 2002; Kovalchuk et al., 2003; Molinier et al., 2006). Stress-related epigenetic variation may also increase phenotypic plasticity (Verhoeven et al., 2010a; b). Environmental stresses can trigger DNA methylation changes in plants (Chinnusamy and Zhu, 2009). Stress-induced methylation changes may be targeted specifically to stress-related genes. Alternatively, methylation changes may generate nonspecific (random) differences between individuals, which may have adaptive significance during times of stress (Rapp and Wendel, 2005), because they increase the range of variation that natural selection can act upon. There are indications that apomictic dandelions may have compensatory mechanisms to generate heritable variation, for instance via increased transposon activity or somatic recombination (Richards, 1989; King and Schaal, 1990).

Intraorganismal selection has been acknowledged by numerous authors (Whitham and Slobodchikoff, 1981; Buss, 1983; Antolin and Strobeck, 1985; Klekowski, 1988; 2003; Sutherland and Watkinson, 1986; Gill et al., 1995; Otto and Orive, 1995; Clarke, 2011) and may be a way both of eliminating deleterious somatic mutations (Klekowski and Kazarinova-Fukshansky, 1984; Michod, 1995; Otto and Orive, 1995; Otto and Hastings, 1998) and to fix advantageous mutations (Otto and Orive, 1995; Fagerström et al., 1998; Otto and Hastings, 1998; Pineda-Krch and Fagerström, 1999; Pineda-Krch and Lehtilä, 2004; Clarke, 2011). This variability may be transmitted to the offspring both sexually and asexually (Whitham and Slobodchikoff, 1981). Genetic variance for effects caused by somatic mutations will be greater among spores than among offspring produced by budding or fission, because the variance of items is greater than the variance of means, and spore production therefore enhances the effect of selection in reducing mutational load (Bell and Koufopanou, 1991). In sponges, species capable of somatic embryogenesis uniformly lacked a repeated colony morphology, whereas species incapable of somatic embryogenesis always form characteristic colony morphologies (Korotkova, 1970; Buss, 1983). Angiosperms, the phylogenetically newest and most successful of all plants, have evolved stratified meristem regions, which make intraorganismal selection maximally effective in three ways: They ensure that deleterious mutations are rapidly purged, they allow high fitness mutations to displace the wild type, and they preserve genetic variance over the long term (Pineda-Krch and Lehtilä, 2002; 2004; Clarke,

2011). Somatic mutation and selection can cause ramets to become genetically distinct from each other, even if they are mitotic descendants from a common zygote. Thus, asexual plant populations can diversify more rapidly than sexual populations because they are free from the homogenizing effects of sexual recombination and segregation (Johnson MT et al., 2011). Although asexual reproduction may often constrain adaptive evolution (Hill and Robertson, 1966; Barton and Otto, 2005; Johnson et al., 2009; Hersch-Green et al., 2012), the loss of recombination and segregation need not be an evolutionary dead end in terms of diversification of lineages (Johnson MT et al., 2011). The parthenogens of *Chara canescens* (Charophyceae), multicellular green algae that superficially resemble land plants, occupy broader geographical and ecological ranges than their sexual counterparts. An experimental study showed that parthenogenetic *C. canescens* individuals from two neighbouring populations are locally adapted to light and differed in their capacity to acclimate to irradiance and salinity suggesting clonal diversity with differentially adapted clonal "microspecies" (Schaible et al., 2012). Artificial selection of intracolonial genetic variation in the branching red seaweed *Asparagopsis armata* demonstrated that intracolonial genetic variation may potentially help clonal organisms to evolve adaptively in the absence of sex and thereby prove surprisingly resilient to environmental change (Monro and Poore, 2009).

Modular organisms have an arsenal of strategies with which they can create non-sexual genotypic/phenotypic plasticity: somatic mutagenesis, polyploidy, seed banks, and epigenetic variation. As result, plants and sessile aquatic animals often exhibit labile asex/sex expression and rather exhibit a near-continuum between sexuality and asexuality (Barrett, 2002; Goodwillie et al., 2005; Whitton et al., 2008) but may turn to sexual reproduction under environmental challenges (Bell and Wolfe, 1985; Harvell and Grosberg, 1988; Kimmerer, 1991; Romme et al., 1997; Korpelainen, 1998; van Kleunen et al., 2001). Most plants combine sexual and clonal reproduction, and the balance between the two may vary widely between and within species (Eckert, 2002; Clarke, 2011). For plants both somatic and germ-line mutations can be passed to the gametes or vegetatively produced organisms. Asexual reproduction may have the advantage that such selected genotypes, unlike in sexuals, are not broken up each generation by recombination. Obviously, stable, undisturbed environments should favor such strategies (Silvertown, 2008). An analysis of more than 2,000 plant populations suggested that the ultimate

clonal plant would be a rare, aquatic, alien apomict living in an undisturbed (very long timescales free from disturbance are needed), geographically marginal habitat (Silvertown, 2008). This was considered such a restrictive set of ecological conditions that it is perhaps better regarded as a recipe for the failure of sexual reproduction than as clonal success (Silvertown, 2008). On the other hand, the geographic distribution of sexual and asexual plant species suggests that more harsh environmental conditions favor asexuals (Peck et al., 1998; Eckert et al., 1999; Dorken and Eckert, 2001; Eckert, 2002). Consistent with these observations, environmental stress, particularly cold and water stress, induces male sterility in a variety of plants (Sawhney and Shukla, 1994; Sheoran and Saini, 1996; Saini, 1997; Knight et al., 2005; Sakata and Higashitani, 2008; Zinn et al., 2010). Moreover, near the limits of species' ranges, factors that severely limit sexual recruitment (e.g., lack of pollinators, short growing season) may tip the balance that would otherwise favor retention of sexuality, facilitating vestigialization of sexual traits in asexual plants (Eckert, 2002; Dorken et al., 2004). Asexual organisms are thought to have fewer disadvantages than sexuals in environments with few biotic interactions, such as in high altitudes, high latitudes and arid habitats (Bell, 1982; Hörandl, 2006).

In the Mojave desert, along a stress gradient of light intensity and moisture availability from understory to intershrub microsites, males of the dioecious desert moss *Syntrichia caninervis* are clustered near the less stressful shrub canopy line and are less stress tolerant than females. Sex expression declined from 76% under the shrub canopy to 5% in the intershrub region (Stark LR et al., 2005). Sexual reproduction in an extremophile bryophyte system, as measured by the number of sporophytes per shoot, decreases with extreme environmental stress at geothermal hot-springs. The number of sporophytes per shoot was found positively correlated with distance from geothermal features. Sporophytes were most common in non-geothermal sites, but very rare in high temperature geothermal sites suggesting that sperm viability may be a significant factor limiting sporophyte formation in geothermal bryophyte communities (Eppley et al., 2011). The reproduction of mosses *Pleurozium schreberi* and *Pohlia nutans* were compared in the surroundings of copper smelters at Harjavalta, Finland (Huttunen, 2003). The production of gametangia decreased in *P. schreberi*, and near the smelters most of the shoots were sterile. The numbers of spores per capsule in *P. nutans* decreased at polluted sites and the proportion of aborted spores increased (Huttunen, 2003). Harsh environmental

conditions are associated with strong selection for the target trait but low genetic variance of this target trait. Consequently, the potential for microevolution is constrained by either a lack of heritable variation (in poor environments) or by a reduced strength of selection (in good environments) (Wilson AJ et al., 2006).

15.3 Asexual reproduction in mobile animals

15.3.1 The “evolutionary scandals”: microscopic organisms in r-selected habitats

In chapter 4.2 it has been argued that it is a unicellular bet-hedging strategy to create mutants and let natural selection decide on their viability. In large multicellular organisms this would mean a large investment into possibly poorly viable mutants, a strategy that in resource-limited environments would not pay off. Obviously, there are two liabilities, resource limitation and stress, that balance the switch from sexual to asexual reproduction and back. Resource limitation of reproduction is determined by resource availability and investment of resources into offspring. In unicellular microorganisms the investment in new organisms is small and hence genetic exploration of fitness landscapes by trial-and-error expeditions at the colony population level is a viable strategy. In multicellular organisms, the balance between resource availability and resource investment into new organisms determines whether this bet-hedge approach at the population level is evolutionarily stable. Only microscopic multicellular organisms in less resource limited habitats can be expected to comply with these requirements.

There is a long-standing debate over the existence of ancient asexual organisms (Martens et al., 2003; Martens and Schön 2008; Birky, 2010). The term ‘ancient asexual’ implies persistence of an asexual lineage longer than expected under the various hypotheses for sex (Neiman et al., 2009a). Because truly ancient asexuals would violate the expectation that sex and recombination are necessary for long-term survival, they have been considered an “evolutionary scandal” (Maynard Smith, 1986; Judson and Normark, 1996; Schön et al., 2009). Various molecular- and organismal-based approaches were used for recognizing signs of (cryptic) sex (Ramesh et al., 2005; Malik et al., 2008; Schurko et al., 2009). Some scientists do not accept the existence of any long-term asexuality at all (Little and Hebert, 1996), or only accept this evidence for the bdelloid rotifers (Hayden, 2008). Without taking sides in this controversy, I delineate the framework within which asexual reproduction may have endured for millions of years.

Given the differences regarding speciosity, individual genetic variability, genetic mechanisms underlying the formation of gametes (apomixis versus automixis), incidence of rare males and prevalence of homogenizing mechanisms between the few putative ancient asexual groups (bdelloid rotifers, darwinulid ostracods, certain lineages within oribatid mites) it is clear that there is no single scenario that will explain the origin and persistence of all three groups (Schön et al., 2009). Yet, some unifying ecological principles can be outlined. At the phenotypic level, relatively old asexuals appear to exhibit a relative preponderance of taxa with traits that may reduce extinction risk, including some combination of high dispersal abilities, dormant resting stages, broad geographical distributions, and large population sizes (Schwander and Crespi, 2009). Most darwinulids and bdelloids live in what could generally be termed "marginal habitats". One possibility is that competition (with sexual species) would be lower, as there are simply fewer species occurring in such highly fluctuating habitats. Another reason could be that asexuals are able to survive in very low densities over many generations, since they do not need to find a mate in order to reproduce (Van Dijk, 2007; Hörandl, 2008). For all sexual populations, there is a density threshold (mediated by size and mobility of animals, amongst other biological characteristics) below which the probability of finding a mate is too low to ensure sufficient reproduction for the population to remain viable. In marginal habitats, such as semi-terrestrial ones, conditions may vary widely and asexuals would have the advantage over sexuals. If asexuals are sufficiently small so that effective population sizes still remain large in spite of low densities (and all three putative asexual groups have very small body sizes), such low densities may not necessarily lead to genetic bottlenecks as sufficient genetic variability might survive (Schön et al., 2009).

15.3.1.1 Bdelloid rotifers

Bdelloid rotifers are abundant invertebrate animals that can be found on every continent in almost any freshwater environment and moist-terrestrial habitats over a wide range of temperature and pH, and are often among the most common microinvertebrates, particularly in ephemeral (transitory) aquatic environments (Ricci, 1987; Wallace and Snell, 2001). Individuals range from about 0.1 to 1 mm in length and have muscles; ganglia; tactile and photosensitive sensory organs; structures for feeding, swimming, and crawling; digestive and secretory organs; and ovaries. Their ability to maintain cosmopolitan metapopulations

is related to their long-distance dispersal abilities, their ability to initiate populations with single females, and their capacity to survive unfavorable periods via the presence of dormant resting stages (Finlay and Fenchel, 2004; Fontaneto et al., 2008). Although individual biomass is minute, large population size, coupled with high turn-over rates make rotifers an important component of food webs (Herzig, 1987; Wallace and Snell, 2001). Adding to their importance is the fact that rotifers are eaten by invertebrate predators and are also the first food of fish fry, thereby making their energy available to higher trophic levels. Bdelloid rotifers constitute the largest, oldest, most diverse animal taxon for which there is morphological, cytological, and molecular evidence for long-term parthenogenesis. Their closest relatives are in the class Monogononta, which reproduce mostly by apomictic parthenogenesis, with an occasional one-generation sexual cycle. The bdelloids are believed to descend from a parthenogenetic female monogonont that lost the ability to enter a sexual cycle (Birky, 2004). The putative role of resource availability in this change of reproductive strategy has been shown experimentally (Boraas, 1983; Bennet and Boraas, 1989; Fussmann et al., 2003, see chapter 3). Fossil evidence shows that the bdelloids are at least 35 to 40 million years old while their genetic diversity suggests they are more than twice that age. In this period, the descendants of the first bdelloid diversified into at least 360 species in three families (Poinar and Ricci, 1982; Waggoner and Poinar, 1993; Mark Welch and Meselson, 2000; 2003; Wallace and Snell, 2001; Birky, 2004; 2010; Mark Welch et al., 2004a; 2004b; 2009; Rice and Friberg, 2007; Neiman et al., 2009a). Two bdelloid features, the ability to survive desiccation at any life stage and obligate parthenogenesis allow an unusual lifestyle (Ricci, 1987; 1998). These features qualify the bdelloids as colonizing organisms in *r*-selected environments. Anhydrobiosis capacitates bdelloids to stably inhabit desiccation-prone habitats and also provides a means of dispersal: when desiccated, a bdelloid contracts into a small flat ellipsoid called a tun, which adheres firmly to substrates such as soil particles, mud, or moss fragments that may be passively transported over long distances (Tunnacliffe and Lapinski, 2003). During quiescence, bdelloids appear to suspend respiration, metabolism, and aging. Thus, anhydrobiosis is the ultimate strategy for eggs or other stages of the life cycle to survive extended periods of environmental stress (Guppy and Withers, 1999; Radzikowski, 2013). On recovery, bdelloids resume reproduction and other life history traits consistent with their age at the start of dormancy ignoring the time spent in anhydrobiosis

(Ricci et al., 1987; Ricci and Covino, 2005). Adults, eggs and embryos of 15 bdelloid species, representing four families and six genera (inhabiting both water bodies and water retained by mosses), were desiccated and kept dry for 7 days. After this treatment, higher recovery rates were observed for the moss species, i.e. those frequently subjected to desiccation events (Ricci, 1998). In a variety of organisms the ability to withstand desiccation confers cross-tolerance to various other extreme environmental stressors, including different types of radiation (Alpert, 2006; Watanabe, 2006; Daly et al., 2007; Watanabe et al., 2007; Gladyshev and Meselson, 2008; Jonsson et al., 2008; Hengherr et al., 2009; Slade et al., 2009; Gusev et al., 2010). During anhydrobiosis, DNA breaks take place (Gladyshev et al., 2008; Gladyshev and Arkhipova, 2010; Gusev et al., 2010) that are repaired by homologous recombination (Rice and Friberg, 2007; Slade et al., 2009; Gusev et al., 2010). Bdelloids may be unusually susceptible to DSBs during anhydrobiosis because, unlike most other organisms known to be capable of anhydrobiosis, they do not produce the disaccharide trehalose, which promotes tolerance to desiccation (Lapinski and Tunnacliffe, 2003; Rice and Friberg, 2007). Bdelloid populations maintained in a hydrated state over many generations show a decline in fitness compared to populations that were cyclically desiccated (Ricci et al., 2007). Repair processes associated with recovery from desiccation may have a beneficial effect beyond desiccation tolerance. Repair of desiccation-induced DNA damage would require the presence of a homologous template, maintaining colinear pairs in gene-rich regions and selecting against insertion of repetitive DNA that might cause chromosomal rearrangements (Gladyshev and Arkhipova, 2010). Mothers who have been through desiccation, produce daughters of increased fitness and longevity (Ricci and Covino, 2005) and desiccation stress is a necessary condition for enhanced fitness in bdelloids (Ricci et al., 2007). This feature is reminiscent of the germline rejuvenating action of mitochondrial oxidative stress in sexually reproducing organisms (Isaeva and Reunov, 2001; van Werven and Amon, 2011). Parthenogenesis allows bdelloids to rapidly re-occupy a habitat after it changed from unfavorable to favorable conditions or single tuns to found a new population and colonize new habitats (Birky et al., 2005).

The rate of molecular evolution in bdelloid rotifers is higher than that of close sexual relatives and points toward mutation accumulation in the absence of sex (Barraclough et al., 2007). However, such accumulation of mutations can be handled without deleterious effects over long time-frames (Mark Welch

and Meselson, 2000; 2001). In bdelloid rotifers many genes were found that appear to have originated in bacteria, fungi, and plants, concentrated in telomeric regions along with diverse mobile genetic elements. The capture and functional assimilation of exogenous genes resembles a bacterial transformation-like type of "parasexual" behavior and may represent an important force in bdelloid evolution (Gladyshev et al., 2008).

The rotifer *Habrotricha elusa* is able to survive long periods of desiccation which, combined with aerial dispersal, allows this invertebrate to escape a deadly fungal parasite, *Rotiferophthora angustispora*, an organism less tolerant to desiccation (Wilson and Sherman, 2010; Leung et al., 2012). If anhydrobiotic dispersal enables bdelloid species to escape temporally and spatially from some or many natural enemies, their coevolutionary burden would be substantially reduced. Therefore, bdelloids may have evaded parasites and pathogens over evolutionary time, without incurring the costs of sexuality, by playing a never-ending game of "hide-and-seek" (Ladle et al., 1993; Judson, 1997; Wilson and Sherman, 2010; Wilson, 2011).

It has been suggested that the absence of meiosis in asexual lineages should lead to higher interallelic divergence at any given locus within an individual (i.e., allelic sequence divergence) compared to sexual populations (i.e., Meselson effect; Mark Welch and Meselson, 2000). However, most studies in putative asexual lineages failed to show high levels of neutral allelic divergence (Kuhn et al., 2001; Schön and Martens, 2003; Pawlowska and Taylor, 2004; Hijri and Sanders, 2005; Schaefer et al., 2006), with the exception of the bdelloid rotifers (Mark Welch and Meselson, 2000; Pouchkina-Stantcheva et al., 2007), Meloidogyne root knot nematodes (Lunt, 2008; Danchin et al., 2011b), and Timema stick insects (Schwander et al., 2011), while they revealed sex in the Placozoa (Signorovitch et al., 2005). However, as was pointed out (Butlin, 2000; Schön et al., 2008), the Meselson effect is asymmetric: its presence may confirm long-term asexuality, but its absence does not necessarily refute it since 'unsexy' processes, such as DNA repair, mitotic recombination, and allelic gene conversion may lead to homogenization between alleles and to the loss of mutations that arose anew on different chromosomes. But the story is even more complicated: part of the high allelic divergence seen in bdelloids probably derived from an initially diploid lineage that underwent whole-genome duplication followed by massive gene loss and karyotype restructuring (Maderspacher, 2008; Mark Welch et al.,

2008; Hur et al., 2009). On the other hand, the level of divergence between ancient alleles was markedly lower (ca. 3%) and not very different from the range observed in sexually reproducing species such as *Ciona savingnyi* (Small et al., 2007). Subsequent observations in *Adineta vaga* (another bdelloid species) confirmed this result (Hur et al., 2009).

In Meloidogyne root knot nematodes, the observed Meselson effect is the result of previous hybridization between species (Lunt, 2008). Thus, the sequence divergence between duplicated chromosome pairs (i.e., paralogous loci) could be misinterpreted as high allelic divergence and the Meselson effect in these lineages (Mark Welch et al., 2008; Schurko et al., 2009).

Taken together, their minute individual biomass (minimizing investment into new individuals), large population size, colonizing lifestyle in r-selected habitats, egg bank, anhydrobiosis and associated extreme stress resistance, DNA repair capacity and functional assimilation of exogenous genes by a type of "parasexual" behavior appear to make asexuality an evolutionarily stable strategy in bdelloid rotifers.

15.3.1.2 Darwinulid ostracods

Ostracods are small, bivalved crustaceans, which occur in almost all aquatic and moist (semi-) terrestrial habitats. Like rotifers, ostracods reach large population sizes (Van Doninck et al., 2003b) and are an important component of food webs (Evans and Stewart, 1977; Pihl, 1985). The fossil record indicates that the ostracod family Darwinulidae (adult size 0.6–0.8 mm; *Vestalenula mathilda* <0.4 mm) has reproduced fully asexually for 200 Myr (Martens et al., 2003) and neither sexual nor mixed extant populations or close sexual relatives are known (Martens, 1998). Rare males in a single darwinulid living species, *Vestalenula cornelia*, have recently been described (Smith RJ et al., 2006), but they may be non-functional, as they seem to have rudimentary reproductive organs; in addition, no spermatozoa have been observed in either males or sympatric females.

Most darwinulids can be found in what could generally be termed "marginal habitats", such as moist mosses and other (semi-) terrestrial environments, much like bdelloid rotifers. The exceptions to a distribution in marginal habitats are the darwinulid species with General Purpose Genotype (GPG), such as *Darwinula stevensoni* and *Penthesilenula brasiliensis*: they are ubiquitous, or nearly so, and can also be found in lakes, rivers, interstitially, etc. (Schön et al., 2009). All darwinulids are brooders, and 4 out of 5 genera have

the posterior part of the carapace inflated so as to create a brood pouch (Horne et al., 1998a; Schön et al., 2009). With an average of 6–8 offspring per female in *Penthesilenula brasiliensis* (Pinto et al., 2007), and 11–15 offspring in *Darwinula stevensoni* (Van Doninck et al., 2003a), darwinulids generally have low fecundity as compared to other ostracods (Geiger, 1998) and, especially in higher latitudes, rather long life cycles. *D. stevensoni* takes 4 years in Canada (McGregor, 1969) and in Finland (Ranta, 1979) to complete its life cycle, although further South, e.g. Belgium, it takes only 1 year (Van Doninck et al., 2003a), which is still considerably longer than in most other Cypridoidea (e.g. Martins et al., 2008; Schön et al., 2009). Darwinulids do not have resting eggs like all of the Cypridoidea and some Cytheroidea (Geiger, 1998), and they do not swim but only crawl slowly. The low fecundity and long life cycles of Darwinulids compared to sexual ostracods argue against the twofold advantage of asexuality vs. sexuality (Maynard Smith, 1971a) and beg for other explanations for their long-term asexuality. Horne and Martens (1999) argued that the absence of sexual freshwater ostracods in northern Europe is not just a consequence of the superior colonization abilities of clones. Fossil evidence indicates that sexual ostracods also inhabited northern Europe during post-glacial times and were replaced as climates gradually became more stable. Consequently, they argue that modern climatic stability favored the replacement of sexual lineages by competitively superior clones.

Use of allozyme markers and direct sequencing of nuclear genomes revealed low genetic diversity between *D. stevensoni* populations that cannot be explained by recent selective sweeps (Rossi et al., 1998; 2004; Schön et al., 1998; 2000, 2003; 2009; Gandolfi et al., 2001). Differences in genetic diversity between embryos and adults furthermore indicate that up to half of the observed genetic changes in adults can be caused by somatic mutations (Schön and Martens, 2003). It has been argued that the presence of homogenizing mechanisms such as gene conversion, DNA repair and mitotic recombination are most likely the most important factors that may reduce mutation rates in darwinulids (Schön and Martens, 1998; Schön et al., 1998; 2008; 2009). Possibly due to these mechanisms the Meselson effect is not observed in Darwinulid ostracods (Schön and Martens, 2003).

The unusually wide tolerance range for both salinity (0–30 g/l) and temperature (10°C, 20°C and 30°C) of the freshwater species *D. stevensoni*, supports the

hypothesis that it has indeed developed a GPG (Van Doninck et al., 2002) (see chapter 15.3.3). It has been argued that a GPG can only originate and persist in fully asexual lineages as recombination will almost certainly break-up the allele-combinations required for a GPG. On the other hand, the chance that a sexual lineage would have a GPG at the time clones originate from this sexual root (and can thus freeze the GPG in the clonal lineage) is very small indeed (Van Doninck et al., 2003b), which might explain why few taxa seem to have evolved a real GPG (Schön et al., 2009). As a further means to conserve the GPG, darwinulids may be able to exert embryo selection. It was shown that *Darwinula stevensoni* and *Penthesilenula brasiliensis* have the ability to detect, select and eject unwanted material such as eggs or embryos from the brood pouch (Horne et al., 1998b; Pinto et al., 2007). In the experiments of Pinto et al. (2007) the majority of the ejected eggs remained viable and hatched and the juveniles moulted to later instars. They survived for several months, but none ever reached adulthood.

The freshwater ostracod *Eucypris virens*, is commonly found in European temporary pools, where its long-term persistence completely relies on the build-up of resting egg banks. Resting eggs of both sexual and parthenogenetic *E. virens* showed extreme tolerance to a variety of environmental stressors (Vandekerckhove et al., 2013) making the egg banks of dormant propagules a source of genetic variation between generations and for temporal bet-hedging. Patterns of allozyme diversity among unisexual and sexual ostracods *Cypricercus* and *Eucypris virens* suggest that the success of unisexual ostracods may also be linked to their ability to recruit clonal diversity through interbreeding with close sexual relatives (Turgeon and Hebert, 1995; Schön et al., 2000). Data derived from a survey of ostracod valves preserved in 34 Holocene freshwater sediment cores suggest that environmental fluctuations during a period of less than 5000 years were sufficient to provide an advantage to sexually reproducing ostracods over parthenogenetic forms (Griffiths and Butlin, 1995).

In summary, their minute individual biomass (minimizing investment into new individuals), large population size, marginal habitats, maintenance of a possible General Purpose Genotype due to embryo selection and DNA homogenizing mechanisms appear to make asexuality an evolutionarily stable strategy in darwinulid ostracods.

15.3.1.3 Oribatid mites

About 10% of all known oribatid mite species reproduce by female parthenogenesis, a rate much

higher than in other invertebrate and vertebrate taxa (Cianciolo and Norton, 2006; Avise, 2008). One reason for this high proportion may be the permanent availability of homogeneously distributed dead organic matter in soil systems (Scheu and Drossel, 2007) that allows densities of up to 400,000 individuals per square meter in forest soil (Schatz and Behan-Pelletier, 2008). In acidic boreal forests, they reach densities of up to 400,000 ind/m² whereas in calcareous forests, densities are usually somewhere between 20,000 and 40,000 ind/m². There is little seasonal fluctuation of oribatid mite densities, indicating that the communities are in equilibrium conditions (Heethoff et al., 2009). Overall, the lower density of oribatid mites in calcareous forest soils presumably is mainly due to macrofauna activity, whereas their density in more acidic forest soils probably is limited by the availability of high quality resources (bottom-up control; Salamon et al., 2006). In parthenogenetic oribatid mite species males are rare (spanandric) and sterile. Spermatophores are non-functional, as spermatogenesis is incomplete (Taberly, 1988), and there is no evidence for recombination or incorporation of paternal genetic material into the offspring (Palmer and Norton, 1992; Heethoff et al., 2009). Constant conditions favor asexuality (Bürger, 1999) which may explain the high incidence of parthenogenesis in environments such as stable forest soils (Cianciolo and Norton, 2006; Domes et al., 2007). Intriguingly, the distribution of reproductive modes of soil fungi follows a similar pattern (Grishan et al., 2003). On the other hand, oribatid mites that dominate on the bark of trees are predominantly sexual taxa (Cianciolo and Norton, 2006; Erdmann et al., 2006; Fischer et al., 2010). In contrast to oribatid mites in soil, communities on bark appear to be less sensitive to disturbances (Erdmann et al., 2006). Densities on the bark of trees are also low as compared to soil (Erdmann et al., 2006). Bark oribatid mites feed on lichens. Lichens grow slowly and may be in limited supply but also defend themselves, e.g. by producing usnic acids (Emmerich et al., 1993). It has been shown in laboratory experiments that parthenogenetic taxa suffer more than sexual taxa from resource limitations (Domes et al., 2007), suggesting that sexual taxa are better adapted to resource limitation.

Divergence levels in the mitochondrial cytochrome c oxidase subunit 1 gene between and within clades of *Platynothrus peltifer* suggest that in this species asexual reproduction is at least 100 million years old (Heethoff et al., 2007). Another fully asexual species in this group, *Mucronothrus nasalis*, is thought to be 200 million years old (Hammer and Wallwork, 1979). There is low genetic divergence and no evidence for the

Meselson effect in parthenogenetic oribatid mites even with the probable absence of genetic recombination (Schaefer et al., 2006).

Oribatids are relatively long-lived and have numerous morphological defensive adaptations. Predation (top-down control) is likely to be of little importance as a regulatory factor for adult oribatid mites that have been proposed to live in 'enemy-free space' (Peschel et al., 2006). Most also possess a pair of large exocrine oil glands that produce species-specific mixtures of hydrocarbons, terpenes, aromatics, and alkaloids with presumably allomonal functions. When the oil glands of the model oribatid species, *Archegozetes longisetosus*, are discharged and the 'disarmed' individuals are offered as prey to polyphagous *Stenus* beetles (Staphylinidae), *Stenus juno* fed on disarmed mites with behavioral sequences and success rates similar to those observed when they prey on springtails, a common prey. In contrast, mites from the control group with full glands were almost completely rejected; contact with the gland region elicited a strong reaction and cleaning behavior in the beetle. Thus, oribatid mite oil gland secretions have an adaptive value for chemical defense (Heethoff et al., 2011). On the other hand, mites suffer a variety of infections (Poinar and Poinar, 1998; van der Geest et al., 2000), so that the coevolutionary value of sexual reproduction may apply.

In summary, their minute individual biomass, stable habitats with abundant resources allowing large population sizes and enemy-free space appear to make asexuality an evolutionarily stable strategy in oribatid mites.

15.3.2 Cyclical parthenogenesis

In some organisms phases of asexual propagation are alternated with bouts of sexual reproduction, called cyclical parthenogenesis, holocycly or heterogony. Cyclical parthenogenesis is generally rare. It occurs in only ~15,000 animal species, spread over seven taxonomic groups (Hebert, 1987). From an evolutionary point of view cyclical parthenogenesis is fundamentally sexual (Vrijenhoek, 1998). The cyclically parthenogenetic life-cycle is believed to retain the advantages of recombination while minimizing the cost of sex. However, this life cycle is also thought to be unstable due to periodic loss of sexual reproduction by directional selection. Yet, cyclical parthenogens are of special interest because they allow a direct assessment of the ecological conditions, costs and benefits of sex versus asex.

15.3.2.1 Monogonont rotifers

Monogonont rotifers are small, aquatic invertebrates that normally reproduce by cyclical parthenogenesis, an alternation between an extended phase with ameiotic parthenogenesis and short sporadic sexual episodes (Arndt, 1993; Nogrady et al., 1993; Armengol et al., 2001; Wallace et al., 2006). Explaining the evolutionary dynamics of the monogonont rotifer life cycle is important for understanding how cyclical parthenogenesis is maintained, and for comparing monogononts with their close relatives, the bdelloid rotifers, which are ancient obligate asexuals. Sex is initiated with the production of sexual females, whose oocytes undergo meiosis and develop into haploid males (if not fertilized), or diploid diapausing eggs (if fertilized), which show a remarkable tolerance to unfavorable conditions that typically occur every year (Serra and Snell, 2009) and remain viable for decades (Marcus et al., 1994; Kotani et al., 2001; Clark MS et al., 2012). Diapausing eggs contain multinucleate diapausing embryos encased in a three-layered shell that protects them from external stressors, like desiccation and temperature extremes (Wurdak et al., 1978). Highly instructive are the dormancy patterns among rotifers: short-lived monogononts produce resting eggs with long-lasting diapause commonly after switching to mictic phase; bdelloids, living 3 times as long, enter anhydrobiosis with short-lasting quiescence at any time during their life cycle as a direct response to changing environment. The two dormancy forms of the rotifers are alternative and mutually exclusive and appear to be related to the temporal variation of their habitats (Ricci, 2001). Molecular characterisation of processes associated with the formation of resting eggs revealed that small heat-shock proteins and some antioxidant genes were upregulated in resting eggs, therefore suggesting that desiccation tolerance is a characteristic feature of resting eggs even though they do not necessarily fully desiccate during dormancy (Denekamp et al., 2009). Screening polymorphic microsatellite loci in populations of the rotifer *Brachionus plicatilis* in a temporary pond, Gómez and Carvalho (2000) analysed: (i) the genetic structure of the resting egg bank; (ii) the changes in the genetic structure of rotifer populations during the parthenogenetic phase; and (iii) the population structure after its initiation from resting eggs. The last sample in the parthenogenetic phase showed evidence of clonal selection, as indicated by a low observed clonal diversity and the appearance of linkage disequilibria. On the other hand, the resting egg bank was in Hardy-Weinberg and linkage

equilibrium, and contained a high genotypic diversity. Unexpectedly, the resting egg bank differed from the planktonic population in its allelic composition, suggesting that resting egg hatching is biased (Gómez and Carvalho, 2000).

At the interface between sexual and asexual reproduction, the role of resource availability for the reproductive mode and the offspring quantity/quality trade-off becomes evident (see chapter 3). There are several documented cases of *Brachionus* strains that have permanently lost the ability to reproduce sexually (Boraas, 1983; Buchner, 1987; Bennett and Boraas, 1988; Fussmann et al., 2003; Stelzer, 2008; 2011; Stelzer et al., 2010). Boraas (1983) found that newly established cultures of *Brachionus calycifloru* collected from the field produced 40% mictic (sexual) females when induced. After 2–3 months in a chemostat, i.e. with unlimited resources, that percentage was reduced to 0 in similarly inducing environments. This work has been confirmed (Bennet and Boraas, 1989; Fussmann et al., 2003; Becks and Agrawal, 2010), establishing the costs of sex under unlimited resources (Stelzer, 2011). Loss of sex has been found to be stable for years in strains used in different laboratories (Stelzer, 2008). Bennet and Boraas (1989) founded their cultures with a single female, and hence genetic variation causing sex loss had to arise during experimental culture. In other experiments not initiated with one female, genetic variation for investment in sex might be present in the founder populations. Nevertheless, the observed evolutionary dynamics did result in selection for sex loss (Serra and Snell, 2009). Resource abundance has been considered to be the most significant factor determining population size. Under various food levels, *Brachionus plicatilis* flexibly changes its reproductive patterns and lifespans (Yoshinaga et al., 2000; 2003). In a food-rich environment, *B. plicatilis* produces approximately 30 offspring during its lifespan of approximately 10 days. In contrast, when fed for only a few hours daily, it suppresses active reproduction and produces less than 10 offspring, while surviving for nearly a month. Long-lived individuals resulting from reproductive suppression are likely to obtain a second chance for reproduction in future. Besides life history parameters, offspring quality (starvation resistance) also increases when *B. plicatilis* reproduces in a food poor environment (Yoshinaga et al., 2001; 2003).

In *Brachionus* and several other monogonont rotifers, the production of sexual females is induced at high population densities by a chemical that is produced by the rotifers themselves (Stelzer and Snell, 2003; Snell et al., 2006; Timmermeyer and Stelzer, 2006), a

process analogous to quorum sensing in bacteria (Kubanek and Snell, 2008). Obligate parthenogens are unable to produce sexual females, thus they also lack males and diapausing eggs. This inability is caused by a loss of responsiveness to the chemical signal that induces sex (Stelzer, 2008). As a consequence, populations of obligate parthenogens can grow to extremely high population densities, without ever inducing sex, whereas cyclical parthenogens readily induce sexual reproduction as soon as population densities exceed one female per ml (Gilbert, 2004; Stelzer, 2012). On the other hand, obligate parthenogenesis may be associated with small body size (Bennet and Boraas, 1989; Stelzer et al., 2010). The linked features of adaptive dwarfing and inflation of population size reflect a bacteria-like reproduction strategy, replacing K-selected sexual reproduction by r-selected asexual reproduction when facing high-resource conditions. In most cases, however, obligate parthenogens are of similar size, or even larger than their closest sexual relatives – the latter can usually be attributed to polyploidy (Suomalainen, 1950).

15.3.2.2 Daphnia

Members of the genus *Daphnia* are small (1–5 mm), largely transparent crustaceans that are found in most still freshwater bodies around the world. They are planktonic filter feeders, eating mainly planktonic algae and are themselves the food for planktivores, such as fish and some invertebrates. Most members of the genus *Daphnia* are cyclic parthenogens. Under most conditions, a female *Daphnia* will produce daughters by apomictic parthenogenesis. Induced by changes in the external environment, the same female can produce asexual sons or haploid eggs that need fertilization by males (Eads et al., 2008). Ephemeral populations of *Daphnia* tend to follow boom-and-bust cycles, whereby high densities often precede steep declines (Dudycha, 2004). Crowding may also indicate decreasing water levels as a result of the pond drying up. Either of these situations should favor investment in diapause as opposed to neonate production. Accordingly, *Daphnia* have been found to produce more diapausing eggs and fewer neonates in response to crowding (Berg et al., 2001; Lürling et al., 2003). These eggs are also resting stages (=ephippia) and can outlive harsh conditions for many decades. Diapausing eggs may hatch the following year, or may remain buried and hatch many years later (Kerfoot and Weider, 2004). Certain *Daphnia* are even able to produce these resting eggs without meiosis and thus do not need males (obligate parthenogenesis).

Genotype x environment interactions affect responses to sex induction cues (Deng, 1996). These cues include high population density, food stress, photoperiod and temperature (Carvalho and Hughes, 1983; Larsson, 1991; Kleiven et al., 1992). Moreover, exposure to parasites (Duncan et al., 2006) and predators (Sluzarczyk, 1995) may induce the sexual formation of dormant stages to ensure persistence in the habitat. Offspring sex ratios, and the very direction in which they changed in response to crowding, differed significantly among genotypes with some genotypes producing more and others fewer males in response to crowding (Fitzsimmons and Innes, 2006). Obligately parthenogenetic genotypes seemed to respond to the crowding stimulus in similar ways as the facultatively parthenogenetic genotypes (Fitzsimmons and Innes, 2006). The frequency of sex, calculated using the proportion of males and sexually reproducing females, may span an ~30-fold difference between high- and low-sex populations (Cáceres and Tessier, 2004). Both the costs and benefits of sex, as measured by changes in means and variances in life-history traits, increased substantially with decreasing frequency of sex (Allen and Lynch, 2012). Brood sizes may vary enormously between maternal environments—from large broods under adult good conditions to very small broods and sexual resting eggs under adult stress conditions (Mitchell and Read, 2005). The cost of males was evident when sexual and asexual females were raised separately: sexuals produced fewer female offspring. However, there was no cost of males when reproductive modes were raised in pairs, as sexuals won the competition with asexuals (Wolinska and Lively, 2008).

The burst of clonal variation immediately after a sexual generation, can be lost rapidly during the asexual phase of the life cycle. Typically, it is assumed that selection at least contributes to this loss, which is supported by studies demonstrating that clones of cyclical parthenogens that are distinguishable by molecular markers also differ significantly in ecologically relevant traits (Weider, 1993b; Epp, 1996). Quantitative traits were influenced by three factors: (1) clonal selection significantly changed the population mean phenotype during the course of the growing season; (2) sexual reproduction and recombination led to significant changes in life-history trait means and the levels of expressed genetic variation, implying the presence of substantial nonadditive genetic variation and genetic disequilibrium; and (3) egg-bank effects were found to be an important component of the realized year-to-year change (Pfrender and Lynch, 2000). DNA transposons constitute approximately 0.7% of the D.

pulex genome. Differences between lineages where sex was prohibited or promoted indicate that recombination has significant effects on TE dynamics (Schaack et al., 2010b).

15.3.2.3 Aphids

Aphids comprise worldwide ~4,400 known species of small sap-sucking insects of the order Hemiptera and are highly specialized plant feeders (Blackman and Eastop, 1994; 2000; 2006). Their life cycles are unusual among arthropods because they can include obligate shifting between unrelated host plant taxa, elaborate polyphenisms (“the ability of organisms with the same genotype to develop two or more distinctly different alternative phenotypes without intermediates”; Nijhout, 1999), and variation in reproductive strategy within a single species (Moran, 1992). Aphid life cycles can encompass cyclical parthenogenesis, obligate parthenogenesis, obligate parthenogenesis with male production and an intermediate ‘bet-hedging’ strategy where an aphid genotype will over-winter by continuing to reproduce by parthenogenesis and by investment in sexually produced eggs (Dedryver et al., 1998; 2001; Wilson et al., 2003). Under ideal conditions (climatic and with a dearth of predators, parasitoids and pathogens), a single parthenogenetic female can typically give rise to 30–90 offspring (Blackman, 1971) and, due to its short generation time (~10 days), can potentially result in billions of individuals in a single growing season (Dixon, 1989; 1998; Harrington, 1994; Loxdale, 2009). Thanks to their aerial dispersal, aphids occur globally (Loxdale, 2009) and can be found in arctic (Strathdee et al., 1993) and sub-antarctic regions (Hullé et al. 2003), have been found far out at sea (Hardy and Cheng, 1986), on mountain tops (Loxdale, 2009), and infest a huge range of plants, usually monophagously. Although, some species are polyphagous within plant genera or families (e.g., Brassicas), and in the case of the ubiquitous and highly polyphagous *Myzus persicae*, this species attacks over 40 plant families worldwide (Blackman and Eastop, 2000).

Aphids are model organisms for the elucidation of phenotypic plasticity (Simon et al., 2011; Srinivasan and Brisson, 2012). In the pea aphid, *Acyrtosiphon pisum*, females respond to specific environmental cues by transmitting signals that have the effect of altering the development of their offspring. The production of alternative morphs, e.g. wing polyphenism (consisting of winged and unwinged females) and reproductive polyphenism (consisting of asexual and sexual individuals), by genetically identical individuals involves epigenetic mechanisms

(Srinivasan and Brisson, 2012). These adaptations (sexual versus asexual, winged versus unwinged) have evolved in response to environmental changes that are predictable (seasons) and unpredictable but common (population density, host plant quality, and predation). Importantly, the developmental response for the morphs is separated by at least one generation from the triggering cue (Srinivasan and Brisson, 2012). Aphids express the wing phenotype to limit predation and competition for resources. The production of sexual morphs coincides with predictable, seasonal changes in photoperiod and temperature. Typically, the tropics and subtropics harbour only obligate parthenogens and cold climates only cyclical parthenogens, while both reproductive modes occur in temperate climate zones because their coexistence is facilitated by temporal variation in winter severity (Rispe and Pierre, 1998; Rispe et al., 1998). Sexual lineages are favored in regions with regular harsh winters because they produce cold-resistant eggs, while asexual lineages do not resist frost but take advantage of their faster multiplication rates in mild winter areas (Rispe and Pierre, 1998; Rispe et al., 1998; Simon et al., 2002). Clonality is associated with viviparity while sexuality is linked with oviparity (Le Trionnaire et al., 2008). With its large size (~517 Mbp) and large number of predicted genes (~35,000 genes) that is due to a large number of gene duplications, the pea aphid genome possesses one of the largest gene repertoires among animals (The International Aphid Genomics Consortium, 2010; Srinivasan and Brisson, 2012), rivaling that of *Daphnia pulex*, another polyphenic arthropod (Colbourne et al., 2011, see chapter 15.3.2.2). Reproductive polyphenism appears to depend on epigenetic modifications such as DNA methylation, chromatin remodeling by histone modifications and regulation by small RNA pathways (Legeai et al., 2010; Walsh et al., 2010; Simon et al., 2011; Srinivasan and Brisson, 2012). Notable among the gene duplications are those of genes involved in DNA methylation, small RNA pathways, and chromatin modifications and remodeling. From an ecological point of view, plasticity of reproductive mode is dependent on epigenetic modifications. As in *Daphnia*, environmental change and hardiness favor sexual reproduction. Aphids present frequent transitions from cyclical parthenogenesis to permanent asexuality. Anholocyclics have abandoned sexual reproduction, reproducing all the year round by sustained parthenogenesis (Blackman, 1971; MacKay, 1989; Dedryver et al., 1998). Both nuclear and cytoplasmic markers of *Rhopalosiphum padi* clearly showed that many asexual lineages have hybrid origins between *R. padi* and an unknown sibling species, and are of

recent origin (Delmotte et al., 2003). Mitotic recombination, although rare in asexual aphids (Sunnucks et al., 1996; Wilson et al., 1999), almost certainly occurs at a low rate or at specific locations in the genome (Blackman and Spence, 1996). In addition, patterns of recombination and segregation at sexual reproduction might be complex (Simon et al., 2002). For example, the aphid *Myzus persicae* shows high levels of recombination at oogenesis, but essentially no recombination during spermatogenesis (Sloane et al., 2001).

Clonal diversity may reflect the balance between the influx of clones and their elimination through drift and/or selection. That clonal diversity can erode quickly has been shown in holocyclic aphids. The burst of clonal variation immediately after a sexual generation can be lost rapidly during the asexual phase of the life cycle (Rhombert et al., 1985). Typically, it is assumed that selection at least contributes to this loss, which is supported by studies demonstrating that clones of cyclical parthenogens that are distinguishable by molecular markers also differ significantly in ecologically relevant traits (Sunnucks et al., 1998; Turak et al., 1998; Vorburger et al., 2003; Vorburger, 2004). Accordingly, selection has a strong influence on the genotypic composition of aphid populations (Sunnucks et al., 1997; Guillemaud et al., 2003; Llewellyn et al., 2004; Zamoum et al., 2005). In semi-natural habitats at least, particular aphid clonal lineages are not that abundant, new genotypes being continually created by sexual recombination (annual) and mutation (ongoing) and are then mainly eliminated by natural selection/drift and competition for limited resources. Hence the retention of sex, even rare sex, is important in generating variation, more than is apparently possible by mutation alone within asexual lineages (Loxdale and Weisser, 2011). In sharp contrast to their southeast Asian and European counterparts, *Sitobion miscanthi* and *S. near fragariae* aphids in Australia and New Zealand exhibit a complete absence of sexual reproduction. A genetic analysis revealed stepwise mutation of microsatellite alleles and also karyotypic change, representing rare evidence of evolution and clonal selection within wild-living parthenogenetic lineages (Wilson et al., 1999; 2003). Strong clonal selection has also been demonstrated in the aphid *Myzus persicae* (Vorburger, 2005a) possibly based on strong fitness differences between clones (Vorburger, 2005b). In one aphid species, the pea aphid (*Acyrtosiphon pisum*), genetic variation for resistance to aphidiid parasitoids has been demonstrated (Henter and Via, 1995; Hufbauer and Via, 1999; Ferrari et al., 2001; Stacey and Fellowes,

2002). Thus, it is possible that more resistant clones are under positive selection when parasitoids are abundant, but – if resistance incurs a cost – under negative selection when parasitoids are scarce (Vorburger, 2005a).

Most parthenogenetic individuals are eliminated by temperatures below -5 to -10°C , depending on species (Williams, 1980; Powell and Bale, 2004) and only fertilised eggs can resist long periods of intense frost (Sømme, 1969; Bale et al., 2007). A result of these selective patterns is that geographic parthenogenesis in aphids is “upside-down” compared to most organisms which have more parthenogenesis northwards (Hughes, 1989; Dedryver et al., 2001). In spring, holocyclic populations were in Hardy-Weinberg equilibrium at individual loci and had a relatively high genotypic diversity. Conversely, anholocyclic populations deviated from Hardy-Weinberg equilibrium and often consisted of a single clone (Simon et al., 1996). These findings argue for the primacy of ecological, and not genetic determinants, for the reproductive mode of aphids (Simon et al., 2002).

15.3.3 Geographical parthenogenesis: when males are too stressed to reproduce

Various quotations taken from Darwin (1859) by Hoffmann and Parsons (1991) indicate that Darwin already appreciated the impact of climatic stress at the extremes of species distributions. Often geographic ranges end at seemingly arbitrary points in space (Kirkpatrick and Barton, 1997; Holt and Keitt, 2005; Gaston, 2009). Historically, ecologists and biogeographers have correlated range boundaries with climate to identify environmental determinants of range boundaries (Griggs, 1914; Good, 1931; Dahl, 1951). Subsequent analyses have shown that range limits are associated with abiotic variables such as temperature or precipitation (Root, 1988; Cumming, 2002), biotic factors such as competitors (Terborgh and Weske, 1975; Bullock et al., 2000), or complex interactions between biotic and abiotic variables (Randall, 1982; Taniguchi and Nakano, 2000). A continuum emerges whereby competition is a factor of consequence in relatively benign environments but less so in more marginal environments where environmental stress is more important as selective regime (Parsons, 1993). Several hypotheses for the evolutionary stability of range limits propose that populations at range boundaries do not have sufficient genetic variation to respond to natural selection (Bradshaw and McNeilly, 1991; Hoffman and Blows, 1994; Gaston, 2003; Pujol and Pannell, 2008). Other hypotheses focus on other factors that may prevent

populations from adapting to the environment at the range margin, such as genetic trade-offs among fitness-related traits in the marginal environment (Antonovics, 1976), genetic trade-offs between fitness in central and border environments (Holt, 2003), or gene flow from populations adapted to the range center (Haldane, 1956; Garcia-Ramos and Kirkpatrick, 1997; Kirkpatrick and Barton, 1997). These hypotheses are not necessarily mutually exclusive, and may act synergistically to constrain range expansion. All of these hypotheses are united by the assumption that populations are maladapted at a range boundary and unfit beyond the current range (Angert and Schemske, 2005). Range equilibrium is suggested by transplant experiments beyond species' current range boundaries; many species have low fitness and exhibit negative population growth in areas beyond present distribution limits (e.g., Angert and Schemske, 2005; Geber and Eckhart, 2005; Griffith and Watson, 2006; Sexton et al., 2009; but see Van der Veken et al., 2007). There are empirical examples of high levels of mortality at range limits (Dekker and Beukema, 1993; Ungerer et al., 1999; Edwards and Hernández-Carmona, 2005; Angert, 2006; Gaston, 2009), and in transplants beyond those range limits (Angert and Schemske, 2005; Bird and Hodkinson, 2005; Geber and Eckhart, 2005). Greater levels of physiological stress at the range limits appear to be causally involved (Parsons, 1991; Tomanek and Somero, 1999; Harley, 2003; Sorte and Hofmann, 2004; Joyner-Matos, 2007; Joyner-Matos et al., 2007; Normand et al., 2009). In many cases, these high rates of mortality occur during or shortly after extreme environmental events. It is thus noteworthy that, conversely, most (especially ‘correlative’) modelling of the distributions of individual species employs spatial variation in mean not extreme environmental conditions (Gaston, 2003). It may not always, however, be the extreme events per se that are significant but the interaction between these events and resource availability, such that insufficient resources are available to enable organisms to cope with the demands of those events. In this sense, physiological and resource limitations on species distributions may be strongly confounded (Gaston, 2009). Inadequate levels of successful reproduction are probably one of the most common demographic explanations for range limits. There is much evidence for reduced or outright failure of reproduction at range limits, particularly among plants (where, if taking place, it is more readily observed), and a sense that this may often be more important in range limitation than subsequent survival of offspring (Gaston, 2009). Depending on taxon, changes in reproduction at range limits can variously

include levels of sexual reproduction (Dorken and Eckert, 2001; Tremblay et al., 2002; Beatty et al., 2008).

Taking into account the pattern of stress-sex relationship as discussed in chapter 14 it can be expected that extreme environments shift the sex-asex balance. The sexual forms have a central, or limited, distribution while clonally reproducing all-female lineages of plants and animals most often surround the central area or are found towards e.g. higher altitudes or latitudes. In a majority of the cases the clones also have a much wider distribution and ecological tolerance than the sexual forms they originate from (Beaton and Hebert, 1988; Parker and Niklasson, 2000; Schön et al., 2000; Stenberg et al., 2003). This spatial distribution of clones has been attributed to reproductive mode, elevated ploidy level or hybrid origin (Kearney, 2005) or all of these.

The great diversity of sex determination mechanisms in animals and plants ranges from genetic sex determination (e.g. mammals, birds, and most dioecious plants) to environmental sex determination and includes a mixture of both, for example when an individual's genetically determined sex is environmentally reversed during ontogeny. Environmental sex determination and environmental sex reversal can lead to widely varying and unstable population sex ratios (Stelkens and Wedekind, 2010). Many reptiles, amphibians, fish, and insects are capable of undergoing either environmental sex determination or sex reversal at early life stages (Stelkens and Wedekind, 2010). There are many different triggers for sex reversal. Most of them are abiotic (e.g. temperature, pH, endocrine-disrupting hormones, photoperiod, hypoxia). Temperature-dependent sex determination has been extensively studied in reptiles, where exposure to elevated temperature results in female development in some species (Bull and Vogt, 1979). These temperature-dependent effects appear to be mediated in part by influencing aromatase activity and estradiol synthesis in female lizards, turtles and crocodylians, and by steroid receptors in both sexes (Crews and Bergeron, 1994; Wibbels and Crews, 1994; Crews, 1996; Lance, 2009). Intriguingly, blocking estrogen synthesis with aromatase inhibitors in embryos of a unisexual, parthenogenetic all-female whiptail lizard, *Cnemidophorus uniparens*, resulted in male offspring (Wibbels and Crews, 1994; Wennstrom and Crews, 1995). The sex of several fish species/populations has been shown to be under the control of many genes of minor effect [e.g. poeciliid fish (Volf and Schartl, 2001), sea bass (Vandeputte et al., 2007), and tilapia

(Baroiller et al., 2008)] and these are particularly good examples of the evolutionary lability of genetic sex determination systems (see also chapter 14.2.1). Asexuality has arisen via hybridization at least 90 times in vertebrates, and all of them are fish, amphibians or reptiles (Dawley and Bogart, 1989; Avise, 2008). I do not insinuate that environmental sex determination systems and parthenogenesis have the same evolutionary basis, but it is striking that both occur in the same or related species, the lability of genetic sex determination possibly being a common denominator.

Clonally reproducing all-female lineages of plants and animals are often more frequent at higher latitudes and altitudes, on islands, arid environments and in habitats described as transient, ecotonal, disturbed or marginal (Glesener and Tilman, 1978; Bierzychudek, 1985; Beaton and Hebert, 1988; Cuellar, 1994; Peck et al., 1998; Eckert, 2002; Kearney, 2003; Hörandl, 2006). That it is parthenogenesis, and not outcrossed sexuality, that prevails in harsh, uncertain, disturbed and novel conditions has been taken as evidence against the idea that sex is creating preadaptation to an uncertain future, either permitting species to adapt more quickly or enabling individual females to produce a few unexpectedly fit offspring (Bell, 1985). Attempts to explain this pattern, known as geographical parthenogenesis, generally treat the parthenogens as fugitive species that occupy marginal environments to escape competition with their sexual relatives (Vrijenhoek and Parker, 2009). Parthenogenetic reptiles are found in arid environments (Wright and Lowe, 1968; Darevsky et al., 1985; Adams et al., 2003; Kearney et al., 2003), another general pattern under the umbrella of geographical parthenogenesis. The aridity of the environments occupied by parthenogenetic lineages of *Heteronotia* has been quantified relative to the sexual races (Kearney et al., 2003). While the two sexual progenitor lineages of parthenogenetic *Heteronotia* also occur within the arid zone of Australia, the parthenogenetic forms inhabit the driest regions and their distributions are very tightly associated with rainfall contours (Kearney et al., 2003; Strasburg et al., 2007). Moreover, the most recently discovered case of natural parthenogenesis in reptiles, the scincid lizard *Menetia greyii*, also occurs in this region (Adams et al. 2003), along with a diverse array of other parthenogenetic taxa (Kearney, 2003; Kearney et al., 2006).

Small populations frequently occur in marginal environments or near the edges of geographic distributions. These situations are associated with exposure to unfavorable conditions (Brown, 1984;

Hoffmann and Blows, 1994). Small populations are expected to suffer particularly from Muller's ratchet (Muller, 1964; Felsenstein, 1974; Gabriel et al., 1993; Charlesworth and Charlesworth, 1997). Hence, within the conceptual framework of Muller's ratchet theory of sexual reproduction (see chapter 18.1), it should be highly counter-intuitive that asexual reproduction occurs preferentially in small marginal populations.

There are two general explanations for this pattern, the General Purpose Genotype (GPG) and Frozen Niche Variation (FNV). In essence, the GPG and FNV models view clonal lineages as generalists versus specialists, respectively. According to the GPG model (Parker et al., 1977; Lynch, 1984), an asexual species consists of clones that can all survive and reproduce in all the different niches. The GPG postulates that asexuals do not need to adapt at all to changing environments, for example to fluctuating climates, if they have a genotype which allows them to survive in a wide range of ecological conditions. If this genotype produces a phenotype with wide ecological tolerance, then the GPG hypothesis predicts that the resulting phenotype will have (i) a broad tolerance against a wide range of environmental factors; and (ii) a very low variance in the tolerances of phenotypes derived from different populations. Both predictions were confirmed in populations of *Darwinula stevensoni* by Van Doninck et al. (2002): the tested specimens (with similar genotypes; Schön et al., 1998 and Van Doninck et al., 2002) showed a wide tolerance for a mixture of temperature and salinity treatments, while a logit linear model analysis of the "survival" data showed that responses between animals from several freshwater lakes (Ireland, France) were indistinguishable. Only the responses of animals from a (slightly) saline Belgian lake deviated to some extent, which might indicate that there was a maternal effect. Responses from other darwinulid species varied: *Penthesilenula brasiliensis* (a species with intercontinental distribution) has even wider tolerances than *D. stevensoni* for some variables, while endemic darwinulids such as *Vestalenula molopoensis* had much narrower tolerance ranges and *P. aotearoa* is found in-between (Van Doninck et al., 2003b; Schön et al., 2009).

One could argue that a GPG can only persist in fully asexual lineages as recombination will almost certainly break-up the allele-combinations required for a GPG. Therefore, a GPG can also only originate and persist in fully asexual lineages. However, the chance that a sexual lineage would have a GPG at the time clones originate from this sexual root (and can thus freeze the GPG in the clonal lineage) is very small indeed (Van

Doninck et al., 2003b), which might explain why few taxa seem to have evolved a real GPG. This represents something of a paradox, as this would imply that a GPG can only evolve through adaptation in asexual lineages, which by definition have impeded evolvability. One of the key generalizations of the GPG theory is that thelytokous races are distributed in areas of lower biotic diversity and more abiotic, mainly temperature, seasonality (Hoy Jensen et al., 2002). From this, Levin (1975) and Glesener and Tilman (1978) proposed the "biotic uncertainty hypothesis" for the maintenance of genetic recombination as an adaptation for frequency-dependent selection response to coevolutionary changes in predators, parasites and/or competitors (Jaenike, 1978; Hamilton, 1980; Hoy Jensen et al., 2002). Under this model, asexual derivatives can only establish themselves in areas of lower (or non-coevolved) biotic diversity, mainly because of their colonizing ability, putatively high reproductive rates and independence from males in environments subject to density-independent mortality factors (Baker, 1965; Gerritsen, 1980; Ladle et al., 1993). Declines in within-population genetic diversity and/or increases in among-population differentiation towards range margins of sexual populations of plants and animals using nuclear molecular genetic markers were detected (Eckert et al., 2008). Small, marginal or colonizing populations go through periods of inbreeding. Inbreeding has adverse effects primarily on male fertility in many animals, including insects and mammals (Saccheri et al., 2005; Asa et al., 2007; Fitzpatrick and Evans, 2009; Zajitschek et al., 2009; Malo et al., 2010; Okada et al., 2011). Moreover, inbreeding generally increases the sensitivity of a population to stress, thereby increasing the amount of inbreeding depression (Miller, 1994; Pedersen et al., 2011; Bijlsma and Loeschcke, 2012). The joint effect of inbreeding and stress is more pronounced for male than for female reproductive performance (Enders and Nunney, 2010; Pedersen et al., 2011).

If marginal populations of sexual ancestral species are subject to genetic drift and inbreeding relative to central populations (da Cunha et al., 1950), then the hypothesized advantages of sex (variation and recombination) may be reduced or lost, even in the presence of coevolving enemies. Moreover, a theoretical model suggests that natural selection for maintenance of adaptation to habitats that contribute little to the population's reproduction, is weak. This can result in loss of fitness in such marginal habitats and involves accumulation of mutations that are deleterious in the marginal habitat but neutral or nearly so in the main habitat (Kawecki et al., 1997), eroding

the advantage of sexual reproduction in marginal habitats. With a few exceptions, experimental studies on parthenogenetic animals (Gade and Parker, 1997; Robinson et al., 2002; Vorburger et al., 2003; Vrijenhoek and Parker, 2009; Loxdale et al., 2011) and apomictic plants (de Kovel and Jong, 1999) do not support the GPG hypothesis. In addition to *Darwinula stevensoni* (see above), the invasive allopolyploid apomictic grass weed, *Pennisetum setaceum* Forsk. Chiov. (fountain grass) may represent a GPG. Numerous molecular markers and extreme low quantitative trait variance in this grass weed indicate complete monoclonality. A single global genotype and widespread invasiveness under numerous environmental conditions even suggests a super-genotype. The super-genotype likely evolved high levels of plasticity in response to fluctuating environmental conditions during the Early to Mid Holocene (Le Roux et al., 2007).

Alternatively, the FNV model (Vrijenhoek, 1979; 1984) postulates that clonal spin-offs from sexual populations will “freeze” the ecological niche of these sexual populations (e.g. with regard to tolerances related to temperature, salinity, oxygen, etc.). Because most sexual populations are adapted to current environmental conditions, their asexual spin-offs will generally inherit these limited tolerance ranges. However, since a species with mixed reproduction can have a large number of different clones spinning off from sexual ancestors [amongst other origins of asexual lineages; see for ostracod examples Schön et al. (2000) and Rossi et al. (1998)], the total ecological tolerance of a set of clones might still cover a wide range of environmental conditions. The phytophagous mite *Brevipalpus phoenicis* (Geijskes) is a species that is found in a wide range of environments. In a cross-transplantation experiment of mites from three populations from three different host plant species (citrus, hibiscus and acerola), fitness was seriously reduced when mites were transplanted to the alternative host plant species, except when the alternative host was acerola. Thus, *B. phoenicis* clones are specialized to different niches and thus the FNV best described the broad ecological niche of this species but that there was also some evidence for host plant generalization (Groot et al., 2005).

Various gynogenetic fish species are thought to be FNV model species. In gynogenetic systems, unreduced eggs are produced by an all-female species. However, gynogens require sperm of closely related sexual species to trigger embryogenesis, but normally the sperm does not contribute any genetic material to the offspring (Dawley, 1989; Vrijenhoek,

1994; Schlupp, 2005). Occasional leakage of genes from a paternal host into sperm-dependent clones may however provide a source of adaptive variation to circumvent the disadvantages of asexuality (Lamatsch and Stöck, 2009; Lampert and Schartl, 2010). Expression of paternal genes may provide a local adaptive advantage in physiological or phenotypic sexual mimicry traits (Beukeboom and Vrijenhoek, 1998). It has also been argued that paternal leakage leading to the expression of paternal genes plays a pivotal role to stop Muller’s ratchet (Schartl et al., 1995a; Schlupp, 2005; Loewe and Lamatsch, 2008). A number of recent studies have shown that parthenogens can have cryptic sex (e.g., D’Souza et al., 2006; Omilian et al., 2006; D’Souza and Michiels, 2009) and suggest that rare sexual processes may be more common than previously thought (Beukeboom, 2007; Lampert and Schartl, 2010).

Due to their sperm dependence, gynogens have to coexist with a closely related sexual species that is likely to be similar ecologically (Beukeboom and Vrijenhoek, 1998; Niemeitz et al., 2002; Choleva et al., 2008). Due to this exploitation of the host, gynogenesis has also been called “sperm parasitism” (Hubbs, 1964). Unless the unisexual form is constrained by a unique carrying capacity or by mating behaviors that limit its reproductive potential, the all-female form should eliminate its sexual host and thereby ensure its own demise (Clanton, 1934; Moore, 1976; Kawecki, 1988; Heubel et al., 2009). Coexistence would be greatly facilitated by resource partitioning that diminishes direct competition between the sexual parasite and its host (Stenseth et al., 1985; Schley et al., 2004) or may be stabilized by parasites (Hakoyama et al., 2001; Hakoyama and Iwasa, 2004). Therefore, it is not surprising that essentially all of the sperm-dependant parthenogens exhibit some degree of niche separation from their sexual hosts. It has been documented that asexual lineages may rarely use sperm from a non-parental species or even switch a host. This pattern most probably results from the expansion of gynogenetic lineages into new areas. Such expansion was independent of the original parental species, suggesting that sperm-dependence is not as restrictive to geographical expansion as previously thought (Choleva et al., 2008).

Sexual and asexual forms of *Poeciliopsis* live in the desert streams of Sonora, Mexico, and are exposed to environmental extremes, ranging from flash floods to hot, desiccating, residual pools. *Poecilia formosa* presumably originated through a single natural hybridization event (between *P. latipinna* and *P. mexicana*) about 120,000 generations ago (Schartl et

al., 1995b; Lampert et al., 2005; Lampert and Scharfl, 2008; Stöck et al., 2010). Asexual and sexual topminnows of the genus *Poeciliopsis* have roughly similar fecundity when in mixed populations, but in monocultures the sexual *Poeciliopsis monacha* has a higher fecundity (Weeks, 1995; Schlupp et al., 2010). The reproductive output of both sexuals and asexuals was strongly affected by density and was higher in lower densities. These findings are in agreement with studies by Hubbs (1964) comparing the offspring numbers of *P. formosa* and *P. latipinna* in dissections and Balsano et al. (1985) comparing the reproductive output of females of *P. mexicana* and *P. formosa*. Neonate survival has been found to be lower in Amazon molly, *P. formosa*, than in Sailfin molly under food stress (Tobler and Schlupp, 2010). Under benign conditions no differences were found (Hubbs and Schlupp, 2008). Two coexisting clones of the triploid gynogenetic fish *P. 2 monacha-lucida* differed dramatically with respect to survival during stress and swimming endurance in an artificial flume: clone MML/II had the best survival during heat and cold stress and the worst survival during hypoxic stress, whereas clone MML/I had the best survival during hypoxic stress and the worst during heat stress. *Poeciliopsis monacha*, the sexual species with which these clones coexist, had intermediate survival during heat and hypoxic stress and very poor swimming endurance in the flume (Vrijenhoek and Pfeiler, 1997). The physiological differences were considered consistent with the FNV model and provide some insights into environmental factors that affect the distribution and abundance of these fishes.

That gynogens are not resource-limited in their habitat is suggested by their lower food stress resistance compared to the sexual mollies that appear to live at their habitat carrying capacity. Considering their distinct niches, not surprisingly, food competition plays a minor role in mediating coexistence between closely related asexual and sexual mollies (Scharnweber et al., 2011). There is evidence for male discrimination ability in this unisexual–bisexual species complex (Schlupp, 2005). Males do discriminate at several levels: they have mating preferences for conspecific females (Ryan et al., 1996; Gabor and Ryan, 2001; Schlupp and Plath, 2005), produce more sperm in the presence of such females (Aspbury and Gabor, 2004), and transfer less sperm in matings with heterospecific females (Schlupp and Plath, 2005; Riesch et al., 2008). It has been shown that is primarily subordinate males that mate with unisexuals (Mckay, 1971) that risk being driven away by dominant males and have less time to identify the female as conspecific (Kawecki, 1988). In asexuals, selection among clones

operates to overcome the mating preference for conspecifics in the sexual species by more aggressive mating behavior or by the evolution of sex-mimicry (Beukeboom and Vrijenhoek, 1998). Altogether, the gynogens appear to be sperm-limited (Mckay, 1971; Moore and Mckay, 1971; Moore, 1976; Moore, 1984; Schlupp and Plath, 2005; Riesch et al., 2008; Mee and Otto, 2010; Schlupp, 2010) so that they cannot fully exploit their habitats' resources. Evidence suggests that in these stressful environments males from sexual species live at the edge of their reproductive capacity exhibiting reduced sexual activity (Plath, 2008).

The *Phoxinus eos*/*Phoxinus neogaeus*/hybrid gynogen complex of cyprinid fishes is widely distributed in north-eastern America and occupies very heterogeneous habitats (Angers and Schlosser, 2007). It originated by multiple hybridizations between males of the northern redbelly dace (*P. eos*) and females of the finescal dace (*P. neogaeus*) (Dawley et al., 1987; Goddard et al., 1998; Angers and Schlosser, 2007). Although these diploid hybrids reproduce by sperm-dependent parthenogenesis (Goddard et al., 1998), the exclusion mechanism, which normally clears the egg from the sperm, often fails in this hybrid complex, leading to an unusually high level of sperm incorporation. As a consequence, five different hybrid biotypes are found in the complex (Goddard and Dawley, 1990; Lamatsch and Stöck, 2009). Intriguingly, there was an extreme lack of clonal diversity in these gynogens across a range of habitat types (Elder and Schlosser, 1995). Despite its genetic uniformity, however, the *P. eos*-*neogaeus* clone is no less variable than its sexual progenitors, suggesting that this single genotype may actually respond to environmental variation with as much phenotypic variation as a genetically variable sexual population (Doeringsfeld et al., 2004). Data from a large number of additional sites indicated that the proportion of polyploid hybrids within an environment was negatively related to hybrid relative frequency. The incorporation and expression of a third genome in triploid and diploid-triploid mosaic biotypes derived from the gynogenetic clone significantly expanded phenotypic variation of the clone (Doeringsfeld et al., 2004).

Phoxinus eos was more abundant in active beaver ponds, while *Phoxinus eos*-*neogaeus* gynogens were at higher frequencies in shallow, collapsed pond and stream environments (Elder and Schlosser, 1995; Schlosser et al., 1998). The increased frequencies of gynogens in pelagic and benthic zones, along with their greater survival times under oxygen stress, indicate that the gynogenetic clone is more general in

its use of marginally suitable habitats and is physiologically more tolerant to anoxic conditions than its sexual progenitors. Oxygen availability, has been shown to alter species composition of fish communities in northern temperate environments (Tonn and Magnuson, 1982) and oxygen level is spatially and temporally quite variable among habitat types within these drainages. In the majority of ponds sampled, parasite loads were higher on asexual than on sexual *Phoxinus* fishes (Mee and Rowe, 2006).

Other types of non mutually-exclusive hypotheses have been proposed to explain geographical parthenogenesis (Hörandl, 2006; Jose and Dufresne, 2010). Asexuals can establish populations from a single individual and hence can colonize remote and disturbed areas more rapidly than sexuals [reproductive assurance hypothesis, (Baker, 1955; Cuellar, 1994)]. They do not suffer from genetic bottlenecks at low population densities and hence may outcompete sexuals at the edge of a geographical range (Peck et al., 1998; Parker and Niklasson, 2000; Haag and Ebert, 2004; Ben-Ami and Heller, 2007; Golovatch and Kime, 2009; Guzmán et al., 2012). Under an ecological scenario, asexuals are better competitors or have fitness advantages over sexuals under certain ecological conditions (Glesener and Tilman, 1978), owing largely to their frequent hybrid origins. Historical explanations refer to the association between parthenogenesis and environments that were strongly affected by the Pleistocene glacial cycles (Stebbins, 1984; Kearney, 2005). The repeated advances and retreats of glaciers have resulted in the creation of refugial races which were free to colonize new environments as glaciers retreated. Due to their better colonizing abilities, asexuals may have been able to follow glacial retreats faster than sexuals, hence the pattern of geographical parthenogenesis.

Many studies argue that plasticity enhances ecological niche breadth because plastic responses allow organisms to express advantageous phenotypes in a broader range of environments (Bradshaw, 1965; Van Valen, 1965; Whitlock, 1996; Sultan et al., 1998a; b; Donohue et al., 2001; Sultan, 2001; Richards et al., 2005; 2006). In invasion biology there are two primary scenarios which describe how a different reaction norm might contribute to invasion success: (i) a jack-of-all-trades situation, where through the plasticity of morphological or physiological traits, the invader is better able to maintain fitness in a variety of environments, a characteristic clearly related to the concepts of a general purpose genotype (Baker, 1965); (ii) a master-of-some situation, in which the plasticity of morphological or physiological traits allows

the invader to take advantage of favorable environments; in addition, an invader might be (iii) a jack-and-master that combines some level of both of these abilities (Richards et al., 2006; Scheiner and Holt, 2012). Theories of the evolution of niche breadth have traditionally depended on the assumption that a "jack-of-all-trades is a master of none" (Levins, 1968; MacArthur, 1972a; Futuyma and Moreno, 1988; Rausher, 1988; Fry, 2003; Richards et al., 2006; Palaima, 2007). According to this view, no genotype can have maximal fitness in each of a set of environments (e.g., habitats or hosts), so that a population's improvement in fitness in one environment comes at the expense of its fitness in others. Evolution of generalization necessarily entails a cost in terms of fitness loss elsewhere along an environmental gradient that leads to a genetic fitness trade-off between a generalist and a specialist (Palaima, 2007). However, empirical evidence that generalists perform less well than specialists on shared resources is scarce (Strickler, 1979; Dykhuizen and Davies, 1980; Bernays, 2001; Straub et al., 2011) and the issue has remained contentious (Huey and Hertz, 1984; Bernays and Graham, 1988; Futuyma and Moreno, 1988; Berenbaum, 1996; Fry, 1996; Palaima and Spitze, 2004).

Computer simulations support the idea that a single basic process may account for much of what is known about geographic parthenogenesis (Peck et al., 1998). Chapter 14.1 presents comprehensive evidence that, compared to female reproduction, male reproduction is more sensitive to environmental disruption. This single factor fits perfectly well with the ecological and experimental data of geographic parthenogenesis. Importantly, the geographic pattern due to various stress factors is superimposed by other factors that determine the sex-asex distribution like resource availability in relation to reproductive resource investment, other strategies that increase phenotypic plasticity like polyploidy, and lability of asex/sex expression e.g. in modular organisms (see chapter 15.2). In mammals and birds, embryonic development at the time of sex determination occurs under controlled temperature conditions. However, fish are poikilothermic, and embryonic development proceeds in full exposure to the external physical environment where relatively large temperature alterations can occur. Sex determination can be influenced by external physical variables such as temperature in most fish families examined. In some cases, the species utilize these influences as a strategy to improve reproductive success, whereas in others, the effects on sex determination may not occur naturally, and may arise from disruptions of normal

sex-determination processes under extreme environmental conditions (Devlin and Nagahama, 2002). In sexual *Poecilia sphenops* from Oaxaca higher temperatures appear to result in a female-biased sex ratio (Barón et al., 2002). Poikilotherm fishes display a male lower-temperature comfort zone. Male guppies prefer a significantly lower temperature (24.5°C) than females (28.2°C) or juveniles (28.1°C). Treatment of juveniles and females with testosterone lowers their preferred temperature to that of males (Johansen and Cross, 1980). This gender-differential temperature preference, at least during the reproductive period, has been observed in other fish species as well (Hagen, 1964; Baker et al., 1970; Swain and Morgan, 2001; Hernández-Rodríguez et al., 2002; Podrabsky et al., 2008). In rainbow trout, the maximal heat shock response of male germ cells, that are located in the same body compartment like the other organs, occurs at a significantly lower temperature (22°C) than for somatic cells (28°C) (Le Goff and Michel, 1999). Reproduction in fishes is especially sensitive to disturbance by hypoxia (Poon et al., 2001; Wu et al., 2003; Thomaset al., 2006). Asexual *Poeciliopsis* are living in an ecological niche that, due to its environmental stress, is inaccessible to sexual *Poeciliopsis*. Obviously in summer, water temperatures and/or water hypoxia rise that, in the gynogens' niche, may be deleterious to male gametogenesis (Wu et al., 2003; Landry et al., 2007; Thomas et al., 2007; Thomas and Rahman, 2010). Due to the higher oxidative stress exerted during male gametogenesis (resulting in male-driven mutagenesis), hyperthermia and hypoxia impair male fish gametogenesis more than the female one (Thomas et al., 2007; Podrabsky et al., 2008). In comparisons between sexuals and asexuals, males of the millipede *Nemasoma varicorne* (Enghoff, 1976; Hoy Jensen et al., 2002) and the cockroach *Pycnoscelus surinamensis* (Niklasson and Parker, 1994; Parker and Niklasson, 1995; Gade and Parker, 1997) were found to be less tolerant to environmental stressors.

16. Germ granules and transgenerational epigenetic information transfer

Summary

Rather than the continuity of the germ cells, it is the continuity of substances passed down from the parent's germ cells to the germ cells of the

progeny that ensures the heredity of the species, hence the collective term "germ plasm" to represent these substances. Electron microscope techniques led to the description of germ cell-specific structures with granular or fibrous shape, no confining membrane, located in the perinuclear cytoplasm, and usually associated with clusters of mitochondria. Germ granules are thought to be a signature feature of germ cells in animals and the site of non-coding RNA biogenesis that play a key role in epigenetic regulation. What makes epigenetic processes fundamentally different from genetic processes is that in some cases environmentally induced epigenetic changes may be inherited by future generations. Epigenetics is closely linked to environmental conditions and mitochondrial bioenergetics. Thus, the epigenome provides the interface between the environment and the regulation of nuclear DNA gene expression. Conditions of stress seem to be particularly important as inducers of heritable epigenetic variation and lead to changes in germline epigenetic and genetic organization. A multitude of mechanisms may convert reversible epigenetic changes into stable epigenetic and genetic transgenerational effects. Cumulative evidence suggests that cytoplasmic ribonucleoproteins that are stabilized in germ granules are the carriers of transgenerational information. The following scenario is proposed: (i) in a close cross-talk with germline cells, somatic gonadal cells determine the ncRNA profile in the germline cells; (ii) after intercellular transfer secondary piRNA biogenesis (ping-pong) amplifies the message in the germline. (iii) the ncRNA message is stored in the germ granules until the information is retrieved for embryonal development (preformation); (iv) in species with extended parent-embryo/fetus developmental support (e.g. in mammals) reprogramming by transgenerational message transfer is not confined to gametogenesis (preformation) but occurs also during embryonal development (epigenesis).

16.1 Germ granules are germ cell markers

Rather than the continuity of the germ cells, it is the continuity of substances passed down from the parent's germ cells to the germ cells of the progeny that ensures the heredity of the species, hence the collective term "germ plasm" to represent these substances (Weismann, 1892; Gao and Arkov, 2012). The first evidence supporting a germ plasm model came from the successful tracing of granules from the

posterior pole cytoplasm of insect oocytes in one generation to the germ cells of the next generation, with the substances referred to as “germ cell determinants” (Hegner, 1914). Also, the term “chromatoid body” was introduced by early investigators to describe a germ cell organelle in mammalian spermatocytes and spermatids, based on the fact that this exhibits structure similar to chromosomes and nucleoli when examined under a light microscope (Benda, 1891; Hermann, 1889; Yokota, 2008). Today, germ plasm can be recognized by various distinctive features (Eddy, 1975), including electron-dense granules composed of ribonucleoprotein complexes, variable association with dense concentrations of mitochondria and nuclear pores and all or part of a conserved set of mRNAs and proteins (notably Piwi, Nanos, Vasa, PL10, Pumilio, Boule/Dazl and Bruno) involved in transposon silencing and mRNA regulation (Ewen-Campen et al., 2010; Juliano et al., 2010; Voronina et al., 2011). The employment of electron microscope techniques from the 1950s to 1970s led to a more detailed morphological description of the germ cell-specific structures: high electron density, granular or fibrous in shape, no confining membrane, frequently surrounded by small vesicles, usually associated with clusters of mitochondria, and located in the perinuclear cytoplasm (Mahowald, 1962; Brokelmann, 1963; Fawcett et al., 1970; al-Mukhtar and Webb, 1971; Eddy, 1974; Russell and Frank, 1978; Gao and Arkov, 2012). Germ cells in more than 80 animals from at least eight phyla contain this characteristic morphological feature variously called germ plasm or germinal plasm, germ granules, sponge bodies, dense bodies, chromatoid bodies, Balbiani bodies, mitochondrial clouds, polar plasm, pole plasm, oosome, nuage. The dynamics of organelle movement during the assembly of these aggregates also shows striking similarity between different animals (Heasman et al., 1984; Holland and Holland, 1992; Carré et al., 2002; Kloc et al., 2004a). Close association of the germ granules with nuclear pores has been reported in ultrastructural studies of *C. elegans* (Strome and Wood, 1982; Pitt et al., 2000; Sheth et al., 2010), *Xenopus* (Czolowska, 1969), zebrafish (Knaut et al., 2000; Kloc et al., 2004a), and mouse (Chuma et al., 2009). Thus, germ granules are optimally positioned for cytoplasmic-nuclear information transfer. Germ granules are thought to be a signature feature of germ cells in animals (Mahowald, 1968; al-Mukhtar and Webb, 1971; Eddy, 1974; 1975; Wilsch-Brauninger et al., 1997; Houston and King, 2000; Extavour and Akam, 2003; Kloc et al., 2004a; Snee and Macdonald, 2004; Updike and Strome, 2010). Germ granules are found in germ cells in many

stages of development, ranging from primordial germ cells (PGCs) in embryos to gametes in adult gonads. In many animals nuage has been shown to contain a combination of RNAs, proteins, endoplasmic reticulum and mitochondria, and may sometimes contain other organelles (such as microtubules) as well. There are two key routes to the embryonal initiation of the germ cell lineage (Extavour and Akam, 2003; Seydoux and Braun, 2006; Extavour, 2007; Rosner et al., 2009). One is through the inheritance of preformed germ cell determinants or germ plasm as observed in *Drosophila melanogaster*, *Caenorhabditis elegans* and *Xenopus* (Eddy, 1975; Saffman and Lasko, 1999; Wylie, 1999). The other route occurs in mammals, where a group of pluripotent cells are first established with seemingly equivalent potential from which both germ cells and somatic cells are derived (McLaren, 1999; 2000; Saitou et al., 2002; Surani et al., 2004; 2008; Saitou, 2009). These two modes of germ cell specification are referred to as preformation and epigenesis, respectively (Extavour and Akam, 2003). The two mechanisms are not necessarily mutually exclusive, but rather are better viewed as two extremes of the continuum along which development of germ cells can be mapped, since at some stage of germ cell development, both types of mechanism are inevitably used (Extavour, 2007).

16.2 Transgenerational epigenetic information transfer

Accumulating evidence indicates that both genetic and non-genetic inheritance, and the interactions between them, have important effects on evolutionary outcomes. There is increasing awareness that epigenetic information can also be inherited across generations (Grishok et al., 2000; Richards, 2006; Jirtle and Skinner, 2007; Alcazar et al., 2008; Youngson and Whitelaw, 2008; Cairns, 2009; Hammoud et al., 2009; Nadeau, 2009; Slatkin, 2009; Cuzin and Rassoulzadegan, 2010; Daxinger and Whitelaw, 2010; 2012; de Boer et al., 2010; Nelson and Nadeau, 2010; Burton et al., 2011; Danchin et al., 2011a; Day and Bonduriansky, 2011; Guerrero-Bosagna and Skinner, 2012; Nelson et al., 2012; Lim and Brunet, 2013).

What makes epigenetic processes fundamentally different from genetic processes is that in some cases environmentally induced epigenetic changes may be inherited by future generations (Richards, 2006; Whitelaw and Whitelaw, 2006; Jirtle and Skinner, 2007). For instance, Fieldes and Amyot (1999) experimentally altered DNA methylation in flax and showed that this significantly affected the phenotypes of at least four generations of progeny. In mice,

environmental toxins (Anway et al., 2005; Crews et al., 2007) and dietary supplements (Cropley et al., 2006) induce changes in DNA methylation that are inherited over several generations (Bossdorf et al., 2008). In *Drosophila*, experimental reduction of the heat shock protein Hsp90 (which also occurs in response to environmental stress) (Jarosz and Lindquist, 2010; Jarosz et al., 2010) causes stable phenotypic changes which appear to be due to the release of hidden epigenetic variation (Sollars et al., 2003). Moreover, Hsp90 can regulate the length of trinucleotide repeats to fine-tune gene function and can regulate the mobility of transposable elements to enable larger functional changes (Fonville et al., 2011). Non-genetic inherited information can arise through several interacting mechanisms, including epigenetics, parental effects and ecological and cultural inheritance (Hercus and Hoffmann, 2000; West-Eberhard, 2003; Jablonka and Lamb, 2005; Bonduriansky and Day, 2009; Helanterä and Uller, 2010).

An extrinsic transgenerational phenotype requires a continued multigenerational exposure to the factor (often at only a specific period of development) triggering an epigenetic change. For example, good maternal behavior towards offspring (e.g., early postnatal pup licking in rodents) can program the same good maternal behavior in the grown-up female adults that then pass this on to their offspring in a similar manner (Champagne, 2008; McGowan et al., 2008; Szyf et al., 2008). Rats that are nurtured by stressed mothers are more likely to be stressed (Francis and Meaney, 1999). This phenotype involves the setting of a 'stressed' state by the hypothalamic–pituitary–adrenal axis (HPA axis) in the pup (Weaver et al., 2004). However, without the continued generational maternal behavior and epigenetic programming of the brain and behavior in the female offspring, the transgenerational phenotype would be lost (McGowan et al., 2008; Szyf et al., 2008). The exposure also has the potential to promote intrinsic transgenerational phenomena, which will promote a transgenerational phenotype independent of continued environmental exposures (Anway et al., 2005; Skinner and Guerrero-Bosagna, 2009). Exposures of mother rats to particular endocrine disruptors can induce epigenetic changes in the male germline that are associated with changes in male fertility and reproductive behavior up to four generations later (Anway and Skinner, 2006; 2008). Several studies in mammals support the hypothesis that transgenerationally inherited epigenetic alterations affect the health and longevity of future generations (Morgan et al., 1999; Lane et al., 2003; Rakyen et al., 2003; Pembrey et al., 2006; Chandler, 2007;

Youngson and Whitelaw, 2008; Franklin and Mansuy, 2010; Bonduriansky et al., 2012). Transgenerational epigenetic inheritance has also been demonstrated in other eukaryotic organisms, for example, plants, yeast, nematodes, rotifers, insects and fishes (Grewal and Klar, 1996; Hercus and Hoffmann, 2000; Chandler and Stam, 2004; Bashey, 2006; Chandler, 2007; Galloway and Etterson, 2007; Youngson and Whitelaw, 2008; Burns and Mery, 2010; Burton et al., 2011; Kaneko et al., 2011; Bonduriansky et al., 2012).

Epigenetics is closely linked to environmental conditions and mitochondrial bioenergetics (Naviaux, 2008; Smiraglia et al., 2008; Wallace and Fan, 2010; Minocherhomji et al., 2012; see chapter 10.3). The epigenome provides the interface between the environment and the regulation of nuclear DNA gene expression (Feinberg, 2007; 2008). Adverse environmental conditions play a key role in transgenerational inheritance. Conditions of stress seem to be particularly important as inducers of heritable epigenetic variation, and lead to changes in epigenetic and genetic organization that are targeted to germline specific genomic sequences (Badyaev, 2005a; Jablonka and Lamb, 2005; Jirtle and Skinner, 2007; Rando and Verstrepen, 2007; Jablonka and Raz, 2009; Boyko et al., 2010; Curley and Mashoodh, 2010; Franklin and Mansuy, 2010; Nätt, 2011; Seong et al., 2011). Stress-induced changes of DNA methylation are common and are mostly heritable (Chinnusamy and Zhu, 2009; Verhoeven et al., 2010a; Richards, 2011; Verhoeven and van Gurp, 2012). In *B. subtilis*, the physiological state of the cell's ancestor (more than two generations removed) does affect the outcome of cellular differentiation and bacterial aging by epigenetic inheritance (Veening et al., 2008b). In plants and aquatic invertebrates, intra- and interspecific competitive interactions and stressors leave their transgenerational signature on life history traits (Galloway and Etterson, 2007; Allen RM et al., 2008; Boyko et al., 2010). Intriguingly, the longevity-extending effect of dietary restriction is transgenerationally inherited by rotifer offspring (Kaneko et al., 2011). In placental animals, maternal conditions such as nutritional stress affect growth rate, immune capacity, survival and breeding performance of offspring (Festa-Bianchet and Jorgenson, 1998; Lummaa and Clutton-Brock, 2002; Lummaa, 2003; Jones OR et al., 2005). A mother's diet during pregnancy may have an enduring influence on succeeding generations, independent of later changes in diet (Waterland and Jirtle, 2003; Lillycrop et al., 2005; Cropley et al., 2006; Langley-Evans, 2009; Chmurzynska, 2010). The inducibility and transmissibility of epigenetic variants depend on

developmental conditions.

Germline and fetal programming of obesity, cardiovascular disease and insulin resistance has been investigated in a wide range of epidemiological and animal studies; these investigations elucidated transgenerational adaptations that effect epigenetic modification of genes involved in a number of key regulatory pathways with long-term sequelae for morbidity and mortality (Armitage et al., 2005; Gluckman et al., 2007; Symonds et al., 2009; Burns and Mery, 2010; Carone et al., 2010; Chmurzynska, 2010; Alfaradhi and Ozanne, 2011; Ferguson-Smith and Patti, 2011; Nätt, 2011; Ozanne et al., 2011; Rakyan et al., 2011; Skilton et al., 2011; Guilmatre and Sharp, 2012; Herring et al., 2012). Female rats that were exposed to a high-carbohydrate diet as neonates spontaneously transmitted the obesity phenotype to their offspring, thus establishing a vicious transgenerational effect (Srinivasan et al., 2003; Patel et al., 2009; Patel and Srinivasan, 2011). Similarly, F1 sons of female mice that are 50% dietary restricted during late gestation but fed ad libitum throughout their own life develop metabolic syndrome and their own F2 offspring also exhibit impaired glucose tolerance (Jimenez-Chillaron et al., 2009). In another study, when the fertilized eggs of adult females born to dietary restricted dams were embryo-transferred to control dams, the inheritance of metabolic syndrome was still observed suggesting that this transmission may occur via alterations in the germline of both parents (Thamotharan et al., 2007). In humans, a link between grandparental and parental periods of low or high food availability and offspring mortality and morbidity was found (Bygren et al., 2001; Kaati et al., 2002; 2007; Pembrey et al., 2006). Thus, evidence suggests that the quality of diet and the caloric regimen can influence the epigenetic state of the genome and its transgenerational modulation. Certain metabolic pathways are also epigenetically controlled revealing a tight crosstalk between metabolism and epigenomes. Particularly, methylation-based epigenetic reactions are controlled by different metabolic pathways and reciprocally can influence metabolism (Chiacchiera et al., 2013). Oxidative stress as the final common effector of stress signaling pathways (Lindquist, 1986; Sanchez et al., 1992; Finkel and Holbrook, 2000; Heining, 2001; Mittler, 2002; Mikkelsen and Wardman, 2003; Sørensen et al., 2003; Apel and Hirt, 2004; Ardanaz and Pagano, 2006; Rollo, 2007; Miller et al., 2008; Slos and Stoks, 2008; Jaspers and Kangasjärvi, 2010; Steinberg, 2012; Choudhury et al., 2013) appears to mediate the epigenetic reprogramming (Franco Mdo et al., 2002; Luo ZC et al., 2006; Cyr and Domann, 2011). This

makes perfect evolutionary sense since stress understood as ecological condition that erodes Darwinian fitness calls for (epi)genetic innovation. Intriguingly, stress exposure in intrauterine life (Entringer et al., 2010; 2011) and during early childhood (Drury et al., 2011) is associated with shorter leukocyte telomere lengths in young adulthood which is a predictor for earlier onset of age-related disease and mortality (Blackburn, 2000; Epel et al., 2004; Serrano and Andrés, 2004; Epel, 2009; Mather et al., 2011).

For intrauterine exposure, maternal-derived, embryonal stress hormones appear to be the mediators, arguing for a common neuroendocrinological mediation via stress-sensing pathways (Dufty et al., 2002; Drake et al., 2005; Robert and Bronikowski, 2010). In fishes and birds, content of stress hormones in egg yolk and albumen has adverse effects on offspring development and longevity (Eriksen et al., 2003; 2007; Hayward and Wingfield, 2004; Love et al., 2005; Rubolini et al., 2005; Saino et al., 2005; Love and Williams, 2008; Gagliano and McCormick, 2009; McCormick and Gagliano, 2009). Importantly, these effects are adaptive under environmental adversity (Meylan and Clobert, 2005; Love and Williams, 2008; Love et al., 2009). A central question in considering evolutionary change in response to environmental change is whether the inherited epigenetic markers could facilitate genomic change (Johnson and Tricker, 2010; Bateson, 2012). There are a multitude of mechanisms that may convert reversible epigenetic changes into stable epigenetic and genetic transgenerational effects (Pembrey, 1996; Young, 2001; Beaudet and Jiang, 2002; Jablonka, 2004; Cullis, 2005; Gallou-Kabani and Junien, 2005; Mittelman and Wilson, 2010). The epigenetic, selectable variation might enable a lineage to adapt and "hold" the adaptation until genetic changes take over; thus, the heritable epigenetic variations in protein architecture pave the way for genetic adaptation (True et al., 2004; Sangster et al., 2004; Jablonka and Raz, 2009). Thus, demographic responses can, over time, evolve into new, genetically mediated traits (Reznick et al., 1990; Kokko and López-Sepulcre, 2007; Jones et al., 2008; Mittelman and Wilson, 2010).

16.3 Are germ granules the vehicles of transgenerational epigenetic information transfer?

Unicellular organisms are directly exposed to the vicissitudes of the environment. This direct exposure elicits the stress responses that result in changes to their genetic make-up in a bet-hedging response. Multicellular organisms have evolved an internal milieu that is increasingly stable, protected from the

environment by outer barriers. This improved barrier, however, has the disadvantage that the germline cells are increasingly shielded from the environment. Germline cells are not equipped to sense the outside environment and are dependent on messages from the neuroendocrine system about changes in their future biosphere. The gonads are integrated into a complex neuroendocrine network that can relay signals. We are only beginning to understand how these signals are transmitted to the germline cells and what (if any) (epi)genetic changes they may induce. Assuming that there is a transgenerational information transfer about environmental conditions, the question is which signals carry this information, how this information is transferred and what type of information can be transferred to the gametes and the embryo. Obviously, most relevant for the future struggle for survival is information about environmental resource availability and stressors. Importantly, throughout their development germline cells are in intimate contact with cells of the somatic gonads. For instance, germ cells in mammals develop in a microenvironment of supporting stromal cells of somatic origin that interact with the former through autocrine/paracrine mechanisms as well as direct cell-to-cell interactions (Matzuk et al., 2002). Deprived of this support, isolated germ cells in culture fail to survive and maintain their characteristics. Signals from these somatic gonad cells are vital for germ cell maturation. However, to act transgenerationally, this information must persist as molecular signals even after the physical contact between gamete/zygote and somatic gonads has been interrupted.

The search for molecules that determine germ cell fate began when Illmensee and Mahowald (1974) showed that cytoplasm taken from the posterior of a *Drosophila* embryo (germ or pole plasm) was sufficient to induce ectopic germ cells, when injected into a host embryo. A major function of the large numbers of noncoding RNAs is to direct chromatin-modifying complexes to their sites of action (Mattick et al., 2009; Koziol and Rinn, 2010). Following the definitions introduced by Youngson and Whitelaw (2008), this may well be called an example of transgenerational epigenetic inheritance. The last decades have revealed that epigenetic processes operate in the transgenerational nongenetic determination of phenotype. This has been termed soft inheritance (Mayr, 1982), non-Mendelian inheritance, parental effects, and fetal programming, among others.

RNA interference (RNAi) is an evolutionarily conserved system mediated by, and targeted against, RNA. The RNAi pathway is triggered by long

double-stranded (ds)RNA that is cleaved by an endonuclease named Dicer to produce short interfering (si)RNAs. A relatively complex RNAi machinery was already present in the last common ancestor of eukaryotes and consisted, at a minimum, of one Argonaute-like polypeptide, one Piwi-like protein, one Dicer, and one RNA-dependent RNA polymerase (Cerutti and Casas-Mollano, 2006). From a mechanistic standpoint, the ancestral RNAi machinery may have been capable of both siRNA-guided transcript degradation as well as siRNA-guided transcriptional repression of homologous sequences (Cerutti and Casas-Mollano, 2006). An intact Dicer/Argonaute RNA processing machinery both in somatic and germline gonadal cells is essential for gametogenesis and fertility (Deng and Lin, 2002; Kuramochi-Miyagawa et al., 2004; Murchison et al., 2007; Tang et al., 2007; Hayashi et al., 2008; Hong et al., 2008; Kalidas et al., 2008; Maatouk et al., 2008; Nagaraja et al., 2008; Otsuka et al., 2008; Gonzalez and Behringer, 2009; Ma et al., 2009; Papaioannou et al., 2009; 2011; Kim GJ et al., 2010; Lei et al., 2010; Korhonen et al., 2011; Romero et al., 2011; Liu D et al., 2012; Wu et al., 2012; Ortogero et al., 2013). In this context it is alarming that a multitude of environmental mutagens form stable complexes with Dicer, that are more stable than those formed by Dicer with its natural substrate, i.e. double strand short RNAs (Ligorio et al., 2011). This may be a critical factor in the human spermatozoon, already a cell in crisis operating near its threshold of error catastrophe, and a possible additional factor in a multifactorial process resulting in deteriorating human semen quality (see chapter 14.1).

It was demonstrated first in plants (Jones et al., 1999; Mette et al., 2000) and then in human cells (Kawasaki and Taira, 2004; Morris et al., 2004), that siRNAs can direct methylation of homologous DNA. When this DNA methylation affects a promoter sequence, it can lead to transcriptional silencing of the downstream gene. In plants and animals, gene silencing by RNA-directed DNA methylation (Aufsatz et al., 2002; Kanno et al., 2004; Kawasaki and Taira, 2004; Mathieu and Bender, 2004; Matzke et al., 2004; Morris et al., 2004; Matzke and Birchler, 2005; Cerutti and Casas-Mollano, 2006; Huettel et al., 2007; Aravin et al., 2008; Aravin and Bourc'his, 2008; Morris, 2008; Zhai et al., 2008; Law and Jacobsen, 2010; Bender, 2012; Lorkovic et al., 2012; Castel and Martienssen, 2013; Dalakouras and Wassenegger, 2013; Sabin et al., 2013) and histone modification (Volpe et al., 2002; Schramke and Allshire, 2003; Noma et al., 2004; Pal-Bhadra et al., 2004; Cerutti and Casas-Mollano, 2006; Weinberg et al., 2006; Gu et al., 2012; Huang et

al., 2013; Sabin et al., 2013) has now been widely demonstrated. Importantly, DNA methylation (Rakyan et al., 2002; Waterland and Jirtle, 2003; Blewitt et al., 2006; Peaston and Whitelaw, 2006; Ekram et al., 2012) and histone modifications (Dolinoy et al., 2010) within metastable epialleles has a stochastic element due to probabilistic reprogramming of epigenetic marks during gametogenesis and embryogenesis. For instance, stress-induced methylation changes may be targeted specifically to stress-related genes. Alternatively, methylation changes may generate nonspecific (random) differences between individuals, which may have adaptive significance during times of stress (Rapp and Wendel, 2005), because they increase the range of variation that natural selection can act upon. Part of the variation may be due to off-target effects since siRNAs may cross-react with targets of limited sequence similarity (Jackson et al., 2003; Scacheri et al., 2004; Lin et al., 2005; Birmingham et al., 2006; Ma et al., 2006; Alemán et al., 2007) with possible adverse effects on cell viability (Fedorov et al., 2006).

Flies have five Argonaute proteins — molecular 'scissors' that use the small RNA guide to bind to and cut a second RNA molecule, the 'target': Ago1, which uses microRNAs to regulate gene expression; Ago2, which uses siRNAs to fight viral infection; and three closely related Piwi proteins — Piwi, Aubergine and Argonaute3 (Ago3) — which use piRNAs to safeguard the animal germline genome against deleterious retroelements (Lau et al., 2006; Saito et al., 2006; Vagin et al., 2006; Aravin et al., 2007a; Brennecke et al., 2007; Gunawardane et al., 2007; Houwing et al., 2007; Li C et al., 2009; Malone et al., 2009). These data have led to the hypothesis that Piwi/piRNA complexes might serve as sequence-specific guides that direct the de novo DNA methylation machinery to transposable elements (Aravin et al., 2007a; 2008; Kuramochi-Miyagawa et al., 2008; Zamudio and Bourc'his, 2010). In the *Drosophila* female germline, two distinct groups of piRNAs are involved in repressing the retroelements in different cell types: one in germline cells and the other in the ovarian somatic cells (Lau et al., 2009; Li C et al., 2009; Malone et al., 2009; Khurana and Theurkauf, 2010; Olivieri et al., 2010). Many transposons are expressed in germ cells, where movement can lead to heritable expansions in their number. Examples in *Drosophila* include TAHRE, TART, HetA, copia, and the I element (Vagin et al., 2004; Brennecke et al., 2008; Chambeyron et al., 2008; Shpiz et al., 2007; 2009). Some transposons are exclusively or additionally expressed in somatic cells of the ovary, with gypsy, ZAM, and idfix occupying this category in the

Drosophila ovary (Prud'homme et al., 1995; Desset et al., 2003; 2008; Sarot et al., 2004; Mével-Ninio et al., 2007; Péliisson et al., 2007). In the *D. melanogaster* female germline TE silencing is dependent on the expression of its own copies and the presence of small RNAs in nurse cells surrounding the oocyte (Brennecke et al., 2008; Chambeyron et al., 2008). Many factors involved in the production of piRNAs localize to germ granules, suggesting that they may function as a site for processing of germline piRNAs (Harris and Macdonald, 2001; Vagin et al., 2006; Brennecke et al., 2007; Gunawardane et al., 2007; Lim and Kai, 2007; Pane et al., 2007; Klattenhoff and Theurkauf, 2008; Aravin et al., 2009; Li C et al., 2009; Malone and Hannon, 2009; Patil and Kai, 2010). The piRNA pathway is active in the follicle cells, nurse cells, and the egg cell of the *Drosophila* egg chamber (Lin and Yin, 2008; Li C et al., 2009; Malone et al., 2009). Nurse cells are connected to the growing egg cell by cytoplasmic bridges and, throughout development, the nurse cells deposit their cytoplasmic contents into the egg cell. Active TE transcripts in the nurse and egg cells are processed into piRNAs through the activity of Piwi, Aubergine (Aub), and *Drosophila melanogaster* Argonaute 3 (dmAgo3). Upon fertilization, these TE-derived piRNAs are maternally inherited in the embryo (McCue and Slotkin, 2012).

In mice, two Piwi family members, MILI and MIWI2, also specify de novo DNA methylation of transposon sequences in embryonic germ cells, leading to their transcriptional repression (Aravin et al., 2007b; Carmell et al., 2007; Kuramochi-Miyagawa et al., 2008). In MIWI-null male mice the nucleolar signal from miRNA and piRNA probes in Sertoli cells is largely diminished (Marcon et al., 2008), implicating Sertoli cell-specific miRNA and piRNA biogenesis as essential for spermatogenesis (Papaioannou et al., 2009; 2011; Kim GJ et al., 2010; Wu et al., 2012; Ortogero et al., 2013). Careful analysis of piRNAs that associate with different PIWI proteins has revealed at least two distinguishable classes of piRNAs in mammalian testis which are named by their expression time as pre-pachytene and pachytene piRNAs (Meikar et al., 2013). Pre-pachytene piRNAs are a strikingly uniform subclass of piRNAs that originate from repeat sequences related to transposable elements and heterochromatic regions. They are now the most studied and understood piRNAs, although they represent only a tiny fraction of all mammalian piRNAs. MILI and MIWI2 together with pre-pachytene piRNAs participate in silencing of transposable elements both at epigenetic and posttranscriptional level in fetal and neonatal germ cells (Aravin et al., 2007b; 2008; Carmell et al., 2007;

Kuramochi-Miyagawa et al., 2008). In knock-out mice of either of these proteins the transposons are uncontrollably expressed, causing damage in the genome integrity of the cell, which eventually leads to meiotic arrest and sterility (Kuramochi-Miyagawa et al., 2004; Carmell et al., 2007). Pachytene piRNAs arise in spermatocytes during meiosis, peak in haploid round spermatids and disappear during later steps of spermiogenesis, overlapping the expression of their binding PIWI partners, MILI and MIWI (Meikar et al., 2013). The amount of pachytene piRNAs per each pachytene spermatocyte or round spermatid is remarkable, around a million molecules, but the individual copy number is low, which means that this piRNA population is very heterogeneous consisting of hundreds of thousands of different piRNAs (Aravin et al., 2006; 2007a). Compared to their pre-pachytene counterparts, the biogenesis and function of pachytene piRNAs is unknown. Pachytene piRNAs are devoid of sequences relative to active transposons (Meikar et al., 2013). Instead they map into large sparse clusters, from tens to hundreds of kilobases along the genome with most of the clusters being derived from one of the two genomic strands (Aravin et al., 2007a; b). Interestingly, pachytene piRNAs in round spermatid are concentrated in chromatoid bodies – male germ cell-specific germ granules of remarkable size and peculiar features (Kotaja and Sassone-Corsi, 2007; Meikar et al., 2010; 2011). As the chromatoid body also concentrates MIWI, RNA binding proteins and helicases in addition to longer polyadenylated RNAs (Kotaja et al., 2006; Meikar et al., 2010), it has been speculated that it serves as a processing centre for pachytene piRNAs and mRNAs. Besides the well-known function of transposon silencing, piRNAs function at various levels in regulating germline stem cell differentiation, mitotic chromosome dynamics, and gene expression (Pek et al., 2012b; Mani and Juliano, 2013). Most piRNAs in mouse spermatocytes do not match transposable element sequences. There is very little conservation of individual piRNA sequences between different mammals, but surprisingly there is a significant conservation of the genomic locations of mammalian piRNA clusters (Betel et al., 2007). It is therefore plausible that many piRNAs in the mouse act through entirely different mechanisms or regulate different biological functions altogether (Stefani and Slack, 2008). It has been proposed (Mani and Juliano, 2013) that the PIWI/piRNA pathway controls genome stability in several ways: suppression of transposons, direct regulation of chromatin architecture and regulation of genes that control important biological processes related to genome stability. An intriguing possibility is

that the PIWI/piRNA pathway is using transposon sequences to coordinate the expression of large groups of genes to regulate cellular function (Mani and Juliano, 2013).

RNAs are intercellular signaling molecules (Dinger et al., 2008; Mittelbrunn and Sánchez-Madrid, 2012). When eukaryotic cells encounter double-stranded RNA (dsRNA), genes carrying a matching sequence are silenced through RNAi. RNAs are known to enter cultivated mammalian cells by natural processes, including direct cell-to-cell contact, membrane receptors, and channels (Winston et al., 2002; 2007; Feinberg and Hunter, 2003; Valiunas et al., 2005; Shih and Hunter, 2011; McEwan et al., 2012). mRNA required for *Drosophila* oocyte specification and growth is transcribed in neighboring nurse cells and trafficked through connecting ring canals to the oocyte in the egg chamber (Steinhauer and Kalderon, 2006). Similarly, RNA within chromatid bodies is transferred between germ cells via cytoplasmic bridges during mouse spermatogenesis (Ventela et al., 2003). In plants, mobile sRNAs promote epigenetic modifications in the genome of recipient cells (Molnar et al., 2010). When the recipient cells are seed or pollen, mobile sRNAs induce transgenerational epigenetic changes to enhance adaptation of progeny to future stresses (Slotkin et al., 2009). Soma-to-germline transfer of information mediated by small RNAs and, more generally, systemic RNAi is gaining experimental support in plants (Chitwood and Timmermans 2010) and protozoans (Gao and Liu, 2012; Schoeberl et al., 2012). There is also emerging evidence for trans-generational transfer of epigenetic information in other systems, including Metazoa (Ashe et al., 2012; Gu et al., 2012; Lee et al., 2012; Shirayama et al., 2012).

In *C. elegans*, gene silencing triggered by injected, ingested, or locally expressed dsRNA can move throughout the organism to reduce endogenous gene expression in all non-neuronal cells, including the germline, thus transmitting gene silencing to the next generation (Fire et al., 1998; Tabara et al., 1998; Timmons and Fire, 1998; Winston et al., 2002; Jose and Hunter, 2007; Whangbo and Hunter, 2008; Jose et al., 2011). In fact, the multigenerational inheritance of RNAi-mediated phenotypes delivered to somatic cells in *Caenorhabditis elegans* demonstrated that soma and germline do communicate (Burton et al., 2011). Key components required for systemic RNAi in *C. elegans* are the broadly expressed transmembrane proteins, systemic RNA interference defective protein (SID) (Winston et al., 2002; 2007; Feinberg and Hunter, 2003; Shih and Hunter, 2011; McEwan et al.,

2012). SID homologs are present in a variety of other invertebrates and in all sequenced vertebrate genomes, indicating an ancient origin and likely conserved function (Duxbury et al., 2005; Li H et al., 2006; Wolfrum et al., 2007; Dinger et al., 2008; Tomoyasu et al., 2008; Xu and Han, 2008; Huvenne and Smaghe, 2010; Ren et al., 2011). One exciting finding to emerge from genetic screens of *C. elegans* was the discovery of three genes, RNAi spreading defective (*rsd*), *rsd-2*, *rsd-3*, and *rsd-6*, required for the transfer of dsRNA into germline cells (Tijsterman et al., 2004). The protein encoded by *rsd-3*, which has both mouse and human orthologs (Wasiak et al., 2002), contains an ENTH (epsin NH₂-terminal homology) domain that is commonly found in proteins involved in vesicle trafficking (Legendre-Guillemain et al., 2004). However, *rsd* mutants do not exhibit generalized defects in endocytosis. These observations suggest that RSD-3 may control vesicle trafficking in a pathway that is specific for the import of the silencing signal into the germline (Tijsterman et al., 2004; Jose and Hunter, 2007) providing a means by which environmental factors may lead to heritable changes. Vastenhouw and colleagues (2006) found that feeding *C. elegans* with bacteria expressing double-stranded RNA that targets specific nematode genes led to morphological and physiological variations that were transmitted for at least 10 generations (Vastenhouw et al., 2006; Jablonka and Lamb, 2008a). Clear evidence of transgenerational epigenetic inheritance in mice involving RNA has recently been provided (Rassoulzadegan et al., 2006; Ashe and Whitelaw, 2007; Li and Lu, 2009). Thus RNA may supplement endocrine and paracrine signaling by small molecules and proteins, and act as an efficient and evolutionarily flexible source of sequence-specific information transfer between cells, both locally and systemically and may play a key role in transgenerational epigenetic information transmission (Dinger et al., 2008).

Another factor worth considering is the half-life of a potential transgenerational factor. Most of the components of the RNA silencing pathways, such as siRNAs and miRNAs, have a rapid turnover with half-lives in the range of a couple of hours (Chatterjee and Großhans, 2009; Krol et al., 2010; Rügger and Großhans, 2012). However, an important feature of RNAs in stress granules is that their translation is suppressed and RNA stability is increased (Anderson and Kedersha, 2002a; b; Kedersha and Anderson, 2002; Stöhr et al., 2006; Barckmann and Simonelig, 2013) that should protect transcripts from decay. The RNA-binding protein HuR (also known as ELAV1) binds to the 3'-untranslated region of mRNAs and

regulates transcript stability and translation. Misregulation of HuR, due to expression of a HuR transgene, prevents the production of fully functional gametes in mice, providing evidence for the importance of mRNA stability in gametogenesis (Levadoux-Martin et al., 2003). 2'-O-methylation on the 3' terminal ribose is a major mechanism that increases the stability of small RNAs (Ji and Chen, 2012). The small RNA methyltransferase HUA ENHANCER1 (HEN1) and its homologs methylate microRNAs and small interfering RNAs (siRNAs) in plants, Piwi-interacting RNAs (piRNAs) in animals, and siRNAs in *Drosophila*. piRNAs and *Drosophila* Ago2-associated siRNAs are 2'-O-methylated at their 3' end by HEN1 homologs in the animal kingdom (Horwich et al., 2007; Kirino and Mourelatos, 2007; Saito et al., 2007; Kamminga et al., 2010). HEN1 mutants have a variety of gametogenic defects in various plants and animals (Ji and Chen, 2012). Most animal Hen1 proteins have a similar accumulation pattern as the Piwi proteins (Kirino and Mourelatos, 2007; Saito et al., 2007; Kamminga et al., 2010) and localize to nuage (Kamminga et al., 2010; 2012; Billi et al., 2012; Scott and Norbury, 2013).

As mentioned earlier, the germline can form (i) early in embryogenesis from an inheritance of maternal factors (maternally derived, also referred to as preformation) as used in flies and nematodes, (ii) by cell-cell interactions early in embryogenesis (inductive, also referred to as epigenetic) as seen in mice, and (iii) any time in the animal's life, even in adulthood, from a multipotent stem cell precursor (persistent multipotent cell-derived germ cells), such as in planaria and hydra (a mode of germ cell specification pathway that also occurs in plants) (Gustafson and Wessel, 2010). In their review on this topic Extavour and Akam (2003) differentiated only between two modes of germline specification: preformation and epigenesis. Mode (iii) in the scheme of Gustafson and Wessel (2010) was grouped with the epigenesis mode (Extavour and Akam, 2003). Mode (iii), occurring in basal Metazoa such as Porifera (sponges) and Cnidaria (corals, jellyfish, hydra), planarians, ascidians, and plants is thought to be the phylogenetically oldest mode of germline specification (Extavour, 2007). In these phyla, germ cells obviously are not preformed but arise from a somatic stem cell population (e.g. archaeocytes, interstitial cells, meristem cells) that also generates other cell types (Müller, 2006; Watanabe et al., 2009). Importantly, these stem cells also play a key role in the almost unlimited regenerative potential of these taxa. In hydrozoan Cnidarians, pluripotent interstitial cells (i-cells) contain electron-dense cytoplasmic bodies similar to those associated with germ cells in all phyla

(Eddy, 1975). In the ctenophore *Pleurobrachia*, expression of *Piwi*, *Vasa* and *PL10* genes occurs in both the germ line and in a variety of non-germ line stem cells (Alié et al., 2011). Likewise, in the hydrozoan cnidarian *Clytia hemisphaerica* the multipotent i-cells in larvae and adult medusae, from which germ cells derive, express a set of conserved germ cell markers: *Vasa*, *Nanos1*, *Piwi* and *PL10* (Leclère et al., 2012). In situ hybridization analyses revealed maternal mRNAs for all these genes highly concentrated in a germ plasm-like region at the egg animal pole and inherited by the i-cell lineage, strongly suggesting i-cell fate determination by inheritance of animal-localized factors. On the other hand, experimental tests showed that i-cells can form by epigenetic mechanisms in *Clytia*, since larvae derived from both animal and vegetal blastomeres separated during cleavage stages developed equivalent i-cell populations (Leclère et al., 2012). Thus *Clytia* embryos appear to have maternal germ plasm inherited by i-cells but also the potential to form these cells by zygotic induction. Reassessment of available data indicates that maternally localized germ plasm molecular components were plausibly present in the common cnidarian/bilaterian ancestor, but that their role may not have been strictly deterministic (Leclère et al., 2012). These bodies become more numerous in i-cells that develop into germ cells, and decrease in number in i-cells that differentiate into nematocytes (Extavour and Akam, 2003).

If germ granules are the vehicles of transgenerational information transfer the differential time course of their formation may tell us something about the mode of information transfer. The situation appears clear-cut for preformation. In animals where the germline is preformed, germ granules are present continuously in germ cells (with the exception of mature sperm) and are inherited maternally with the germ plasm (Seydoux and Braun, 2006). Oocytes carry transgenerational messages in the cytoplasmatic ribonucleoproteins of the germ granules. The soma-germline information transfer and, hence, the formation of the germ granules is completed with the release of the gametes/offspring into the environment. Epigenesis implicates that germ granules are not observed before, or immediately following, fertilization but are induced by cell-cell interactions during early embryogenesis. However, epigenesis is an umbrella term for various modes of formation. In basal Metazoa transgenerational information transfer appears to occur via maternal germ plasm that is only detectable by in situ hybridization analyses and that is distributed among the somatic stem cells (Alié et al., 2011; Leclère et al., 2012). In vertebrates, epigenesis occurs

in urodele amphibians and mammals. In both, experimental manipulations can induce re-specification of cells from various embryonic regions to PGC fates, and there is no detectable mRNA or protein localization for the germ plasm "markers", or localization of electron-dense granules during early development (Extavour and Akam, 2003).

The regeneration of body tissues and organs is a widespread phenomenon among urodele amphibians (Tanaka, 2003). The Mexican axolotl (*Ambystoma mexicanum*) has an unparalleled regenerative capacity among vertebrates (McCusker and Gardiner, 2010). Among various vertebrate tissue/organ regeneration models in axolotls, limb regeneration is the most intensively studied (Brockes and Kumar, 2005). Cells at the site of amputation form a blastema, a mass of undifferentiated cells. Both lineage-committed progenitor stem cells and lineage-uncommitted pluripotent stem cells appear to be present throughout the individual as reserve populations of stem cells. During tissue replacement these quiescent stem cells become activated, proliferate, and differentiate into the missing tissues (Young, 2004). Recent evidence suggests that the regenerating blastema may acquire a germline-like state (Zhu et al., 2012a; b). The *DAZ*-like gene is essential for meiosis or gametogenesis in several systems and is a molecular marker for germ cells (Johnson et al., 2001). Importantly, maternal *dazl* RNA is inherited in the animal cap and *Axdazl* RNA is found quite equally distributed in all regions of the axolotl embryo with similar concentrations in the ventral and dorsal marginal zone (Johnson et al., 2001). However, the products of germ cell-specific genes, such as *Dazl* and *Vasa*, are not localised in the oocytes and are not zygotically transcribed in PGCs until they approach the gonadal ridges (Johnson et al., 2001; Johnson et al., 2003). Thus, epigenetic information transfer in axolotls is reminiscent of the mode of information transfer in basal metazoan that, like axolotl, have a high regenerative potential.

Mammals are unique in that there is an intimate mother-embryo/fetus communication during gestation. The epigenetic formation of germ cells has been well characterized in mice and appears to be common to all placental mammals. The placenta has an important role in embryonal/fetal programming (Jansson and Powell, 2007; Gheorghe et al., 2010). Since this epigenetic programming may persist for several generations (Stewart et al., 1975; Aerts et al., 1990; Oh et al., 1991; Aerts and Van Assche, 1992; Zambrano et al., 2005; Burdige et al., 2007; Pinheiro et al., 2008; Dunn and Bale, 2011; see also chapter

16.2), this programming can be expected to include also the germline cells. Between fertilization and implantation, both the maternal and paternal genomes lose their DNA methylation (although methylation of imprinted germline differentially methylated regions is faithfully maintained after fertilisation as a lifelong memory of parental origin of the allele in the new generation) (Smallwood and Kelsey, 2012). Concomitant with blastocyst implantation and cell-lineage determination, new methylation landscapes become established. PGCs emerge in mouse embryos at E7.5 and, concomitant with their proliferation and migration towards the genital ridge, DNA methylation is globally erased. Following sex-determination, new DNA-methylation landscapes are established in germ-cell precursors in an asymmetrical fashion in male and female embryos. In the male embryo, de novo methylation takes place before meiosis in mitotically arrested cells and is completed before birth. In the female embryo, DNA methylation is established after birth during the follicular/oocyte growth phase and is completed at puberty (Smallwood and Kelsey, 2012). Importantly, nuage formation in mouse PGC parallels the loss of DNA methylation during migration towards the genital ridge (Eddy, 1974; 1975). Overall, the dynamics of germ granule formation and zygote/gamete reprogramming suggest a role of germ granules in transgenerational information transfer. Hence, the different time course and regulation of germline specification reflects the various reproductive systems ranging from recruitment of somatic stem cells in basal Metazoa to mammal fetal programming as parental start-up support in a capricious environment. The following scenario is proposed: (i) in a close cross-talk with germline cells, somatic gonadal cells determine the ncRNA profile in the germline cells; (ii) after intercellular transfer secondary piRNA biogenesis (ping-pong) amplifies the message in the germline; (iii) the ncRNA message is stored in the germ granules until the information is retrieved for embryonal development (preformation); (iv) in species with extended parent-embryo/fetus developmental support (e.g. in mammals), reprogramming by transgenerational message transfer is not confined to gametogenesis. In mammals, reprogramming occurs also during embryonal development (epigenesis) and may even extend to maturity as is suggested by the completion of oocyte DNA methylation pattern.

Although posttranscriptional mechanisms likely contribute to silencing, CpG methylation is critical for transposon repression in mammals (Yoder et al., 1997; Liang et al., 2002; Lippman et al., 2003; Bestor and Bourc'his, 2004; Bourc'his and Bestor, 2004; Gaudet

et al., 2004; Aravin et al., 2007a). Loss of CpG methylation can be expected to weaken the control of TE mobilization. During reprogramming, covalent modification such as DNA methylation is replaced by non-covalent RNA-RNA and RNA-DNA base pairing interactions. Mostly, however, non-covalent interactions are considerably weaker (by one to three orders of magnitude) than covalent bonds (Hobza et al., 2006). Thus, in germ cells, pre- and postimplantation embryos, the host surveillance of TEs becomes less than optimal (Dupressoir and Heidmann, 1996; Loebel et al., 2004; Peaston et al., 2004; Svoboda et al., 2004; Taruscio and Mantovani, 2004; Maksakova et al., 2008; Leung and Lorincz, 2012). During both male and female gametogenesis, temporary relaxation of the epigenetic control of TEs during early germline development opens a risky window that can allow TEs to escape from host constraints and to propagate abundantly in the host genome (van der Heijen and Bortvin, 2009; Bao and Yan, 2012). Under the prevailing paradigm that it is the primary mission of the germline to faithfully transmit the genome to the next generation, the question has not been asked whether it could be of evolutionary significance that germline cells endanger their mission by unleashing the destructive potential of TE, stripping their DNA methylation during epigenetic reprogramming. Taking into account the huge evolutionary significance of TE mobility (see chapters 10.6 and 12.4) this evidence should be another opportunity to reconsider the paradigm of the immutable germline.

17. Stochasticity and selection, the organizing principles of evolution

Neither a purely reductionist approach nor a merely holistic perspective is sufficient to encompass the intrinsic nature of the system's behavior.

Pahl-Wostl, 1993

Summary

There is an important difference between breeding (Darwin's role model of evolution) and evolution itself: while in breeding the final goal is preset and constant, adaptation to varying biotic and abiotic environmental conditions is a moving target and selection can be highly fluctuating. Evolution is a cybernetic process that can be understood as a learning automaton with input and output channels. The output/outcome has been defined:

selection. The input has been less rigorously defined. In learning automata, output variables allow to make inferences about the informational input. Variation is pervasive at every level of biological organization. Variation is the bet-hedging strategy that tries to cover all bases in an often unpredictable environment when it does not make sense to “put all your eggs into one basket”. Importantly, most revealing is that variation is created condition-dependently, when variation is most needed— in organisms under stress. Bet-hedging is the risk-spreading response to environmental uncertainty. Bet-hedging is the output variable that allows to infer that environmental uncertainty/stochasticity is the informational input in evolution. Sexual reproduction with its regulated genetic-variant generation is the proof of concept that (epi)genetic variation is no happenstance outcome but a highly regulated process and environmental stochasticity is its evolutionary “mastermind”. A dual system, characterized by stochasticity and selection is the organizing principle of evolution. Both are interdependent. Sexual reproduction is the ultimate bet-hedging enterprise and its evolutionary success is the selective signature of stochastic environments.

The Modern Synthesis built on Darwin's two major realizations: (i) that all living organisms are related to one another by common descent; (ii) that a primary explanation for the pattern of diversity of life—and especially for the obvious “fit” of organisms to their environments—is the process that he called natural selection. Importantly, he recognized the importance of variation for the action of selection (1859, chapters I, II and V). However, he had no idea how this variation arose: “our ignorance of the laws of variation is profound” (1859). In Darwin's tradition, the Modern Synthesis understood selection as the only driving force in evolution. Genetic variation was the result of accidental mutations. Thus, variation was understood as the accidental outcome of error-prone replication. Darwin's concept of evolution was molded by his role model of artificial selection. But there is an important difference between artificial selection and evolution. In breeding, artificial selection has the goal to improve a certain predefined trait, e.g. oil content in maize (Laurie et al., 2004), milk quantity and quality in dairy cattle breeding, a certain morphological trait in pigeons, or, in the laboratory, flight speed in *Drosophila* (Weber, 1996). The target is pre-defined by the breeder. Importantly, breeding is an iterative process (Hill and Caballero, 1992; Williams and Lenton, 2007) in which the ultimate goal, e.g. increased oil content in maize

(Laurie et al., 2004), is reached after many generations, but the setting of the ultimate goal and thus the direction of selection remain constant (figure 2B). Here, variation is an often unwanted noise, at least when it does not serve the ultimate target of selection. The breeder has at least two functions: he determines the goal of the breeding operation and selects the individual for the next round of breeding. In evolution, the direction and selective regime are established by the environment (figure 2C). However, the target, adaptation to varying biotic and abiotic environmental conditions, is a moving target and selection can be highly fluctuating (Bell, 2010). In this chapter, I argue that our understanding of the “laws of variation” has a key role in our understanding of evolution.

17.1 The cybernetics of evolution

Cybernetics is the study of control systems (Wiener, 1948, Ashby, 1956). Cybernetic systems are systems with feedback. They are a special class of cause-and-effect (input-output) systems. Patten and Odum (1981) offered a minimalist definition that distinguished cybernetic systems from non-cybernetic systems by the presence of feedback control; in cybernetic systems, “input is determined, at least in part, by output”. Evolution is a cybernetic process (Ashby, 1954; 1956; Schmalhausen, 1960; Corning, 2005). Cybernetic systems are characterized by input and output variables and it is essential to distinguish the one from the other (Ashby, 1956) (figure 1A). Darwin was vague in the meaning of his new concept of “Natural Selection,” using it interchangeably as one of the causes for evolutionary change and as the final outcome (= evolutionary change). (Since evolution is a continuous iterative process where the resultant population of the previous contest becomes the input population to the next contest, Darwin's ambiguity was not completely unfounded.) But his clearest definition of natural selection (Darwin, 1859 p. 61: “I have called this principle, by which each slight variation, if useful, is preserved, by the term of Natural Selection, in order to mark its relation to man's power of selection.”) is an outcome definition, not that of a cause (Bock, 2003). First, natural selection is a metaphor, an umbrella term that serves to label and characterize a vast array of specific factors with survival consequences. The generally accepted modern definition of natural selection is that it is an outcome (Fisher 1930; Endler, 1986; Bock, 2003; 2010; Reese, 2005), corresponding to an output in a cybernetic system. Arguably, the most fundamental impact on this outcome comes from the environment. Surprisingly, the input into the process of evolution has been less

rigorously defined. That the environment informs the evolutionary agent on its state is an statement that is rather trivial. More meaningful for the interpretation of evolutionary processes is the recognition that environments have a high degree of uncertainty/stochasticity (Yoshimura and Clark, 1991; Lenormand et al., 2009) or capriciousness (Lewontin, 1966). To deal with this uncertainty organisms had to acquire the capacity to learn from past environments to generalize to new environments (Kirschner and Gerhart, 2005; Gerhart and Kirschner, 2007; Parter et al., 2008). However, evolution does not "know" in advance which evolutionary path will lead to the increase of fitness or how fluctuating, often unpredictable, environments will change. Therefore, prospectively, the best "strategy" to increase fitness is to take every possible path at every next step. As a result, no configurations should be missed (Fu, 2007). Which configuration is a "fit" one, is finally decided by the survival and reproductive success of the individual. Both an unpredictable, fluctuating abiotic environment and constantly coevolving web of life (Thompson, 2005; 2009) contribute to the stochasticity. There are winners and losers in this game. Evolution is a stochastic process (Lenormand et al., 2009; Kupiec et al. 2012). But what makes evolution a stochastic process? Is it the inherent error susceptibility of evolutionary processes or is it the bet-hedging in response to some unpredictable, stochastic event?

To address this question let us consider evolution as a cybernetic, learning box. Learning automata are adaptive decision-making devices operating on unknown random environments (Narendra and Thathachar, 1974; 1989). The automaton updates its action probabilities in accordance with the inputs received from the environment so as to improve its performance in some specified sense (Narendra and Thathachar, 1974; 1989). The basic operation carried out by a learning automaton is the updating of the action probabilities on the basis of the responses of the environment. The learning automaton has a finite set of actions and each action has a certain probability (unknown to the automaton) of getting rewarded by the controlled system, which is considered as environment of the automaton. The aim is to learn to choose the optimal action (i.e. the action with the highest probability of being rewarded) through repeated interaction on the system. If the learning algorithm is chosen properly, then the iterative process of interacting on the system can be made to result in the selection of the optimal action (Zeng et al., 2000). The learning model that is closest to the evolutionary approach is "reinforcement learning" based on the insight that successful strategies will be reinforced and

used more frequently. Reinforcement learning has been successfully applied for solving problems involving decision making under uncertainty (Narendra and Thathachar, 1989; Barto et al., 1983; Zikidis and Vasilakos, 1996; Zeng et al., 2000). (When speaking of 'decisions', use of the term is in an evolutionary sense, not implying any conscious rationalization on the part of individual organisms.) In general, a reinforcement learning algorithm conducts a stochastic search of the output space, using only an approximative indication of the "correctness" (reward) of the output value it produced in every iteration. Based on this indication, a reinforcement learning algorithm generates, in each iteration, an error signal giving the difference between the actual and correct response and the adaptive element uses this error signal to update its parameters (Zeng et al., 2000).

By looking at its output we should be able to make inferences about the quality of the informational input to this learning automaton. Clearly, the fact that the black box generates winners and losers suggests that some type of lottery unfolds, that stochastic processes play a role within the learning box. The outcome of any evolutionary process is not a single result; it is at best a probability distribution of possible outcomes (Proulx and Adler, 2010). Hence, evolution can be described by a lottery model (Chesson and Warner, 1981; Proulx and Day, 2001; Svardal et al., 2011). On the other hand, the descents of the winners of this lottery (that were fit enough to reproduce) again are a raffle ticket in another round of this iterative evolutionary game. During the iterative process the direction of selection can fluctuate, often unpredictable (see figure 2).

17.2 Bet-hedging as response to stochasticity

In a review of published studies on variation in recruitment, Hairston et al. (1996) found that reproductive success of long-lived adults varied from year to year by factors up to 333 in forest perennial plants, 4 in desert perennial plants, 591 in marine invertebrates, 706 in freshwater fish, 38 in terrestrial vertebrates, and 2200 in birds. These figures represent the variation among years when some reproduction occurred; many of the studies also report years in which reproduction failed completely. Similarly, the recruitment success of diapausing seeds or eggs varied by factors of up to 1150 in chalk grassland annual and biennial plants, 614 in chapparal perennials, 1150 in freshwater zooplankton, and 31,600 in insects (Ellner, 1997). In response to uncertainty as to which phenotype will have highest fitness in the future, biological systems exert risk minimization by risk-spreading. Bet-hedging is a response to environmental uncertainty (Einum and

Fleming, 2004; Marshall et al., 2008; Beaumont et al., 2009; Crean and Marshall, 2009; Gourbière and Menu, 2009; Olofsson et al., 2009; Rajon et al., 2009; Simons, 2009; Nevoux et al., 2010; Simons, 2011; Morrongiello et al., 2012) and risk minimization strategy on all levels of biological organization (Cohen, 1966; Gillespie, 1974a; Slatkin, 1974; Tonegawa, 1983; Hairston and Munns, 1984; Seger and Brockmann, 1987; Philippi and Seger, 1989; Frank and Slatkin, 1990; Moxon et al., 1994; Sasaki and Ellner, 1995; Ellner, 1997; Danforth, 1999; Hopper, 1999; Menu et al., 2000; Lips, 2001; Meyers and Bull, 2002; Fox and Rauter, 2003; Friedenberg, 2003; Balaban et al., 2004; Einum and Fleming, 2004; King and Masel, 2007; Venable, 2007; Acar et al., 2008; Ackermann et al., 2008; Gourbière and Menu, 2009; Olofsson et al., 2009; Simons, 2009; 2011; Childs et al., 2010; Monro et al., 2010; Gremer et al., 2012; Morrongiello et al., 2012; Starrfelt and Kokko, 2012). Bet-hedging may involve the production of fewer and larger offspring (conservative) or of variable-sized offspring (diversified). As the environment becomes more stable, the bet-hedging strategies have a lower fitness advantage. Metazoan bet-hedging usually involves phenotypic diversification among an individual's offspring, such as differences in seed dormancy. Almost all known microbial bet-hedging strategies in contrast, rely on low-probability stochastic switching of a heritable phenotype by individual cells in a clonal group (Stumpf et al., 2002; Thattai and van Oudenaarden, 2004; Kussell et al., 2005; Kussell and Leibler, 2005; Wolf et al., 2005; Avery, 2006; Veenning et al., 2008a; b; Beaumont et al., 2009; Fraser and Kaern, 2009; Ratcliff and Denison, 2010; Rainey et al., 2011; Levy et al., 2012).

The key point in Evolutionary Game Theory (EGT) models is that the success of a strategy is determined by how good the strategy is in the presence of other alternative strategies, and of the frequency that other strategies are employed within a competing population. To create a sufficient amount of winners under all realistic assumptions an evolutionary stable strategy (ESS) must 'cover all bases'. Both theoretical and experimental approaches demonstrated that in the face of variable and unpredictable environments, bet-hedging is the ESS (Haccou and Iwasa, 1995; Sasaki and Ellner, 1995; Beaumont et al., 2009; Olofsson et al., 2009; Rees et al., 2010; Ripa et al., 2010; Starrfelt and Kokko, 2012). In constant environments natural selection leads to each individual organism maximizing its expected number of descendants left far in the future. If there are no environmental fluctuations, fitness can be measured by the arithmetic mean number of surviving descendants. In fluctuating environments it may be

optimal for different individuals of the same genotype to take different actions to spread the risk and ensure the genotype is represented in future generations. The fitness of the genotype is determined by the, perhaps complementary, actions of all individuals of the genotype, and the best action for one individual depends on the actions of others (McNamara et al., 1995). The standard criterion for evaluating the fitness of genotypes in stochastic environments is the geometric mean of the growth rates (geometric mean fitness) (Dempster, 1955; Cohen, 1966; Lewontin and Cohen, 1969; Frank and Slatkin, 1990; Yoshimura and Clark, 1991; Yoshimura and Jansen, 1996; Hopper, 1999; Simons, 2009; Yoshimura et al., 2009). In unstable environments, the geometric mean is always lower than the arithmetic mean. A rigorous definition of bet-hedging includes lower expected arithmetic mean fitness, as well as greater expected geometric mean fitness (Seger and Brockmann, 1987; Simons, 2009). In fluctuating environments, when geometric mean fitness is maximized, individual optimization fails (Cohen, 1966; Ellner, 1986; McNamara 1995; 1998; McNamara et al., 1995; Yoshimura and Jansen, 1996). As egg phenotype is linked to offspring phenotype, increased within-brood variation in egg phenotype can have a selective advantage in unpredictable environments by increasing maternal geometric fitness (Marshall et al., 2008; Crean and Marshall, 2009; Crean et al., 2012). The best action of an individual depends on the states and actions of other population members (McNamara et al., 1995; McNamara, 1998; Török et al., 2004; Simons, 2009). Under the geometric mean criterion, behavior appears to be determined largely by a worst case scenario; behavior may appear suboptimal if observed only under normal or average conditions (Yoshimura and Clark, 1991; Yoshimura and Jansen, 1996). For example, except under extreme environmental conditions, mammalian litters (Murie and Dobson, 1987; Risch et al., 1995) and avian clutches (Perrins, 1965; Klomp, 1970; Murray, 1979; Lessells, 1986; Murphy and Haukioja, 1986; Boyce and Perrins, 1987; Vander Werf, 1992) larger than those that are observed in nature might result in increased fecundity, with little if any cost of reproduction in terms of parental survival. However, in unusually bad years such large clutches might be disastrous, in terms of parental survival (Yoshimura and Clark, 1991; Yoshimura and Shields, 1992). An illustrative example was given by Philippi and Seger (1989): "Suppose that years are 'good' or 'bad' with equal probability, and that the wild type produces, on average, 9 offspring in good years and 1 offspring in bad years, for an average of 5. Now introduce a

mutant that produces 5 offspring in good years and 3 offspring in bad years, for an average of only 4. Despite its lower mean fitness, the mutant quickly goes to fixation because its geometric mean fitness (3.87) is much higher than that of the wild type (3.0) and its variance lower. The mutant's best performance is much worse than the wild type's best, but its worst is better, and this is the key to its success." Variance reduction can be accomplished in two ways, risk avoidance and risk spreading (den Boer, 1968). Risk-avoidance strategies reduce variance by producing relatively constant outputs under different environmental conditions. Risk-spreading strategies, on the other hand, reduce population-level variance by some process of averaging over independent events.

According to Lynch (2007a; b) out of the four major forces in evolution, natural selection, mutation, recombination and drift, the latter three are stochastic in nature (however, in chapter 12, I discussed that at least mutation and recombination are non-random). In addition to these stochastic genetic mechanisms, there is growing evidence of evolutionary selection for stochastic diversity-generating mechanisms in unicellular and multicellular organisms on a variety of epigenetic, developmental, physiological and behavioral levels (True and Lindquist, 2000; Elowitz et al., 2001; Fraser et al., 2004; Raser and O'Shea, 2004; 2005; Kærn et al., 2005; Kussell and Leibler, 2005; Avery, 2006; Peaston and Whitelaw, 2006; Smits et al., 2006; Lim and van Oudenaarden, 2007; Mamar et al., 2007; Acar et al., 2008; Davidson and Surette, 2008; Freed et al., 2008; Losick and Desplan, 2008; Shahrezaei and Swain, 2008; Lenormand et al., 2009; Dercole et al., 2010; Lidstrom and Konopka, 2010; Huang, 2012). Comparing RNA sequences from human B cells of 27 individuals to the corresponding DNA sequences from the same individuals, Li et al. (2011) uncovered more than 10,000 exonic sites where the RNA sequences did not match that of the DNA, revealing infidelity of information transmission from DNA to RNA as an additional aspect of genome variation. The number of events varied among individuals by up to sixfold across 27 subjects (Li et al., 2011).

The question whether all these variation-generating processes are accidental or are evolutionarily intended amounts to the question whether bet-hedging is a haphazard process or an ESS. Bet-hedging can be represented by an evolutionary game (Olofsson et al., 2009). Variation is the bet-hedging strategy to cover all bases in an often unpredictable environment. It does not make sense to "put all your eggs into one basket". In bet-hedging, spreading of the bets is a must to

improve one's chances to win. Examples of risk spreading include dispersal of progeny (spatial averaging: Levin et al., 1984), iteroparity (Murphy, 1968; Bulmer, 1985; Orzack and Tuljapurkar, 1989; Wilbur and Rudolf, 2006), delayed germination of seeds (temporal averaging: Ellner, 1985) and phenotypic polymorphism (Levins, 1968; Roughgarden, 1979, p. 272). Importantly, most revealing is that variation is created condition-dependently, when variation is most needed— in organisms under stress. Thus stress elicits increased mutagenesis, increased epimutagenesis, increased recombination, increased transposon mobility, increased repeat instability, increased phenotypic plasticity, and, in organisms that can reproduce both asexually and sexually, increased sexual reproduction. Several theoretical models confirm that sexual reproduction is selected for in variable environments (Hines and Moore, 1981; Weinshall, 1986; Roughgarden, 1991; Robson et al., 1999). Sexual reproduction is the ultimate bet-hedging enterprise and its evolutionary success the selective signature of stochastic environments.

Thus environmental stochasticity elicits bet-hedging as risk-spreading response resulting in (epi)genetic, developmental, phenotypic, physiological and behavioral variation on which selection can act (figure 2C).

17.3 Stochasticity and selection: dualism in evolution

This work has provided compelling evidence that a change of environmental conditions that reduce Darwinian fitness (see the ecological stress definition chapter 2) may elicit

1. stress-induced mutagenesis
2. stress-induced epimutagenesis
3. increased recombination rate
4. increase mutability of simple sequence repeats
5. increased mobilization of transposable elements

all of which, when acting on the germline, increase heritable (epi)genetic variation. Sexual reproduction regulates these processes and, by changing the SMSC balance, is the process modulating the (epi)genetic variation-selection balance, e.g. by the action of hormones (see chapter 14.2). Theoretical models suggests that fluctuating selection may be an important factor in maintaining genetic polymorphism (Korol et al., 1996; Kirzhner et al., 1998; Bürger and Gimelfarb, 2002). Likewise, empirical studies of cyclical and fluctuating selection suggest an association between temporal environmental heterogeneity and the amount of genetic variation (Korol et al., 1996; Kondrashov and Yampolsky,

1996). These processes and their quasi-stochastic generation of variation appear to have an evolutionary rationale: fighting change with change (Meyers and Bull, 2002), risk-spreading in the face of environmental uncertainty, creating lottery tickets for the raffle of life. On the other hand, sexual reproduction as evolutionarily highly successful strategy, highlights an eminent characteristic of evolution: it pays off to diversify and be prepared for the unlikely event. And: generation of variation is no happenstance outcome but a highly regulated process and environmental stochasticity is its evolutionary “mastermind”.

According to Mayr (1980), selection is “the only direction-giving factor in evolution”. On the other hand, Monod (1971) argued that chance is both the major creative force and a crucial problem for evolving biological systems. The paradigm of calculability, determinism and monocausality dominated the sciences until the beginning of the 20th century. Since the end of the 19th century, monocausal approaches in many different sciences started to collapse. Even in pure mathematics and logics, problems with the calculability of the universe arose (e.g. Russell’s paradox). Hilberts program failed with Kurt Gödel’s proof. At the level of physics, many different problems (ultraviolet catastrophe, wave-particle dualism, ...) lead to the development of new physics (Brunner and Klauninger, 2003). Like the wave paradigm could not explain a variety of physical properties of light, explaining evolution by natural selection as only organizing principle creates various implausibilities. As it stands, it is accepted that it makes sense to use stochastic models in population genetics. But why should a selection-only process be stochastic? It is agreed that natural selection has its limits (Barton and Partridge, 2000). But so far these limits have been explained by e.g. genetic architecture, historical contingency or developmental constraints.

Understanding evolution as cybernetic box and learning automaton identifies the informational input into the evolutionary self-corrective system: environmental stochasticity. Darwin already realized that variation is an essential commodity in evolution but he was unaware of its cause. The Modern Synthesis regarded variation as the result of accident, happenstance and imperfection. It is textbook knowledge that selection needs variation to work on. The central question, however, is whether variation is the result of accident and chance or whether it evolved as a means to create many lottery tickets in response to the unpredictability of life. The recognition that variation arises at all levels such as the genetic, epigenetic, developmental, physiological, behavioral

and life-history level, that it is malleable in response to stress (when it is most needed) and that sexual reproduction evolved as master tool creating pre-selected variation, clearly points to the latter interpretation. And promoting stochasticity to the boardroom of evolution opens a new dimension of insight into a variety of evolutionary phenomena and enigmas (see chapter 19).

In the dualism of stochasticity and selection, variation is recognized as the result of a multitude of processes, resulting in a bet-hedging response to stochasticity. In essence, stochasticity and selection work against each other within the limits of total chaos and complete order, the two extremes where evolution is no longer feasible. On the other hand, stochasticity and selection are interdependent. None can prevail without depriving evolution of its very basis. Selection could not work without the stochastic phenomenon of variation; and stochasticity needs the ordering power of selection to create the complex structures of self-organized criticality (Bak et al., 1987; 1988). Intriguingly, part of the stochasticity is created by selection itself, e.g. through coevolutionary cycles, density- and frequency-dependent selection, or niche construction (Meyers and Bull, 2002). On the other hand, stochasticity drives variation and variation is the raw material for selection to work on. Although within wide boundaries, stochasticity and selection have to be balanced. Evolutionary biology already acknowledged mutation-selection equilibrium as evolutionary phenomenon; it is time to realize that there is a stochasticity-selection balance. Too much stochasticity would be detrimental for learning: if the cybernetic feedback concerning fitness effects would not behave with a certain stability and change too irregularly, learning would be impaired. Fortunately, with respect to living organisms, nature is capricious rather than completely random (Lewontin, 1961; 1966). There is a variable degree of ecological predictability: demographic cycles due to e.g. predator/prey interactions, seasons with their cyclicity of resource availability, circadian cycles, tides, etc. Bet-hedging only makes sense in a more or less stochastic environment. As the environment becomes more stable, bet-hedging strategies have a lower fitness advantage (Philippi and Seger, 1989). Stochasticity is ambiguous (e.g. beneficial, neutral and deleterious mutations) with regard to outcome while selection filters and directs the ambiguity. And learning attenuates the randomness. Selection is the stabilizing force that brings order into the chaos and provides the feedback for learning to occur. Both stochasticity and selection render evolution opportunistic.

There is compelling evidence, of which this paper only could sample a small amount, that whenever organisms and cells are in stress, i.e. are maladapted and in need of genetic novelty, they upregulate mutagenesis and hedge their bets in the face of environmental stochasticity. Modifying Dobzhansky's notorious quote, Lynch (2007a) wrote: "Nothing in evolution makes sense except in light of population genetics". However, in 1961 Lewontin did not consider population genetics an "adequate theory of evolutionary dynamics. On the contrary, the theory of population genetics, as complete as it may be in itself, fails to deal with many problems of primary importance for an understanding of evolution." In this paper, Lewontin (1961) suggested that the modern theory of games (von Neumann and Morgenstern, 1944; 1953) may be useful in finding exact answers to problems of evolution not covered by the theory of population genetics. A first application of game theory to evolutionary issues was the work of Maynard Smith and Price (1973) on animal conflicts and their concept of an "evolutionarily stable strategy" (ESS). The vast body of theoretical work based on the concept of an ESS, often disregards environmental stochasticity; for example, Maynard Smith's often quoted book (Maynard Smith, 1982) contains no reference to stochasticity. An important feature of evolutionary game theory (EGT) models is repetition. If the games were not repeated, these EGT models would not be able to provide any insight into adaptive behaviors and strategies due to the dynamic nature of the mechanisms of evolution. Importantly, evolution "plays" both within-generation and trans-generation games. At each game repetition population make-up in turn is determined by the results of all of the previous contests before the present contest- it is a continuous iterative process where the resultant population of the previous contest becomes the input population to the next contest. Evolution is a stochastic process (Lenormand et al., 2009; Kupiec et al. 2012) that can be described by a lottery model (Chesson and Warner, 1981; Proulx and Day, 2001; Svardal et al., 2011). Bet-hedging is an ESS in the face of environmental capriciousness (Lewontin, 1966) and sexual reproduction with its mutagenesis-selection cascades, is the evolutionary commander in chief, "master-minded" by evolutionary unpredictability.

The identification of stochasticity/uncertainty as input variable into the cybernetic machine of evolution (Ashby, 1956) has far-reaching implications for a multitude of evolutionary enigmas as discussed in chapter 19.

18. Earlier theories that attempted to explain why most organisms reproduce sexually

...that an opinion has been widely held is no evidence whatever that it is not utterly absurd....

Bertran Russell (1929)

Summary

What all current theories have in common is their focus on recombination as the only perceived mechanism in sexual reproduction. Thus they had to fail to decipher the evolutionary rationale of sexual reproduction. Deeply entrenched in population genetics thinking, the so-called genetic theories of sexual reproduction (Fisher-Muller-model, Muller's ratchet and Kondrashov's hatchet) completely missed the dynamic aspect of evolution. Apart from highly deleterious mutations that endanger viability, whether a mutation is beneficial, neutral or slightly deleterious is context-dependent and highly volatile. Evolution is opportunistic and to take every possible path at every next step, no viable configurations should be missed. Homologous recombination may have been used for DNA repair in microbes but as is often in evolution was later co-opted for innovation rather than conservation. That sexual reproduction evolved in hosts to counter the pressure of parasitic coevolution as the "Red Queen" hypothesis states, reflects a too narrow scope of ecological challenges in a constantly coevolving, highly dynamic web of life.

Up to now, the general perception with regard to sexual reproduction suffered from a too narrow perspective on the mechanism of recombination (e.g. Agrawal, 2006b). Consequently, theories of the evolution of sex were very much like searching for the lost key under the lamppost. Missing the most "ingenious" innovation of sexual reproduction, preselected (epi)mutagenesis, these theories had to fail.

18.1 Fisher-Muller-model, Muller's ratchet and Kondrashov's hatchet

How can such a rich theoretical structure as population genetics fail so completely to cope with the body of fact? Are we simply missing some critical revolutionary insight that in a flash will make it all come right, as the Principle of Relativity did for the contradictory evidence on the propagation of light?

Lewontin (1974)

Sex and recombination have long been seen as adaptations that facilitate the work of natural selection. The so-called genetic theories of sexual reproduction try to explain the evolutionary success of sexual reproduction within the framework of population genetics.

1) The positive mutation models or Fisher-Muller hypothesis propose that sex, allowing for recombination and segregation, is advantageous because beneficial mutations that arise in different individuals can be united in the same genome and therefore offspring with above average fitness can be produced (Fisher, 1930; Muller, 1932; Crow and Kimura, 1965, 1970; Manning, 1976; Bell, 1982; Wolf et al., 1987; Findlay and Rowe, 1990; Peck, 1993; 1994; Dunbrack et al., 1995; Otto and Barton, 1997; Peck et al., 1997). In fact, a number of specific evolutionary scenarios lead to the general conclusion that higher levels of adaptation can be achieved when recombination is frequent than in its absence, because of the associated reduction in the amount of Hill-Robertson effect (a reduction in the efficacy of natural selection that occurs because finite populations accumulate associations of linked genes that interfere with selection) (Gordo and Charlesworth, 2001; Otto and Lenormand, 2002; Marais and Charlesworth, 2003). However, when the only evolutionary process acting is viability selection (no mutation, no departures from random mating, no drift, etc.), evolutionary theory predicts that populations should evolve lower and lower rates of sex and recombination. The underlying reason is that sex and recombination break apart the favorable gene combinations that have been built up by past selection (recombination load), offsetting the benefits of combining advantageous mutations (Maynard Smith 1968, 1978; Feldman et al., 1980; Altenberg and Feldman, 1987; Charlesworth and Barton, 1996; Otto, 2007). The balance of these two forces determines whether modifiers that increase recombination are favored. Recombination load has been shown in *Chlamydomonas* (Colegrave et al., 2002b; Kaltz and Bell, 2002), rotifers (Becks and Agrawal, 2011), and in yeast (Greig et al., 1998). In a constant environment these genetic associations are typically favorable, and theoretical analyses have demonstrated that decreased levels of recombination selection evolve under such circumstances (Feldman, 1972; Feldman et al., 1980; Altenberg and Feldman, 1987; Feldman et al., 1997). Moreover, the theory does not take into account that interactions between pairs of beneficial mutations may be antagonistic (Sanjuán et al., 2004b;

Kryazhimskiy et al., 2009; 2011; Chou et al., 2011; Khan et al., 2011) leading to decompensatory epistasis with the double mutant being less fit than each single mutant (Wolf JB et al., 2000). Although homologous recombination increases genetic diversity by breaking haplotypes, it may also homogenize alleles through gene conversion (Gordo and Charlesworth, 2001; Chen JM et al., 2007; Mancera et al., 2008). Thus, recombination randomizes genotypes and homogenizes sequences between the participating alleles without regard to the fitness of the alleles being recombined (Ferreira, 2002; Hunter, 2006; Keeney, 2007; Otto, 2009).

2) Another genetic explanation for the predominance of sexual reproduction, called Muller's ratchet, points to the purging of deleterious mutations from the genome by recombination (Muller, 1964; Felsenstein, 1974; Manning and Dickson, 1986; Kondrashov, 1988; 1993; Kondrashov and Turelli, 1992; Zeyl and Bell, 1997). There is support for the action of Muller's ratchet in experimental laboratory populations (Chao, 1990; Duarte et al., 1992; Andersson and Hughes, 1996; Zeyl et al., 2001), indirectly from studies on the long-term effects of reduced population sizes on genetic diversity and fitness in the wild (Westemeier et al., 1998; Johnson JA et al., 2003; Rowe and Beebe, 2003) and in mitochondrial genomes of animals evolving in nature (Howe and Denver, 2008; Neiman et al., 2010). In the homothallic fungus *Aspergillus nidulans*, Bruggeman et al. (2003) were able to show that sex slows down the accumulation of deleterious mutations. The question is, however, whether Muller's ratchet may be the cause for the evolution and maintenance of sexual reproduction. These arguments require genomic mutation rates that are higher than typically observed (Keightley and Eyre-Walker, 1999; Lynch et al., 1999; Bataillon, 2000; Fry, 2004; Haag-Liautard et al., 2007). Most well characterized asexual lineages fail to exhibit the high levels of allelic divergence expected in the absence of recombination (Normark, 1999; Schön and Martens, 2003; Omilian et al., 2006; Schaefer et al., 2006). Moreover, as outlined by Melzer and Koeslag (1991), due to the model's constraints imposed on the modeled asexual isolates, namely immortality and constancy in isolate size, Muller's ratchet operates only when mutations affect the outcome of intraspecific contests but not the organisms' intrinsic ability to survive in the ecosystem. Barton (1995) outlined the contributions of short- and long-term effects to the evolution of sex in a general theoretical framework. Both the faster combination of favorable mutations (Fisher, 1930; Muller, 1932) and the avoidance of the accumulation of deleterious mutations (Muller, 1964) are long-term advantages

since they operate very slowly in large populations and can be avoided with very little sex (Pamilo et al., 1987; Charlesworth et al., 1993; Green and Noakes, 1995; Hurst and Peck, 1996; Chasnov, 2000; Keightley and Eyre-Walker, 2000; Bengtsson, 2003; Haddrill et al., 2007; D'Souza and Michiels, 2010; Lampert and Scharl, 2010). Therefore, both processes have been deemed unlikely to explain the short-term maintenance of obligate sexuality. Moreover, even weak purifying selection may eventually lead to the complete cessation of the ratchet (Fontanari et al., 2003; Maia, 2009; Goyal et al., 2012; Parmakelis et al., 2013). Evidently, the long-term stability of an asexual population requires an influx of beneficial mutations that continuously compensates for the accumulation of the weakly deleterious ones. Mathematical model suggested that such a state can exist for any population size N and mutation rate U and that a surprisingly low fraction of beneficial mutations suffices to achieve stability, even in small populations in the face of high mutation rates and weak selection, maintaining a well-adapted population in spite of Muller's ratchet (Goyal et al., 2012).

Asexually reproducing all-female lineages of plants and animals are often more frequent at higher latitudes and altitudes, on islands, arid environments and in habitats described as transient, ecotonal, disturbed or marginal, a phenomenon called geographical parthenogenesis (Glesener and Tilman, 1978; Bierzychudek, 1985; Beaton and Hebert, 1988; Cuellar, 1994; Peck et al., 1998; Hörandl, 2006). These situations are associated with exposure to unfavorable conditions (Brown, 1984; Hoffmann and Blows, 1994). Small populations frequently occur in marginal environments or near the edges of geographic distributions. Small populations are expected to suffer particularly from Muller's ratchet (Muller, 1964; Gabriel et al., 1993; Charlesworth and Charlesworth, 1997). Hence, within the conceptual framework of Muller's ratchet theory of sexual reproduction, it should be highly counter-intuitive that asexual reproduction occurs preferentially in marginal populations. On the other hand, several studies have revealed higher levels of nonsynonymous amino acid substitutions in asexually reproducing organisms as compared to their sexually reproducing sister species (Moran, 1996; Normark and Moran, 2000; Schön et al., 2003; Paland and Lynch, 2006; Barraclough et al., 2007), which supports the idea of deleterious mutation accumulation, although the negative fitness effects of these mutations are generally only assumed. The same patterns (i.e. increased rates of nonsynonymous substitutions), however, are a major line of evidence for strong positive selection on genes in sexually

reproducing organisms (e.g. Eyre-Walker, 2006), which emphasizes the importance of discerning the causes and population-level effects of selection at the molecular level (Schwander and Crespi, 2009).

3) The mutational deterministic hypothesis for the origin and maintenance of sexual reproduction (Kondrashov's hatchet) posits that sex enhances the ability of natural selection to purge deleterious mutations after recombination brings them together into single genomes (Kondrashov, 1988; 1993; Kondrashov and Turelli, 1992). A situation, when the fitness effect of one allele state depends on the allele states at other loci, is called epistasis (Wolf et al., 2000; de Visser et al., 2011; Lehner, 2011; Macía et al., 2012). Kondrashov's hatchet requires negative/synergistic epistasis, a type of genetic interaction where the combined detrimental effect of two unfavorable alleles is greater than the sum of the individual effects. Several authors have speculated that synergy emerges from competition for resources (King, 1967; Sved et al., 1967) and a mathematical model suggested that, if individuals usually compete in small groups, then competition can lead to synergistic epistasis (Peck and Waxman, 2000). However, theoretical modelling has questioned the importance of epistasis for the evolutionary fate of sexual reproduction (Howard and Lively, 1998; Keightley and Otto, 2006; Kouyos et al., 2007; MacCarthy and Bergman, 2007; Barton, 2009). Moreover, empirical studies on a variety of organisms have not supported the theory (Keightley and Eyre-Walker, 2000; de Visser and Elena, 2007; Kouyos et al., 2007; Barton, 2009), reporting every conceivable form of directional epistasis: synergistic (Mukai, 1969; de Visser et al., 1996; 1997a; Rivero et al., 2003; Salathé and Ebert, 2003), antagonistic (Bonhoeffer et al., 2004; Burch and Chao, 2004; Sanjuán et al., 2004b) and no significant directional epistasis (de Visser et al., 1997b; Elena and Lenski, 1997; Elena, 1999; Peters and Keightley, 2000; Whitlock and Bourguet, 2000; Wloch et al., 2001b; Rivero et al., 2003; Cooper et al., 2005; Martin et al., 2007). Positive epistasis is almost as prevalent as negative/synergistic epistasis (de Visser and Elena, 2007), and this variability in the form of epistasis tends to select more strongly against recombination than in its favor (Otto and Feldman, 1997). There is a common intuition that stress increases selection (Agrawal and Whitlock, 2010). Theoretical analyses of metabolic pathways and biological networks show that a genetic stress (the first mutation) can increase or decrease selection on a subsequent mutation (i.e. negative or positive epistasis) depending on the structure of the network and the relative positions of the two mutations within

these pathways (Szathmáry, 1993; Keightley, 1996; Segrè et al., 2005; Sanjuán and Nebot, 2008). Depending on the position of the initial mutation within the pathway, average selection on subsequent mutations could be stronger or weaker than in the absence of the genetic stress (i.e. the initial mutation) (Agrawal and Whitlock, 2010). Sanjuán and Elena (2006) pointed out that epistasis correlates to genomic complexity associated with mutational robustness. Moreover, under constant mutation rates, which is one of the basic assumptions of the deterministic mutation hypothesis (Kondrashov, 1988), sexual and asexual populations of infinite size have equal fitnesses at equilibrium. When mutation rates are fitness-dependent, as is the case in real life, the fitness of a sexual population depends on the shape of the curve relating fitness to mutation rate while the fitness of an asexual population depends only on the mutation rate of the least loaded class (Agrawal, 2002).

Importantly, these theories are rooted in population genetics. According to Lewontin (1961): “the theory of population genetics, as complete as it may be in itself, fails to deal with many problems of primary importance for an understanding of evolution.” and Lewontin (1974, p. 267): “...population genetics is not an empirically sufficient theory Built into both deterministic and stochastic theory are parameters and combinations of parameters that are not measurable to the degree of accuracy required.”

Importantly, none of these theories were tested with more realistic assumptions introducing the additional costs of gamete overproduction (see chapter 8.1), and decreased benefit of sex due to canalization (the buffering of deleterious mutations, see chapter 10.4) and phenotypic plasticity. One can predict that with these assumptions, explaining the evolutionary rationale of sex within the framework of population genetics principles would have ended in a grandiose failure.

18.1.1 Flawed static concepts

I always go by official statistics because they are very carefully compounded and, even if they are false, we have no others ...

Jaroslav Hašek, 1911

There is a message hidden in Hašek’s aphorism (Baluška and Mancuso, 2007). “All those mathematical models, scientific theories and concepts, however appealing, harmonious and long-standing ... but which do not correspond to reality ...; inevitably will be ‘killed by ugly’ facts generated by scientific progress, and

finally replaced by new models, theories, and concepts” (Baluška and Mancuso, 2007). A fundamental weakness of mathematical modeling is, as was conceded by Maynard Smith and Brookfield (1983): “A mathematical model is only as good as its assumptions.” (And the assumptions are often rather dictated by computational constraints than by evolutionary reality). However, the assumptions of the genetic theories of sexual reproduction are not based on evidence but deduced from assumed laws or premises set up by population genetic theory (Fisher, 1930). With the “right” assumptions it is even possible to model that under evolving mutation rates, asexuals are able to spread to fixation even when sexuals faced no cost of sex whatsoever (Sloan and Panjeti, 2009). Empirical observations that were made to support the genetic theories showed the long-term advantage of sexual reproduction but did not vindicate the genetic theories despite assertions to the contrary (Rice, 2002). And so, with regard to the genetic theories of sexual reproduction, in Hašek’s sense “even if they are false, we have no others ...”.

Fitness effects of mutations strongly depend on genotype (epistasis) and environment (Cuevas et al., 2002; Elena and de Visser, 2003; Kishony and Leibler, 2003). Regulatory plasticity generates a distribution of phenotypes of a given genotype in response to variation in the environment, or a norm of reaction (Schlichting and Pigliucci, 1998), a term originally coined by Woltereck (1909). All theories come down to the fact that a broad reaction norm smoothes the path of increasing fitness (Frank, 2011). Whether a mutation is adaptive or maladaptive is not an inherent property of the mutation itself but is determined by the environmental conditions (including the genetic background, Estes and Teotónio, 2009) in which the mutation manifests its fitness effects. Adaptation to a new environment will often have negative pleiotropic effects on fitness in the original environment, the so-called ‘cost of adaptation’ (Bell and Rebound, 1997; Agrawal, 2000a; Kassen, 2002; Strauss et al., 2002; Palaima, 2007; Hereford, 2009). There is extensive evidence for the occurrence of genotype x environment interactions (Falconer and Mackay, 1996). In this sense, any adaptive, “beneficial” trait in one environment may become maladaptive, “deleterious” in another ecological context (Elena and de Visser, 2003; Kishony and Leibler, 2003). A population can adapt to a sudden environmental change by using either new mutations or alleles from the standing genetic variation. In the first case the population must wait for the appearance of the desired allele, while in the second it can respond immediately. Species with larger population sizes may have more

standing variation with which to respond to novel selection pressures, leading to a smaller fraction of adaptations from new mutations (Hermisson and Pennings, 2005; Leffler et al., 2012). If a population uses standing variation, the alleles selected may have been previously neutral or deleterious and are maintained in the ancestral population through a balance of recurrent mutation, selection and drift (Orr and Betancourt, 2001; Hermisson and Pennings, 2005; Przeworski et al., 2005; Barrett and Schluter, 2008; Pritchard et al., 2010). It has been shown theoretically (Falconer and Mackay, 1996; Kawecki, 1997; Orr and Betancourt, 2001; Lenski et al., 2003; Hermisson and Pennings, 2005; Cowperthwaite et al., 2006) and experimentally (Mills et al., 1967; Futuyma and Moreno, 1988; Fry, 1990; Bennett and Lenski, 1993; Cooper and Lenski, 2000; Elena and Lenski, 2003; Barrett and Schluter, 2008; Beaumont et al., 2009; Philippe et al., 2009; Seixas et al., 2012) that the properties of mutations, whether beneficial or deleterious, are not fixed but depend on a variety of ecological and genetic factors. Thus, a variety of environmental stresses' influence on deleterious mutations is strongly biased towards the alleviation of mutation effects (Kishony and Leibler, 2003). Due to the costs of adaptation (Kassen, 2002; Hereford, 2009; Fankhauser, 2010), traits that are disadvantageous at one time and environmental condition may be advantageous at another and vice versa (Ellner et al., 1999; Grant and Grant, 2002; Kassen, 2002; Kishony and Leibler, 2003; Childs et al., 2004; Seamons et al., 2007; Sletvold and Grindeland, 2007; Robinson et al., 2008; Beaumont et al., 2009; Simons, 2009; 2011; Greene et al., 2010).

A couple of examples may illustrate the issue. Probably the earliest known demonstration of the existence of a cost of adaptation was an experiment by the Rev. Dallinger (1887), who grew bacteria at steadily increasing temperatures for 7 years. The optimum temperature for his founding population was between 15.5 and 18.3 °C. By the end of his experiment these bacteria were growing and reproducing normally at 70 °C, well beyond their normal thermal limit of 60 °C, but did no longer survive at the ancestral 15.5 °C optimum. Crow (1957) was the first to predict that resistance alleles should have fitness costs in the absence of the selective agent. It can be expected that resistance carries costs when it is not needed, lowering the fitness of defended individuals in the absence of enemies (Rhoades, 1979, Simms and Rausher, 1987, Clark and Harvell, 1992, Sheldon and Verhulst, 1996; Jokela et al., 2000). This prediction has been verified in plants for herbicides, pathogens, and herbivores (Simms and Rausher,

1987; Simms and Triplett, 1994; Bergelson and Purrington, 1996; Purrington and Bergelson, 1999; Burdon and Thrall, 2003; Vila-Aiub et al., 2009), in animals for pathogen resistance (Kraaijeveld and Godfray, 1997; Yan et al., 1997; Langand et al., 1998; Searle and Blackwell, 1999; Webster and Woolhouse, 1999; Woolhouse et al., 2002; Carton et al., 2005), in bacteria for antibiotic resistance (Andersson and Levin, 1999; Komp Lindgren et al., 2005; Andersson, 2006; Rozen et al., 2007; Andersson and Hughes, 2010), and in many pest species for pesticide resistance (Roush and McKenzie, 1987; Andreev et al., 1999; Coustau et al., 2000; Bourguet et al., 2004). Likewise, defences themselves are costly and therefore enhance fitness only when enemies are present (Lively, 1986; Moran, 1992). Individuals with chemical or behavioral defences against predators or herbivores may enjoy high fitness in risky environments compared with undefended individuals, whereas the undefended phenotype may do better in the absence of risk (De Meester et al., 1995; Van Buskirk et al., 1997; Agrawal, 2000b; van Hulten et al., 2006). Whereas studies of susceptibility and pathogenicity generally take a static view of the underlying population genetics, co-evolution is a dynamic process: if host and pathogen co-evolve, then a 'good' gene in one time and place may be a 'bad' gene in another time and place (Woolhouse et al., 2002). Having eyes, due to their energetic costs, is clearly "deleterious" when an animal is living in a cave (Heininger, 2012). "Thrifty" genotypes are "beneficial" during times of food shortage but are clearly "deleterious" in times of nutritional abundance, as is highlighted by the epidemics of non-insulin-dependent diabetes mellitus and obesity in indigenous populations exposed to Western diets (Neel, 1962; Crespi, 2010; Chakravarthy and Booth, 2004; Prentice et al., 2005; Gluckman and Hanson, 2006; Hancock et al., 2010; Carrera-Bastos et al., 2011). The decline of lactase activity after the suckling period is a physiological, beneficial process in all mammals (Sebastio et al., 1989; Buller et al., 1990; Lacey et al., 1994). However, in dairy economies adult lactose maldigestion may become deleterious and has been profoundly selected against (McCracken, 1971; Gudmand-Høyer, 1994; Vesa et al., 2000; Matthews et al., 2005; Hancock et al., 2010). Thus, lactase gene expression has evolved repeatedly to continue throughout life in dairy farming populations in Europe, East Africa, and the Middle East (Bersaglieri et al., 2004; Harris and Meyer, 2006; Tishkoff et al., 2007; Enattah et al., 2008; Ingram et al., 2009).

Owing to the dynamics of evolution, the beneficial or deleterious value of mutations may change repeatedly.

For example, the selective value of a genotype is frequency dependent when its contribution to the following generation relative to alternative genotypes varies with the frequency of the genotype in the population (Ayala and Campbell, 1974). As a gene conferring disease resistance spreads through a population, the incidence of infection declines, reducing the fitness advantage of carrying the resistance gene. Thus genes conferring complete resistance cannot become fixed (i.e., universal) by selection in a host population, and diseases cannot be eliminated solely by natural selection for host resistance (Roy and Kirchner, 2000). Moreover, this frequency-dependent selection has its short- and long-term components. In the latter, density dependence becomes essential (Heino et al., 1998). Moreover, an adaptive mutation's effect may depend on the presence of other, possibly nonadaptive, mutations (Zuckermandl and Pauling, 1965; Lockless and Ranganathan, 1999; Reetz et al., 2005; Weinreich et al., 2006; Bloom and Arnold, 2009; Breen et al., 2012). Particular mutations appear to have different effects in high- versus low-fitness virus lines (Silander et al., 2007) and more complex organisms such as *C. elegans* (Estes and Lynch, 2003; Betancourt, 2007).

If one considers mutations at more than one locus, they may combine in several ways in their final effect on fitness. Two mutations that individually have no significant effect on a trait under selection can in combination be highly advantageous or deleterious. Well known examples for such epistatic interactions (Phillips, 2008) include resistance evolution in pathogens (Hall, 2002; Weinreich et al., 2006; Lozovsky et al., 2009) or metabolic changes in yeast (Segrè et al., 2005). Epistasis describes an important property of genotype-phenotype maps: the phenotypic effect of a genetic change at a single locus may depend on the values of other genetic loci, in other words, the nonlinear interaction of effects among alleles at different loci (Wolf JB et al., 2000). That such correlations should exist is not at all surprising. Given the many multi-scale physical processes involved in translating a genotype into a phenotype, it is rather the absence of epistasis that might be expected to be the exception to the rule (Schaper et al., 2011). Genetic constraint on fitness landscapes is due to fitness epistasis, where a mutation's adaptive value depends on the genetic background in which it arises (Phillips, 2008). Sign epistasis occurs when mutations are beneficial within the context of some genetic backgrounds, but detrimental within others. To exhibit multiple fitness peaks, a biological system must contain reciprocal sign epistatic interactions, which are defined as genetic changes that are separately

unfavorable but jointly advantageous. Reciprocal sign epistasis should be pervasive in nature as it is a logical consequence of specificity in molecular interactions and it creates rugged fitness landscapes (Weinreich et al., 2005; 2006; Poelwijk et al., 2007; 2011; Schoustra et al., 2007; Carneiro and Hartl, 2010; Kvitek and Sherlock, 2011). The presence of sign epistasis was established in several recent experimental studies, where all combinations of a selected set of individually beneficial or deleterious mutations were constructed and their fitness effects (or some proxy thereof) were measured (Weinreich et al., 2006; Lozovsky et al., 2009; de Visser et al., 2009; Carneiro and Hartl, 2010). In genetic networks that differ in their complexity and robustness against perturbations but that perform the same tasks, robustness increased with complexity and epistasis was found to be positive for small nonrobust networks but negative for large robust ones (Macía et al., 2012). Epistasis is pervasive in long-term protein evolution: about 90 per cent of all amino-acid substitutions have a neutral or beneficial impact only in the genetic backgrounds in which they occur, and must therefore be deleterious in a different background of other species (Breen et al., 2012): This raises the possibility that similar epistatic interactions may be prevalent in short-term evolution (Salverda et al., 2011; Woods et al., 2011) and that situations when a polymorphism is benign or beneficial to one individual but deleterious to another individual within the same population may be more common than is thought at present (Breen et al., 2012). An *in silico* evolution experiment (Lenski et al., 2003) demonstrated that a mutation that was highly deleterious when it appeared was highly beneficial in combination with a subsequent mutation. In some cases, mutations that were deleterious when they appeared served as stepping-stones in the evolution of complex features.

Under these circumstances, the beneficial-deleterious distinction becomes a moving target. **Fisher (1930) was able to show that, unless the degree of inbreeding varies or the environment deteriorates, the mean fitness always increases (MacArthur, 1962). However, Fisher thought that environmental changes are so ubiquitous that, as he once said, Wright's peaks and valleys are more like the undulating wave crests and troughs of an ocean than a mountainous landscape. He believed that a population rarely, if ever, finds itself in a position where no allele frequency change could increase its fitness (Crow, 1987). This forces us to think of selection itself as a dynamical process, that is, to promote the static picture of fitness landscapes to dynamic fitness "seascapes". Recently, the static**

concepts of fitness and fitness landscape were supplemented by the dynamic concepts of fitness seascape (Mustonen and Lässig, 2010) that takes the ever changing nature of environmental conditions into account. The dynamical approach leads to a quantitative measure of adaptation called fitness flux, which counts the excess of beneficial over deleterious genomic change (Mustonen and Lässig, 2009). The recently formulated fitness flux theorem generalizes Fisher's fundamental theorem of natural selection to evolutionary processes including mutations, genetic drift, and time-dependent selection. It shows that a generic state of populations is adaptive evolution: there is a positive fitness flux resulting from a surplus of beneficial over deleterious changes. Fitness flux is a universal measure of adaptation in molecular evolution (Mustonen and Lässig, 2010). An increase of cumulative fitness flux is an almost universal evolutionary principle of biological systems. Positive contributions to the fitness flux arising from adaptive genotype changes accumulate over evolutionary periods of time. Negative contributions are limited to time intervals with a systematic loss of adaptation which cannot occur continuously in viable populations. These predictions are in accordance with experiments in bacteria and bacteriophages and with genomic data in *Drosophila*. In this sense, fitness flux is a more fundamental characteristic of evolution than fitness, for which no comparable growth law holds (Mustonen and Lässig, 2010).

The genetic theories of sexual reproduction completely ignore a variety of gene x environment interactions:

- the fitness effects of genes only unfold within a certain ecological context
- a multitude of genes has pleiotropic effects, that can be both synergistic or antagonistic, i.e. many genes may have both beneficial and deleterious effects (e.g. on soma and germline cells) that can be described by cost-benefit trade-offs (see Heininger, 2012)
- alleles have both frequency- and density-dependent effects
- epistatic effects are widespread and may be both synergistic and antagonistic and highly context-specific (sign epistasis)
- the phenotypic effects of genes are subject to profound epigenetic regulation and canalization hiding deleterious mutations from purging by selection
- the fitness landscape is in constant motion and should rather be described as fitness seascape (as already perceived by Fisher, see Crow, 1987)

Finally, Muller's ratchet and Kondrashov's hatchet face

a fundamental dilemma. Evolution depends on genetic variation (Whitehead and Crawford, 2006). Classical theory holds that genetic variation is largely determined by neutral and slightly deleterious mutations (Barton and Turelli, 1989; Charlesworth and Hughes, 2000). Neutral mutations, since they, by definition, should not be seen by selection should not have any influence on the selective advantage of sexual reproduction. If Muller's and Kondrashov's theories would be correct, sexual reproduction would reduce genetic variation, slowing evolvability in variable environments.

18.1.2 Flawed teleological concepts

Evolution is not teleological in the sense that its processes or actions are for the sake of an end, i.e., the Greek "telo" or final cause. Clearly, once an organism has survived and/or reproduced one can point to its various attributes and say "yes, that attribute appears to have contributed to the organism's survival/reproduction". However, that is no more evidence of "foresightedness" than a lottery winner saying "I chose these lottery numbers (or bought those particular scratch-off tickets) because I knew they would be winners". This is known as the "fallacy of affirming the consequent" (also called post hoc, ergo propter hoc argumentation) and is logically inadmissible in the natural sciences (MacNeill, 2009). 'Backwards causation', by which some future state or event influences ('causes') an action in the present or past, is often characteristic of teleological arguments. The Modern Synthesis took pride in having discouraged such thinking (Mayr, 1992).

On the basis of genome-wide sequencing it has been estimated that, on average, each person carries approximately 250 to 300 loss-of-function variants in annotated genes and 50 to 100 variants previously implicated in inherited disorders (The 1000 Genomes Project Consortium, 2010). There is no reason to think that in other species the situation is fundamentally different. (Although, maybe the relaxed selection in modern human societies has aggravated the situation. But, on the other hand, this relaxed natural selection does not yet exist for too many generations and the SMSCs keep relaxed natural selection from doing too much harm.) Obviously, evolution and its bet-hedging strategy tolerate a lot of imperfection. Presumably, every organism is a mosaic of beneficial and deleterious mutations. Mind you, probably hundreds of both. Could recombination work assortative to combine the deleterious and beneficial mutations in separate organisms? On the basis of which information? Assuming that recombination, a quasi-stochastic, uncoded, process with e.g. an

estimated 25,000–50,000 crossover hotspots in the human genome should be able to help natural selection to discriminate between beneficial or deleterious mutations, in essence implies that evolution is understood to be designed and foresighted. Isn't it more probable that recombination just shuffles the mutations in varying composition irrespective of their fitness value? And often enough the deleterious mutation is not "seen" by evolution due to canalization. And who knows, maybe around the evolutionary corner the now deleterious mutation is the stepping stone of an innovation (Lenski et al., 2003)? In the end, what really counts is the compound effect of beneficial and deleterious mutations and most of all the variation.

The genetic theories use an outcome measure (the deleterious or beneficial fitness effect of a mutation) to explain the evolutionary rationale of sexual reproduction. The only evolutionary process that can differentiate between deleterious and beneficial mutations is natural selection that selects organisms for their reproductive success (Ellegren and Sheldon, 2008). The Modern Synthesis' concept of natural selection is only plausible when one assumes a straightforward causation of phenotype by genotype (Huang, 2012). However, such simple 1:1 mapping must now give place to the concepts of gene regulatory networks and gene expression noise. Both can, even in the absence of genetic mutations, jointly generate a diversity of inheritable randomly occupied phenotypic states that could serve as a substrate for natural selection (Huang, 2012). Sexual reproduction uses several genetic and epigenetic tools such as mutations, epimutations, recombination, transposon mobility and mutability of simple sequence repeats that may yield functionally equivalent fitness results. This degeneracy of the molecular tools in addition to the stochasticity of the genotype-phenotype mapping are so ambiguous that no certain molecular process can be assigned to a phenotypic effect. Thus, the myriad of molecular processes that determine an individual's phenotype have no built-in sensor and allow no feedback that informs about the selective value of an action. These processes are totally blind with regard to their fitness-relevance.

According to Darwin (1859) evolutionary trajectories are determined not by the individuals in the trailing tail of the fitness distribution but by the more competitive, fitter individuals. It can hardly be advocated that the evolutionary success of sexual reproduction is based on purging the population from less fit individuals. Accordingly, the model proposed by Kondrashov has been criticized for modeling assumptions far from

real-world observations (MacCarthy and Bergman, 2007). In fact, Wallace advocated the elimination of the unfit (Smith CH, 2012a; b) but this elimination is brought about by competition with the fitter individuals. Beneficial mutations that do occur are much more likely to achieve long-term evolutionary success and the dynamics of populations than deleterious mutations (Haldane, 1927; André and Godelle, 2006; Patwa and Wahl, 2008). Several mathematical models have demonstrated that deleterious mutations do not contribute significantly to overall evolutionary dynamics in larger populations when at least some fraction of mutations is beneficial (Rouzine et al., 2003; 2008; Desai and Fisher, 2007; 2011; Desai et al., 2007; Zeyl, 2007; Fogle et al., 2008; Park SC et al., 2010). Accordingly, as has been shown by Hallatschek (2011), evolutionary dynamics of an asexual population are determined by traveling waves of increasingly fitter genotypes (Fisher, 2011; Hallatschek, 2011). These theoretical findings were confirmed by experimental evolution dynamics: in the process of periodic selection, evolution is characterized by a series of clonal replacements, and diversity is reduced each time a beneficial mutant arises and sweeps through the population (Novick and Szilard, 1950; Atwood et al., 1951; Zambrano et al., 1993; Radman et al., 1999; Elena and Lenski, 2003; Maharjan et al., 2012). Thus, evolutionary dynamics are rather determined by fitness-dependent competition between members of the population than the accumulation of deleterious mutations (Maharjan et al., 2012). Since deleterious mutations do not affect adaptive evolution in asexual populations, the theoretical, so far even unproven, consideration that sexual reproduction may be able to purge the genome from deleterious mutations by truncation selection hardly can serve as rationale for the evolutionary origin of sexual reproduction. Moreover, selection reduces the effect of Muller's ratchet over time (Itoh et al., 2002; Allen et al., 2009). The operation of Muller's ratchet, resulting in mutational meltdown (Lynch et al., 1993; Vrijenhoek, 1998) may be a consequence of being not sexual, but it cannot serve as rationale for the origin of sexual reproduction which has to be searched at the other end of the fitness distribution, contingent upon the evolutionary dynamics of beneficial mutations. Thus, sexual selection does prevail because it is able, at least under most ecological conditions, to generate **and** select for the fitter individuals. Thus, when competitive fitness, as in K-selected habitats is relevant, sexual reproduction prevails.

18.2 DNA repair

The DNA repair hypothesis for the maintenance of sex invokes a proximate (or mechanistic) explanation positing that recombination is necessary for the repair of double-strand DNA damage eliminating new genetic variation (Bernstein et al., 1984; 1985a; Bernstein and Bernstein, 1991; Michod, 1993). Cells with DNA damage have been shown to undergo sex at higher rates in viruses (Bernstein, 1987), bacteria (Wojciechowski et al., 1989), and yeast (Bernstein and Johns, 1989). It was suggested that the evolutionary function of transformation may be to provide template strands for DNA repair (Felsenstein, 1974; Bernstein et al., 1985a; b; 1989; Michod et al., 1988; 2008; Long and Michod, 1995; Hörandl, 2009). As consequence of the maintenance of ploidy, elimination of chromosomal rearrangements and DNA repair by homologous recombination, sexual reproduction may reduce genetic variation (Shields, 1982; 1988; Gorelick and Heng, 2011). In fact, many proteins that function during somatic DNA-damage detection and repair are also active during homologous recombination. However, their meiotic functions may be altered from their somatic roles through localization, posttranslational modifications and/or interactions with meiosis-specific proteins (Marcon and Moens, 2005). Redfield (1993a; b) argued that if DNA repair is the primary function of transformation, one would expect competence to be regulated by DNA damage. However, this is not the case in *B. subtilis* and *H. influenzae* (Redfield, 1993a). Szathmáry and Kövér (1991) tested the repair hypothesis by comparing outcrossing sexuality with a hypothetical parthenogenic strategy (the Prudent Repairator) which destroys as little heterozygosity during repair as possible. The Prudent Repairator could solve the problem of repairing damage as well as that of invading an existing outcrossing population. They concluded, as we do not see this strategy widely adopted instead of sexuality, the repair hypothesis is likely to miss some essential feature of the evolution of sex. Burt (2000) asked: "Why should sexual taxa carry the costs of sex if they could engage in asexual DNA repair, e.g. by ameiotic recombination, at considerably lower costs?" Burt (2000) dismissed the idea that "meiotic crossing-over is just an incidental by-product of DNA repair processes" by arguing: "The most pressing problem with the idea is that (meiotic) crossing-over involves only one of the two sister chromatids of each chromosome, and so under the hypothesis only one of them should be damaged. However, if this is the case, why not just repair it with the sister chromatid? This is what usually happens in mitotic cells if damage occurs between DNA replication and cell division (Fabre et al., 1984; Kadyk

and Hartwell, 1992). However, in meiotic cells, the preferred template for "repair" is the homolog, not the sister chromatid (Schwacha and Kleckner, 1994; 1997). This is as expected if the function of meiotic crossing-over is to produce recombinant chromosomes, but not if it is simply to repair broken chromosomes."

Many asexual taxa are thought to be particularly efficient in DNA repair, which would allow them to reduce the accumulation of deleterious mutations (Castonguay and Angers, 2012). There is evidence for this in asexual taxa such as asexual weevils (Tomiuk and Loeschcke, 1992), aphids (Normark, 1999), darwinulid ostracods (Schön et al., 1998), *Daphnia* (Omilian et al., 2006), and oribatid mites (Schaefer et al., 2006). This led Schaefer et al. (2006) to ask "why not more taxa are ancient asexuals if the long-term disadvantages of parthenogenetic reproduction can be defeated."

Stressing the conservative role of sexual reproduction, the proponents of the DNA repair hypothesis largely ignore the innovative role of sex (but see Hörandl, 2009). Whether recombination is DNA reparative, or mutagenic is condition-dependent. Thus, recombination as genetic variability- and innovation-creating mechanism (Bürger, 1999; Ochman et al., 2000; Narra and Ochman, 2006; Jeon et al., 2008) was advocated as the evolutionary rationale of bacterial transformation and hence the evolution of sex, while the role of DNA repair was contested (Mongold, 1992; Redfield, 1993a; Redfield et al., 1997). In microorganisms environmental stress can alter the balance between stability/repair and mutagenesis/exploration/bet-hedging (Foster, 2005). In an *E. coli* model, stationary-phase sigma factor RpoS (which encodes the stress response σ^S transcription factor)-controlled switch from high-fidelity to mutagenic double-strand break repair activates stress-induced mutagenesis during stationary phase/starvation (Ponder et al., 2005). *B. subtilis* has similar stationary phase/starvation-dependent mutagenic programs (Robledo et al., 2007). Lower levels of oxidative stress favor DNA repair while higher levels favor mutagenesis (Greenberg and Demple, 1988; DeRose and Claycamp, 1991; McBride et al., 1991; Escarceller et al., 1994; Kato T et al., 1994; Blanco et al., 1995; Hu et al., 1995; Touati et al., 1995; Urios et al., 1995; Wang and Humayun, 1996; MacPhee, 1999; Ruiz-Laguna et al., 2000; Bjedov et al., 2003; Cooke et al., 2003). Cellular stress also downregulates DNA repair and elicits mutagenesis in mammals (see chapter 10.1). Importantly, the repair/mutagenesis balance is modulated by

interactions with heat shock proteins (Liu and Tessman 1990a; b; Donnelly and Walker, 1989; 1992; Petit et al., 1994) which, in dependence of the cellular energy level may provide the regulatory feedback with cellular metabolic/oxidative homeostasis and its derangement during stress (MacPhee, 1985; 1994; 1996; Seetharam and Seidman, 1992, Keszenman et al., 2000).

Different evolvability characteristics can be optimal under different circumstances as suggested by experimental studies in a variety of organisms (Drake et al., 1969; Nöthel, 1987; Sniegowski et al., 1997; Schapper, 1998), and computational evolutionary models (Bedau and Packard, 2003; Clune et al., 2008; Dees and Bahar, 2010). The fossil record indicates that evolutionary dynamics proceed by punctuational episodes rather than gradual change (Eldredge and Gould, 1972; Gould and Eldredge, 1977; 1993; Sneppen et al., 1995; Eldredge et al., 2005). In well adapted populations living in stable habitats, conservation may become more important than innovation. Well-documented examples of stasis range from Paleozoic brachiopods (Lieberman et al. 1995) to late Cenozoic bivalves (Stanley and Yang, 1987) and bryozoans (Jackson and Cheetham, 1999). But species-wide depletion of accessible beneficial mutations requires a degree of environmental constancy that is not typical of the earth's history (Lambeck and Chappell, 2001; Zachos et al., 2001; Eldredge et al., 2005). Evolutionary models based on the asexual and sexual replication pathways in *Saccharomyces cerevisiae* suggested that sexual replication can eliminate genetic variation in a static environment, as well as lead to faster adaptation in a dynamic environment (Gorodetsky and Tannenbaum, 2008).

18.3 Host-parasite coevolution: the Queen abdicates in favor of the pluralistic, coevolving web of life

Now here, you see, it takes all the running you can do, to keep in the same place.

Lewis Carroll: Through the Looking Glass

The cited lines were the Red Queen's explanation to a confused Alice as to why she could run as fast as she could in Wonderland but never get anywhere, a situation analogous to the constant evolutionary pressure exerted by a changing environment. Species evolve in response to their biotic environment and this can lead to coevolution between species that interact in either a mutualistic or an antagonistic fashion (Futuyma and Slatkin, 1983). Parasites are generally under selection to infect the most common genotypes

in the local host population, assuming that (i) they contact hosts at random and (ii) that the different parasite genotypes are only able to infect a subset of the host-resistance genotypes. This parasite-mediated frequency-dependent selection can then lead to genetic polymorphism in both the host and parasite, as first recognized by Haldane (1949). Hence, if an asexual clone becomes the most common genotype in an otherwise sexual population, the parasites would be expected to quickly evolve to infect it. If the parasites evolve to disproportionately infect the clone, they may prevent, or help prevent, the clone from replacing the sexual population (e.g., Jokela et al., 2009). Thus, it is argued that parasites have contributed to the short-term maintenance of sex, even if they do not drive the clone to extinction (Lively, 2010). Accordingly, one of the most widely accepted hypotheses posits that sexual reproduction evolved in hosts to counter the pressure of parasitic coevolution (Levin, 1975; Jaenike, 1978; Hamilton, 1980; Hamilton and Zuk, 1982; Hamilton et al., 1990; Howard and Lively, 1994; 1998; 2002; Møller and Saino, 1994; Able, 1996; John, 1997; Ooi and Yahara, 1999; Martins, 2000; Agrawal, 2006a; Salathé et al., 2008; Lively, 2010; Morran et al., 2011). The "Red Queen" hypothesis predicts an immediate advantage of being sexual, essentially because the highly diverse offspring resulting from sexual reproduction provide a moving target for parasites, whereas the genetically very uniform offspring of clonal females should be easily exploited by parasites. This type of "over-reactive" frequency-dependent selection has been shown to lead to cyclical dynamics, where parasites eventually track common host genotypes and, assuming there is a fitness cost associated with infection, drive them to lower frequency (Hamilton, 1980; Neiman and Koskella, 2009). The occurrence and characteristics of the predicted oscillatory cycles have been the focus of numerous theoretical and empirical studies (e.g., Jaenike, 1978; Bell, 1982; Hamilton et al., 1990; Dybdahl and Lively, 1998; Koskella and Lively, 2007). Covariance between the relative frequency of sex/outcrossing and the frequency of parasitism is now established in a wide range of taxa, providing broad but indirect support for a role for the Red Queen in the maintenance of sex (Lively, 1987; 1989; 1999; Lively et al., 1990; Moritz et al., 1991; Schrag et al. 1994; Lively and Dybdahl, 2000; Lively and Jokela 2002; Busch et al., 2004; Kumpulainen et al., 2004; Lively et al., 2004; Fischer and Schmid-Hempel, 2005; Tobler and Schlupp, 2008; Jokela et al., 2009; King et al., 2009; King and Lively, 2009; Morran et al., 2011). A number of studies indicate that host genetic diversity plays an important

role in buffering populations against widespread epidemics, and that parasites represent powerful selective agents in natural populations (Jokela and Lively, 1995; Gaffney and Bushak, 1996; Dwyer et al., 1997; Paterson et al., 1998; Coltman et al., 1999; Little and Ebert, 1999; 2001; Hedrick et al., 2001; Altizer et al., 2003; Paterson et al., 2010). Comparative studies have found particularly high rates of molecular evolution in genes associated with infection (Buckling and Rainey, 2002b; Brockhurst et al., 2003; Blanc et al., 2005; Mu et al., 2006; Barrett et al., 2009; Paterson et al., 2010) or resistance to infection (Hedrick, 1994; Hughes et al., 1994; Kuma et al., 1995; Obbard et al., 2006; Clark et al., 2007). It has been argued that escape from coevolving parasites allows desiccation-tolerant rotifers (Wilson and Sherman, 2010) and microscopic algae that alternate between virus-sensitive diploid and virus-resistant haploid phases (Frada et al., 2008) to keep up asexual reproduction, vindicating the Red Queen hypothesis (Leung et al., 2012). Likewise, desiccation-tolerant (Clegg, 2005) and diapausing eggs (Lass and Ebert, 2006) may represent an escape strategy from infectious agents (Ladle et al., 1993).

However, the role of host-parasite interactions for the maintenance of sexual reproduction is not uncontested. Empirical studies testing the predictions of the Red Queen hypothesis have also shown negative results (Brown et al., 1995; Hanley et al., 1995; Vernon et al., 1996; Weeks, 1996; Ben-Ami and Heller, 2005; 2008; Tobler and Schlupp, 2005; 2008; Killick et al., 2008; Elzinga et al., 2012). Data from cyclical parthenogenetic *Daphnia* even suggest that sexual reproduction may erode immunocompetence (see also Heininger, 2012) and could inhibit the evolution of parasite resistance (Duncan et al., 2006). Furthermore, the host-parasite coevolutionary dynamics that are required for operation of the Red Queen select for genetic diversity rather than sex per se (Lively and Howard, 1994). This means that, all else being equal, a genetically diverse array of asexual lineages is as well-equipped to deal with parasitism as a sexual population (Glesener and Tilman, 1978; Lively and Howard, 1994; Lythgoe, 2000). Accordingly, positive associations between parasitism and outcrossing are not a ubiquitous feature of mixed sexual/asexual animal (Ben-Ami and Heller, 2005; 2008) and plant populations (Parker, 1994). Stearns (1990) argued that parasites, and the diseases they cause, are only important agents of selection when they have significant consequences for the fitness of the host. Reduced virulence and prevalence of, and increased resistance to, parasites may work against the maintenance of sexual reproduction. The strong

selection required to maintain sex in many models has also been a source of concern for many theoreticians because it implies that only very virulent and/or highly prevalent parasites will be able to maintain sex and outcrossing (May and Anderson, 1983; Howard and Lively, 1994; Ochoa and Jaffé, 1999; Otto and Nuismer, 2004; Peters and Lively, 2007; Salathé et al., 2008; Neiman and Koskella, 2009). In a broad-scale assessment of ecological and genetic interactions that could underpin the Red Queen process, Otto and Nuismer (2004) concluded that interactions between species are an unlikely explanation of the prevalence of sex (given the restricted definition of sex = recombination). If anything, species interactions select against higher levels of recombination. To derive general results, an assumption was made that the populations studied were at quasi-linkage equilibrium (QLE). This assumption follows from Barton's (1995) genome-wide model for studying the evolution of recombination, which Otto and Nuismer extended to several interacting species. As QLE means that host and parasite populations are essentially able to track changes in the genotypic composition of one another's populations, the negative effect of increased recombination predominates. There is therefore little advantage to modifiers that increase the rate of recombination. Even if the modifier becomes associated with rare favored combinations, this advantage is weak when recombination is frequent and is swamped by the cost of producing unfit combinations of alleles (Pomiankowski and Bridle, 2004).

Coevolutionary interactions in a dynamic ecosystem are highly pluralistic (Stenseth, 1985; Dieckmann and Law, 1996; Raffel et al., 2008; Thompson, 2009). This amounts to allowing feedbacks to occur between the evolutionary dynamics of a species and the dynamics of its environment (Lewontin, 1983). Abiotic and biotic environments are highly variable across space and time. Nature is relentlessly tooth-and-claw, continually reshaping the evolution of antagonistic interactions within and among species such as predator-prey interactions (Glesener, 1979; Yoshida et al., 2003). And, species inherently form intraspecific and interspecific partnerships that are often commensalistic or mutualistic and allow diversification into new adaptive zones. Populations continually evolve and interacting species continually coevolve, building a constantly coevolving web of life (Thompson, 2005; 2009). Thus it has a too narrow scope to only concede host-parasite interactions the status of a "queen-maker". It is the incessantly changing biotic and abiotic environment acting in Red Queen and Court Jester dynamics (Benton, 2009; Ezard et al.,

2011) whose adaptive stress on organisms may interact condition-dependently (Murray et al., 1998; Folt et al., 1999; Siva-Jothy and Thompson, 2002; Harley, 2003; Vinebrooke et al., 2004; Bolnick and Preisser, 2005; Mitchell et al., 2005; Kolluru et al., 2006; Beketov and Liess, 2007; Doroszuk et al., 2007; Rollo, 2007; Coors and De Meester, 2008; Ebert, 2008; Seppälä and Jokela, 2010; Violle et al., 2010; Seppälä et al., 2011) making sexual reproduction the superior reproductive strategy (Gessler and Xu, 2000; West et al., 2001; Hadany and Beker, 2003b; Hadany and Otto, 2007; 2009; Schoustra et al., 2010). Taken together, host-parasite coevolution is only one of a multitude of factors in a world of coevolutionary ecological webs (Thompson, 2005; 2009) that select for risk-spreading bet-hedging.

19. Evolutionary enigmas and controversies

Understanding sex and recombination has been perhaps the most puzzling issue in evolutionary biology—which suggests that its solution might give us a much better intuition about the evolutionary process in general.

NH Barton (2010)

Summary

Recognizing both stochasticity and selection as the organizing principles of evolution helps to resolve some of the most enigmatic characteristics and long-standing controversies of evolution, including the selection-genetic variation enigma, the levels of selection controversy, the selectionist-neutralist controversy, the adaptationism controversy and the mystery of low heritability. All of them are based on the perpetual combat of chaos and order, uncertainty and direction, between arithmetic and geometric mean fitness, making choices to optimize either individual- and population-level fitness. During the rise in atmospheric oxygen, sexual reproduction appears to have “learned” to use oxidative stress as evolutionary innovation that gave the coevolutionary germ-soma conflict an unprecedented dynamic, resulting in the Cambrian explosion.

The obvious environmental modulation of patterns of inheritance has renewed interest in Lamarckian-type interpretations of evolutionary processes. However, the concepts advocating a

Lamarckian type of evolution did not take into account that the various processes, perfectly designed as they may appear, have inherently stochastic elements that allow a large sampling of the (epi)genetic search space. Selective sampling from this quasispecies cloud makes the process Darwinian. Darwinian principles of quasi-stochastically generated variation and selection also operate between sub-organismal entities, e.g. organelles and cells. If the process of germ cell competition generating pre-selected variation is overlooked, phenotypically the impression of a Lamarckian-type evolutionary process may be created.

Reproduction systems affect many population genetic processes, and thus genome evolution. Accordingly, the presented insight into sexual reproduction-related mutagenesis-selection cascades can shed light on a variety of evolutionary enigmas and controversies. Importantly, recognizing the dualism of stochasticity and selection in evolution helps to resolve some of these enigmas, e.g. the levels of selection enigma, the selection-genetic variation enigma, the adaptationism controversy, and the mystery of low heritability.

19.1 The selection-genetic variation enigma

A conundrum of evolutionary biology and population genetics is the coexistence of two basic observations (Walsh and Blows, 2009; Leffler et al., 2012): in natural populations genetic variation is found in almost all traits (Mousseau and Roff 1987; Houle 1991; 1992; 1998; Hill and Caballero 1992; Lynch and Walsh, 1998) in the presence of strong stabilizing natural and sexual selection (Haldane, 1949b; Clarke, 1979; Endler, 1986; Kingsolver et al., 2001; Hereford et al., 2004; Johnson and Barton, 2005). These two observations are in direct conflict as stabilizing selection should deplete genetic variation (Tomkins et al., 2004; Johnson and Barton, 2005; Walsh and Blows, 2009). Two main models of stabilizing selection have been developed. In one, a high rate of mutation at each locus is assumed and, therefore, very many alleles segregate: this assumption predicts high variance in the quantitative trait, but requires mutation rates per locus that are much higher than those observed (Kimura, 1965). In the other model, a low, realistic (at least according to classical theory) rate of mutation per locus with large effects of each mutant is assumed: but this predicts much less variation in the trait than is observed (Turelli, 1984). Lewontin (1974, p. 267) recognized the paradox of genetic variation and dismissed its explanation by the balance (Dobzhansky, 1970) and neutral (Kimura, 1983) theories: “On the one hand, there are strong reasons for rejecting a

balance theory because it predicts tremendous inbreeding depressions that are not observed, because the rates of evolution of different molecules strongly suggest that the least functional evolve fastest, because heterozygosity does not seem to be sensitive to ecological stringency, and because selection has proved extremely difficult to find in operation. On the other hand, the theory that standing variation and most substitutions of amino acids have been neutral also strains our credulity to the limit, because it requires us to believe that population sizes for all species are effectively the same, because it requires adaptive mutation, to be several orders of magnitude less frequent than neutral changes, because there is too much variation from locus to locus in the amount of divergence between populations, because of striking similarities in allelic frequency distributions in closely related species, and because the majority of polymorphic substitutions do alter the functional properties of enzymes." In fact, the increase in additive genetic variance due to mutation is $\sim 10^{-3}$ of the standing variation, which makes a significant contribution after ~ 50 generations of selection (Hill, 1982b; Lynch and Walsh, 1998; Partridge and Barton, 2000). Lack of mutations does not limit straightforward selection response. Sustained responses to long-term artificial selection do not exhaust genetic variation (Frankham, 1980; Yoo, 1980b; Hill, 1982a; b; Dunnington and Siegel, 1996; Eitan and Soller, 2004; Laurie et al., 2004; Carlborg et al., 2006; Burke et al., 2010), arguing for a steady supply of new mutations.

A related conundrum that has been a constant challenge to evolutionary biologists is the problem of polymorphism maintenance in small populations (Wright, 1931; Dobzhansky et al., 1970; Carson, 1990; Grant, 1991). How can genetic diversity be maintained in small isolated populations, in spite of genetic drift, potential inbreeding, or sporadic bottleneck events? Long-term studies in natural populations (Nevo et al., 1974; 1994; 1997a; b; Nevo, 1989, 1991; 1999; Carson, 1990; Coates, 1992; Hartl and Hell, 1994) indicate that polymorphism could be preserved in rather small populations (less than 50-100 individuals), or even in those subjected to or recovered from narrow bottlenecks (Bryant and Meffert, 1986; Carson, 1990; Dinerstein and McCracken, 1990; Coates, 1992; Hartl and Hell, 1994).

The coexistence of selection and high genetic variation in natural populations is what can be expected in the light of the stochasticity-selection dualism of evolution. The genomic "fossil record" (Buss, 1987 p. 90) reflects in contemporary genomes which evolutionary forces shaped the genomic

architecture during deep evolutionary time. Thus, the high genetic variation in populations witnesses the strong premium that evolution paid in the evolutionary past to populations that took precautions for change. Sexual reproduction and its bet-hedging strategy is the evolutionary tool that integrated the generation of genetic variation (the response to stochasticity) and pre-selection (ensuring viability even in small populations) into a single process.

19.2 Levels of selection controversy

Darwin consistently saw natural selection as choosing between individual organisms. Since Darwin (1859) wrote: "...natural selection works solely by and for the good of each being, all corporeal and mental endowments will tend to progress towards perfection.", natural selection is often characterized as an optimizing process that results in maximizing of mean fitness via the differential reproduction of highly adapted phenotypes (Emlen, 1966; MacArthur and Pianka, 1966; Williams, 1966a; Dawkins, 1976; Maynard Smith, 1978b; Alexander, 1982; Grafen, 1999). The individual-as-maximizing-agent (Grafen, 1999), however, is a contradiction in itself. Evolutionary endpoint of such an organism would be a Darwinian demon (Heininger, 2012). A Darwinian demon can produce infinitely many offspring and live indefinitely. This "the winner takes it all" scenario is ruled out in a world of limited and unpredictably available resources. Accordingly, the proponents of the individual-as-maximizing-agent concept do have nothing in favor of their strong beliefs, nothing in addition to the orthodoxy of Darwinian thinking and population genetic dogmas. But: "A mathematical model is only as good as its assumptions" (Maynard Smith and Brookfield, 1983). Observational data reflect another evolutionary reality. Not surprisingly, there is a long-standing controversy about the units of selection. In the 1960ies and '70ies there was a strong opposition (Maynard Smith, 1964; 1976b; Williams 1966a) to the group-selective concept as advocated by Wynne-Edwards (1962). It was argued that group selection forces are weak and that only in special circumstances an advantage to the group can outweigh a disadvantage to the individual (Williams 1966a; Dawkins 1976; Maynard Smith, 1976b; Leigh, 2010b). In the last decades there has been a renaissance of group-selective concepts often formulated as hierarchical or multi-level selection theory (Lewontin, 1970; Frank, 1998; Sober and Wilson, 1998; Keller, 1999; Michod, 1999b; Gould, 2002; Hammerstein, 2003; Borrello, 2005; 2010; Okasha, 2006; Godfrey-Smith, 2009; Wilson, 2012). Regrettably, the level-of-selection debate was often

loaded with ideological ballast. The good-for-the-individual or good-for-the-species arguments are anthropomorphic concepts that do not reflect evolutionary reality. Evolution does not act in terms of selfish (e.g. Dawkins, 1976) or selfless (eg. Wilson and Wilson, 2007) categories. Subliminally insinuating a goal-directed intention, these concepts reveal teleological thinking.

The recognition of the stochasticity-selection dualism in evolution lays the conceptual groundwork for a deeper understanding of the levels of selection. When the fitness of a genotype varies over generations, the appropriate measure of its relative growth rate is its geometric mean fitness, rather than its arithmetic mean fitness. The geometric mean of n numbers is the n th root of their product. If the numbers vary, then the geometric mean is always less than the arithmetic mean; in general, the geometric mean becomes smaller as the numbers being averaged become more variable. Thus the geometric mean fitness of a genotype can be increased by reducing the variance of its fitness (over generations), even if the reduction of variance also entails a reduction of the arithmetic mean. The principle is similar to risk aversion in utility theory; the cost of a negative deviation from the mean is larger than the benefit of an equivalent positive deviation (Philippi and Seger, 1989).

When fitness fluctuates through time and the fluctuations are modest, the identity of the allele that predominates in a population depends on both the mean and the variance in fitness. Consequently, if two alleles have the same (arithmetic) mean fitness through time, the allele that 'wins' is the one with the smaller variance in fitness. Thus, it is advantageous for alleles to avoid large fluctuations in fitness. When there are no fluctuations in fitness through time (constant environments), the geometric mean fitness collapses to the arithmetic mean fitness (Orr, 2009).

In constant environments natural selection leads to each individual organism maximizing its expected number of descendants left far in the future. If there are no environmental fluctuations, population fitness is maximized and measured by the arithmetic mean number of surviving descendants. In evolutionary computation, the Genetic Algorithm (GA) is based on the "survival of the fittest" principle and simulates natural evolution on computer systems to solve complex problems. Individuals are selected and reproduced according to a fitness performance criterion. The fitter the individual, the higher are its chances to produce offspring. Since the process is biased towards the regions of the solution space which enclose the fittest individuals, the evolving population

gradually loses diversity and converges. After a population has converged, it is very difficult to readapt to a new optimum when the environment changes (Cobb and Grefenstette, 1993; Simões and Costa, 2002; Bui et al., 2005). Thus, premature convergence is a problem for the GA as it gradually loses its exploratory ability during the evolutionary process under an oversimplified "survival of the fittest" principle.

The standard criterion for evaluating the fitness of genotypes in stochastic environments, however, is the geometric mean of the growth rates (geometric mean fitness) (Dempster, 1955; Cohen, 1966; Lewontin and Cohen, 1969; Frank and Slatkin, 1990; Yoshimura and Clark, 1991; Yoshimura and Jansen, 1996; Hopper, 1999; Simons, 2009; Yoshimura et al., 2009). Geometric mean fitness is a concept widely used in ecology and evolutionary biology to understand persistence of populations in fluctuating environments (Lewontin and Cohen, 1969; Levins, 1969; Gillespie, 1974a; b; Kuno, 1981; Yoshimura and Jansen, 1996; Jansen and Yoshimura, 1998). In variable environments, the geometric mean fitness is always lower than the arithmetic mean. In fluctuating environments it may be optimal for different individuals of the same genotype to take different actions to spread the risk. Risk spreading polymorphism makes sense only for groups - by definition an individual cannot be polymorphic. The fitness of the genotype is determined by the, perhaps complementary, actions of all individuals of the genotype, and the best action of an individual depends on the states and actions of other population members (McNamara et al., 1995; McNamara, 1998; Török et al., 2004). Risk-sensitive reproductive strategies may reduce the average (arithmetic mean) of individual reproductive output, while yet maximizing the populational geometric mean; this trade-off in terms of average reproduction is 'bet hedging' (Gillespie, 1973; 1974a; Slatkin, 1974; Seger and Brockmann, 1987; Philippi and Seger, 1989). A rigorous definition of bet-hedging includes lower expected arithmetic mean fitness, as well as greater expected geometric mean fitness (Seger and Brockmann, 1987; Simons, 2009). Bet-hedging involves a trade-off between the mean and variance of fitness. If the environment varies temporally, phenotypes with low variances of fitness may be favored over alternatives with higher variances and higher mean fitnesses (Philippi and Seger, 1989). This reduction in among-generation variation in fitness (yielding a higher geometric mean) forms the basis of bet-hedging theory: bet-hedgers, reducing variance in fitness, don't necessarily do best all the time, but they perform most consistently and are therefore favored by selection (Cohen, 1966; Roff, 1992). Thus, in

stochastic environments, individual fitness maximization regimes are replaced by population-level fitness maximization strategies that yield suboptimal fitness results for individuals (Cohen, 1966; Ellner, 1986; McNamara 1995; 1998; McNamara et al., 1995; Yoshimura and Jansen, 1996).

Intriguingly, evidence for the evolutionary merit of reproductive restraint comes from multiple theoretical and experimental studies in various taxa (Gilpin, 1975; Nathanson, 1975; Wade, 1980; Walker, 1984; Rand et al., 1995; Savill and Hogeweg, 1998; Sober and Wilson, 1998; Boots and Sasaki, 2000; Haraguchi and Sasaki, 2000; Rauch et al., 2002; 2003; Werfel and Bar-Yam, 2004; Borrello, 2012). Reproductive prudence of cells arose as a necessary prerequisite of multicellularity (Buss, 1987; Maynard Smith and Szathmáry, 1995; Frank and Nowak, 2004). The overarching issue of this behavior is the prudent and sustainable use of resources. Resource availability is stochastic. And bet-hedging is a way to cope with this stochasticity. The tragedy of the commons (a situation where individual competition reduces the resource over which individuals compete, resulting in lower overall fitness for all members of a group or population) provides a useful analogy allowing to understand why shared resources tend to become overexploited (Hardin, 1968). The tragedy of the commons analogy has become increasingly used to explain why, in principle, selfish individuals in a multitude of animal and plant populations evolved means to avoid the overexploitation of limited collective resources (Frank, 1995; Gersani et al. 2001; Falster and Westoby, 2003; Foster, 2004; Wenseleers and Ratnieks, 2004; Rankin and López-Sepulcre, 2005; Kerr et al., 2006; Rankin and Kokko, 2006). Factors such as high relatedness in social groups (Wenseleers and Ratnieks, 2004), diminishing returns (Foster, 2004), policing and repression of competition (Frank, 1995; 1996b; Hartmann et al., 2003; Ratnieks and Wenseleers, 2005), pleiotropy (Foster et al., 2004) or control of population density (Suzuki and Akiyama, 2005; Hauert et al., 2006; Kokko and Rankin, 2006; Rankin, 2007; Frank, 2010) have been argued to constrain the evolution of overexploitative behavior, and thus reduce the potential for a tragedy of the commons to arise in such populations.

According to Fisher (1930), as noted in his treatment of sex ratio evolution, some evolutionary phenomena require the consideration of offspring counts over more than one generation. Thus, there are short-term and long-term aspects to fitness (Beatty and Finsen, 1989; Sober, 2001). This distinction is not trivial. In fact, short-term reproductive success may threaten the

evolutionary success of a geno-/phenotype, by placing too great a demand on available resources (Beatty and Finsen, 1989). Long-term concepts of fitness have been forwarded by Thoday (1953; 1958) and Cooper (1984). Thoday suggested that fitness should be defined as the probability of leaving descendants in the very long run; he proposed 10^8 years as an appropriate time scale. Cooper argued that the “expected time to extinction” of a particular genotypic or phenotypic subpopulation may be the adequate measure of fitness.

In this context, a highly contentious issue revolved around the obvious reproductive restraint of predators. The classical model of predator-prey dynamics, the Lotka-Volterra equation, predicts that under most conditions predator populations, like prey populations, go through a series of oscillations between feast and famine, at each cycle approaching the brink of extinction (Holland, 1995; Mitteldorf et al., 2002; Mitteldorf, 2010). The “prudent predator” concept (Slobodkin, 1961; 1974; Goodnight et al., 2008) has revealed evolutionary outcomes of predator-prey interactions and provided evolutionary mechanisms to resolve the tragedy of the commons dilemma. Original studies by Wynne-Edwards (1962), suggesting that predators executed restraint in reproduction in order to avoid overexploitation of resources were dismissed as inadequate since any such restraint appears to require group selection (Maynard-Smith, 1964; Williams, 1966a). However, there is theoretical justification for a self-consistent limitation of reproduction by predators (Mitteldorf et al., 2002). The rapidly reproducing types modify their local environment, depleting resources in a way that is detrimental to their survival, but this environmental modification and its feedback to population growth may require many generations (Mitteldorf et al., 2002; Goodnight et al., 2008). When a predator evolves, the evolutionarily stable type is outcompeted in the short term by seemingly fitter mutants, which have the highest numbers of offspring for many generations but go extinct in the long term (e.g., after ~200 generations) (Rauch et al., 2002; 2003). The benefit of restraint is that better resource management may prolong the persistence of the group. Thus, the prudent predator attenuates the oscillations predicted by the Lotka-Volterra equation and stabilizes populations (Holland, 1995; Mitteldorf, 2006; 2010). To my knowledge, so far no formal mathematical treatment of the “prudent predator” concept with regard to the trade-off between mean and variance of fitness has been provided. Without going into the mathematical details, the graphical representation of the issue (e.g. Mitteldorf et al., 2002) makes it highly plausible that the “prudent predator” is

yet another animal bet-hedging behavior (i.e. reducing variance in fitness) in response to environmental uncertainty.

Darwinian evolution favors genotypes with high replication rates, a process called 'survival of the fittest'. However, knowing the replication rate of each individual genotype may not suffice to predict the eventual survivor (Wilke et al., 2001). According to quasi-species theory, selection favors the cloud of genotypes, interconnected by mutation, whose average replication rate is highest (Eigen, 1971; Eigen and Schuster, 1979; Schuster and Swetina, 1988; Eigen et al., 1989; Nowak, 1992).

A related issue concerns the population fitness of sexual and asexual populations. Agrawal (2002) pointed to a key difference in the equilibrium genetic load (the reduction in fitness of a population of interest relative to a population composed solely of the most-fit genotype) in sexual and asexual populations under constant and fitness-dependent mutation rates. If the mutation rate is constant (in constant environments, dependent on constant, accidental mutations), then sexual and asexual populations are expected to have the same genetic load at mutation-selection equilibrium. In contrast, if the mutation rate is fitness-dependent (as in fluctuating environments), the expected fitness in an asexual population at equilibrium will be that of the most-fit genotype, while in a sexual population, the equilibrium fitness will be less than that of the most-fit genotype, perhaps much less. And yet sexual reproduction, the commander in chief of bet-hedging strategy prevails in fluctuating environments.

It doesn't make much sense to play a lottery with one lottery ticket and one individual. Raffles are played with many tickets and several players. If the goal is to have at least a couple of winners (i.e. individuals that are able to reproduce), it is worthwhile to buy as many lottery tickets as possible and to cover all bases (avoiding to put all eggs in one basket). The larger the size of the population, the better are its chances to survive the many iterations of the evolutionary game. In a variable world it is probably wise to take precautions against changes. At the next iteration of the game, the cards are being reshuffled and the winners of today may be the losers of tomorrow. Thus stochasticity and iteration of the game turn the individual-level selection pattern into a population-level selection regime. The evolutionary stochasticity-selection balance is dynamic. That means, a bet-hedging strategy is the ESS in stochastic environments. In relatively stable environments, the bet-hedging strategies have a lower fitness advantage.

However, the evolutionary success of sexual reproduction implies that stable environments are rather the exception than the rule.

In the dualism of the evolutionary world the welfare of individuals and populations are inseparably connected. Clearly, the individual is the **target** of selection. But evolution, like statistics, cannot be done on $n=1$. Variation (the result of stochasticity) at the level of populations/groups is required for selection. And variation can only be feature of populations. Thus, populations/groups are the **level** of selection. This applies for groups of genes, cells, or organisms. When the individual would be the sole target of selection, selection would not go for variation but for individual perfection. In the face of pervasive environmental change and unpredictability not the fittest individual (which always means the fittest at the prevailing conditions) but variation of less fit individuals is the survival insurance of a population.

19.3 The selectionist-neutralist controversy

Neutral models characterize evolutionary or ecological patterns expected in the absence of specific causal processes, such as natural selection or ecological interactions. The discovery in mid-20th century of extensive variation in protein and DNA sequence, both within and between species, stimulated Kimura (1968) to propose that most of this variation has no effect on fitness, on the grounds that it could not all be maintained by selection (Barton and Partridge, 2000). Kimura (1968; 1983; 1991) argued that most mutagenic changes are selectively neutral or near-neutral and put forward the neutral theory of molecular evolution. "...the neutral theory claims that the overwhelming majority of evolutionary changes at the molecular level are not caused by Darwinian natural selection acting on advantageous mutants, but by random fixation of selectively neutral or very nearly neutral mutants through the cumulative effect of sampling drift (due to finite population number) under continued input of new mutations" (Kimura, 1991). At face value, confirmation of various predictions of the theory provided evidence for its correctness:

- in protein sequences, conservative changes—substitutions of amino acids that have similar biochemical properties and are therefore less likely to affect the function of a protein—occur much more frequently than radical changes.
- synonymous base substitutions of the third nucleotide in a triplet (i.e., those that do not cause amino acid changes) occur almost always at a much higher rate than nonsynonymous substitutions.
- noncoding sequences, such as introns, evolve at a

high rate similar to that of synonymous sites.

- entirely untranslated pseudogenes, or dead genes, evolve at a high rate, and this rate is about the same in three-codon positions.

Since the formulation of the Neutral Theory of Molecular Evolution by Motoo Kimura (Kimura, 1968; 1983; King and Jukes, 1969), the neutralist–selectionist debate (Beatty, 1984; Gillespie, 1991; Millstein, 2002; Nei, 2005) has been around and is still on the agenda of evolutionary biologists. The debate was articulated around the relative importance of genetic drift and selection (Hey, 1999) with cases made both for selection (Gillespie, 2001; Hahn, 2008) and nonadaptive processes (Lynch, 2006; 2007a;b; Ellegren, 2009). However, the neutral theory is now a theory in retreat (Lewontin, 1974; Chamary et al., 2006; Begun et al., 2007; Hahn, 2008). First of all, the theory is hypothetico-deductive and rooted in population genetics that as Lewontin (1974, p. 267) put it: “... is not an empirically sufficient theory”. That the theory provides accurate predictions may be owed to correlation and not causation and does not vindicate the basic assumptions. Most importantly, the theory advances a static approach to selection implying that even in the face of pervasive ecological and genetic change the selectively neutral status of a mutation is unchanged. Positive and negative selection have been shown to be more extensive than predicted by the neutral theory (Fay et al., 2001; 2002; Smith and Eyre-Walker, 2002; Clark et al., 2003). Recent studies based on DNA sequence data from large numbers of genes have increasingly suggested the prevalence of adaptive evolution in coding (Sawyer SA et al., 2003; Bierne and Eyre-Walker, 2004; Bustamante et al., 2005; Macpherson et al., 2007; Shapiro et al., 2007; Kosiol et al., 2008; McVicker et al., 2009; Nielsen et al., 2009; Sella et al., 2009; Halligan et al., 2010) as well as noncoding (Kohn et al., 2004; Andolfatto, 2005; Haddrill et al., 2008; Sethupathy et al., 2008; McVicker et al., 2009; Sella et al., 2009) regions to an extent which is incompatible with the Neutral Theory of Molecular Evolution.

According to the Neutral Theory, mutation rate and substitution rate should be the same (Kimura, 1968). The fate of neutral mutations in a population is determined solely by genetic drift and, unless there is strong linkage to sites under selection, the fixation rate depends only on the rate at which the mutations are generated (Kimura, 1968). At a given population size, the fixation rates of beneficial and deleterious mutations are higher and lower, respectively, than the neutral fixation rate. However, pedigree studies suggest that mutation rates are much higher than

substitution rates (Bendall et al., 1996; Howell et al., 1996; 2003; Mumm et al., 1997; Parsons et al., 1997; Sigurdardóttir et al., 2000; Ho et al., 2005; 2008; 2011; Santos et al., 2005). For instance, the mutation rate estimated from pedigrees of humans is a hundredfold higher than the substitution rate for the primate mitochondrial DNA control region (Sigurdardóttir et al., 2000). Highest estimates of mtDNA mutation rates have since been obtained in pedigree studies of other organisms, including *Caenorhabditis* (Denver et al., 2000), *Drosophila* (Haag-Liautard et al., 2008) and Adélie penguins (Millar et al., 2008).

As has been emphasized by A. Wagner (2005c; 2008b), neutrality is not an essential feature of a mutation. That is, a once neutral mutation may cause phenotypic effects in a changed environment or genetic background. He argued that most, if not all, neutral mutations are of this sort, and that the essentialist notion of neutrality should be abandoned. Thus, two opposing views on the forces dominating organismal evolution, natural selection and random drift are reconciled: neutral mutations occur and are especially abundant in robust systems, but they do not remain neutral indefinitely, and eventually become visible to natural selection, where some of them lead to evolutionary innovations (Wagner, 2012).

Mayr denied that random genetic drift is an evolutionary mechanism. In 2001, Mayr wrote: “Molecular genetics has found that mutations frequently occur in which the new allele produces no change in the fitness of the phenotype. Kimura (1983) has called the occurrence of such mutations ‘neutral evolution’, and other authors have referred to it as non-Darwinian evolution. Both terms are misleading. Evolution involves the fitness of individuals and populations, not of genes. When a genotype, favored by selection, carries along as hitchhikers a few newly arisen and strictly neutral alleles, it has no influence on evolution. This may be called ‘evolutionary noise’, but it is not evolution”. However, Stebbins and Ayala (1981) argued that the “selectionist” and the “neutralist” views of molecular evolution are competing hypotheses within the framework of the synthetic theory of evolution.

The Neutral Theory was formulated under the impression of extensive variation in protein and DNA sequence, questioning the pervasive action of selection. Importantly, it was only assumed (arguing that this level of variation could not be tolerated under the pressure of natural selection) but never shown that the extensive variation in protein and DNA sequence is in fact selectively neutral. Within the framework of the stochasticity-selection dualism, the degeneracy of

molecular processes (see chapter 13), and the pre-selection of mutations in the SMSCs, extensive non-neutral variation is recognized as the genetic signature of the bet-hedging strategy in response to environmental unpredictability.

19.4 The adaptationism controversy

There is a longstanding controversy about adaptationism, the “programme based on the faith in the power of natural selection as an optimizing agent” (Gould and Lewontin, 1979; Godfrey-Smith, 2001; Lewens, 2009). Adaptationism seeks to identify adaptations and the specific selective forces that drove their evolution. But many aspects of genomic, cellular, and developmental evolution can only be understood by invoking a lower level of adaptive involvement (Kimura, 1983; Lynch, 2007a; b). Dobzhansky (1950), in a seminal statement on adaptation to diverse environments, wrote ‘Changeable environments put the highest premium on versatility rather than on perfection in adaptation’. In particular, Gould and Lewontin (1979) argued that adaptationists often use inappropriate evidentiary standards for identifying adaptations and their functions, analogous to Rudyard Kipling’s *Just So Stories* (outlandish explanations for questions such as how the elephant got its trunk). Of course, Gould and Lewontin freely admitted that adaptation by natural selection has been, and still is, a powerful force in shaping the phenotypic traits of organisms. The question they wished to raise was: what kind of evidence is necessary to support the hypothesis that a trait is an adaptation formed by natural selection and what evidence could point towards some other cause of the current state of the trait in question (Pigliucci and Kaplan, 2000)? The past 50 years have seen an increased recognition of sluggish evolution and failures to adapt (Futuyma, 2010). According to Lewin (1980), the existence of constraints meant that natural selection was involved at only one stage of the evolutionary process and thus was not the only essential factor in evolution. It has been speculated that these additional forces may be forces like drift, gene flow, epigenetic inheritance, pleiotropy, developmental, structural and phylogenetic constraints (Gould and Lewontin, 1979; Amundson, 1994; 2001; Futuyma, 2010). Natural selection apart, all evolutionary processes are random with respect to adaptation, and therefore tend to degrade it (Barton and Partridge, 2000). In the reformist counterparadigm, one invokes “chance”, “constraints”, and “history” to explain imperfections: some features don’t turn out perfectly, due to statistical noise, in-built limitations, and so on; some features, due to “historical

contingency”, are side-effects or vestiges. Selection still governs evolution, as Darwin said, but there are “limits to selection” (Barton and Partridge, 2000).

With the recognition of the stochasticity-selection dualism of evolution these limits have a unified conceptual basis. Stochasticity contributes to maladaptation or limits adaptation (Travisano et al., 1995; Hereford, 2009; Lenormand et al., 2009). Bet-hedging is driving suboptimal adaptive strategies. Dempster (1955) introduced the model in which temporal fluctuations in reproductive success for competing genotypes favor the genotype with the highest geometric-mean reproductive success. The geometric mean criterion implies that evolution tends to minimize the variance (or, more precisely, to optimize the trade-off between mean and variance) in intergenerational per capita reproduction (Gillespie, 1977; Frank and Slatkin, 1990). Almost any individual life history or behavioral adaptation may be affected by environmental stochasticity. Environmental fluctuations preclude optimal adaptation to any single environment (Levins, 1968). Crow (1958) showed that the phenotypic variance of relative fitness places a limit on the evolution of fitness.

19.5 Paradox of viability

Dobzhansky (1937) noted the “paradox of viability”. On the one hand, each species needs to have variation present in order to adapt to environmental changes. On the other hand, the particular variations that might prove adaptive in the future are very likely maladaptive at present. “Evolutionary plasticity can be purchased only at the ruthlessly dear price of continuously sacrificing some individuals to death from unfavorable mutations.” (Dobzhansky, 1937, p. 127). Importantly, the viability costs of mutations are paid during the sexual selection cascades. By subjecting the mutated gametes to a rigorous quality selection, the SMSC succeed to reduce the viability costs of mutations and to keep the investment in mutagenic-selective “trial-and-error cycles” and its associated viability risk at a low economic rate.

19.6 Mystery of low heritability

Heritabilities are often less than 0.5. Of traits in *Drosophila* and other non-domestic animals classified as life-history, behavior, physiology and morphology, only morphological traits in animals, excluding *Drosophila*, average about 0.5; all other categories are less (Roff, 1997; Franklin and Frankham, 1998). This is particularly important for traits closely related to reproductive fitness where heritabilities are typically 10-20% (Roff, 1997). Moreover, field data demonstrate that heritability decreases under stressful conditions,

at least for morphological traits (Charmantier and Garant, 2005). Genome-wide association studies (GWAS) have led to the identification of >1,200 loci harboring genetic variants associated with >165 common human diseases and traits, revealing previously unknown roles for scores of biological pathways (Manolio et al., 2008; Hirschhorn, 2009; Eichler et al., 2010; Lander, 2011; Zuk et al., 2012). However, early GWAS were puzzling because they appeared to explain only a small proportion of the “heritability” of the traits. With larger GWAS, the proportion of heritability apparently explained has grown (to 20–30% in some well-studied cases and >50% in a few), but, for most traits, the majority of the heritability remains unexplained (Lander, 2011).

Of course the expectation that heritabilities should be much higher is owed to the anticipation that natural selection and its effects on the (epi)genome and thus heritability play a large role in evolution. Bet-hedging as response to environmental stochasticity and its manifold effects on (epi)genotypic variation and phenotypic plasticity dissipates the action of selection (Wilson et al., 2006; Simons and Johnston, 2006; Simons, 2011). Environmental variance reduces heritabilities, both through an increase in the environmental component of variance and a reduction in the additive genetic variance (Simons and Roff, 1994), and a recent meta-analysis shows that heritabilities are generally reduced under unfavourable conditions (Charmantier and Garant, 2005). Another evidence that stochasticity as second organizing principle in evolution counteracts selection.

19.7 The Cambrian explosion

For reasons that have remained unclear, almost all of the modern animal phyla arrive in the fossil record during a geologically short period of about twenty million years, starting about 540-545 million years ago (Valentine, 1995; Valentine et al., 1999; Baker, 2006; Marshall, 2006). The so-called Cambrian explosion (CE) with its dramatic increase in both disparity and diversity has been a unique and troubling anomaly in the history of life. Speculation about the rise of animals has run the gamut from purely intrinsic biological causes (Bengtson and Morris, 1992; Parker AR, 1998; Smith and Peterson, 2002; Peterson et al., 2005; Baker, 2006) to extrinsic triggers (Derry et al., 1994; Canfield and Teske, 1996; Hoffman et al., 1998; Brasier and Lindsay, 2001; Kirschvink and Raub, 2003; Horvath, 2003; Squire et al., 2006) or some combination of both (Peterson et al., 2005). Several factors that may be prerequisites for the explosion have been identified, necessary but not sufficient. By the start of the Cambrian, the large supercontinent

Gondwana, comprising all land on Earth, was breaking up into smaller land masses. This increased the area of continental shelf, produced shallow seas, thereby also expanding the diversity of environmental niches in which animals could specialize and speciate (Veevers, 2004; Meert and Lieberman, 2008). Rapid change following a long period of quasi-stasis (due to “Snowball Earth”?) (Hoffman et al., 1998; Hyde et al., 2000) suggests the existence of a triggering or enabling event, either external to organisms or incorporated in organisms (Butterfield, 2007). The time of onset is constrained by the evolution of the environment, whereas its duration appears to be controlled primarily by rates of developmental innovation (Marshall, 2006). The real question is what drives morphological evolution (as opposed to what merely allows it, or might hold it back – the focus of most Ediacaran/Cambrian explosion models) (Butterfield, 2007). It has been noted that the oxygen content of the atmosphere was slowly rising (Thomas, 1997; Fike et al., 2006; Canfield et al., 2007). This was likely an enabler, and possibly a trigger (Nursall, 1959; Berkner and Marshall, 1965; Canfield and Teske, 1996; Ohno, 1997b; Canfield et al., 2007). Most animals require molecular oxygen in order to produce their energy, and this has led to the widespread presumption that a rise in atmospheric oxygen was the essential precursor to the evolution of animals (Runnegar, 1991; Catling et al., 2005; Shields-Zhou and Och, 2011). Multiple lines of evidence from evolutionary biology (Falkowski et al., 2005; Acquisti et al., 2007), geochemistry (Bekker et al., 2004), and systems biology (Raymond and Segre, 2006) build a compelling case for a central role of O₂ in the evolution of complex multicellular life on earth (Catling et al., 2005; Falkowski, 2006; Raymond and Segre, 2006; Thannickal, 2009). Both a surge in seawater calcium and phosphate have been implied as capacitating environmental factors (Cook, 1992; Brennan et al., 2004; Porter, 2007; Fernández-Busquets et al., 2009).

So far, explanations for the acceleration of the evolutionary tempo during CE center on the invention of new trophic capacities, whether predation (Vermeij, 1990; Bengtson, 2002) or the related cropping (Stanley, 1973; 1976). Many of these theories emphasize the role of predation, specifically in an effort to explain the massive skeletonization event that characterizes the fossil record of the explosion (Vermeij, 1990). All of these have a common thread of coevolution, escalation, or arms races (Vermeij, 1987; 2004; Butterfield, 2007).

The animal phyla are divided into three groups. First are the sponges (Porifera) that do not have organized

cell layers. Second are the diploblasts, which have two primary cell layers: an outer ectodermal layer and an inner endodermal layer. The Cnidaria (corals and jellyfish) and the jellyfish-like group, the Ctenophores, are the only diploblastic phyla. All of the remaining animal phyla are triploblasts, also collectively referred to as the bilateria. These grow from three primary cell layers: the outer ectoderm, the intermediate mesoderm (from which our skeleton and most of our muscles are derived), and the inner endoderm, which includes the gut. Over 99% of all living animals are triploblasts (Marshall, 2006). Both the geological fossil, ontogenetic and genetic records support the Ediacaran (c. 585–542 Myr ago) emergence of triploblasts (Aris-Brosou and Yang, 2002; 2003; Peterson et al., 2008; Rokas, 2008; Xiao and Laflamme, 2008; Erwin, 2009). A fact that has received relatively little attention in the attempts to explain the causes of the CE: it is a phenomenon restricted to triploblasts and thus its causes should be sought in some evolutionary innovation unique to these organisms. Hence, cellular differentiation that was proposed as a candidate new technology associated with CE (Phoenix, 2009), is an improbable cause of CE since it is a property of all multicellular organisms. The fact that the developmental toolkit was unequivocally established in the last common protostome-deuterostome ancestor (Valentine et al., 1996; Martindale et al., 2004, Martindale, 2005; Couso, 2009; Erwin, 2009) and that the last common protostome-deuterostome ancestor probably lived prior to 555 million years ago strongly suggest that developmental innovation may have been necessary but cannot be a sufficient cause of the main Cambrian radiation. The developmental innovations were a precondition to the later events and may explain the extraordinary breadth of the radiation, but not the triggering of the event itself (Erwin, 2005).

According to S. Ohno: "Assuming a spontaneous mutation rate to be a generous 10^{-9} per base pair per year and also assuming no negative interference by natural selection, it still takes 10 million years to undergo 1% change in DNA base sequences. It follows that 6-10 million years in the evolutionary time scale is but a blink of an eye. The Cambrian explosion denoting the almost simultaneous emergence of nearly all the extant phyla of the Kingdom Animalia within the time span of 6-10 million years can't possibly be explained by mutational divergence of individual gene functions" (Ohno, 1996).

Let's look at the ingredients for the Cambrian stew that we have assembled so far. We have an abiotic enabler, and possibly a trigger, the slowly rising

oxygen content of the atmosphere. And we have the bilateria. What distinguishes the bilateria from the non-bilateria? Generally, in basal metazoa (Porifera, Ctenophora, Placozoa, Cnidaria) the adult body is itself the reproductive unit in which germ cells arise from a somatic stem cell population. Bilateria have a germline that is segregated from the soma (see chapter 6.2). The segregation of the germline underlies the germ-soma conflict (Heininger, 2012) and promoted the functional specialization in differentiated tissues (Simpson, 2012). But how can oxygen and the germ-soma conflict be brought together into a coherent process underlying the CE? Intriguingly, the missing link is sexual reproduction. Current evidence suggests that sex has a single evolutionary origin and was present in the last common ancestor of eukaryotes (Dacks and Roger, 1999). Sexual reproduction and eukaryotes probably evolved together (Cavalier-Smith, 2002), about 2.0 to 3.5 billion years ago (Miyamoto and Fitch, 1996; Gu, 1997). Despite their sexual reproduction, at least 1.5 billion years before the CE, the overarching pattern of pre-Ediacaran eukaryotes is one of minimal morphological diversity and profound evolutionary stasis (Butterfield, 2007). In pre-Ediacaran time, sex hardly was a dynamic evolutionary motor. But during the rise in atmospheric oxygen, sexual reproduction may have "learned" to use oxidative stress as a tool for evolutionary innovation that gave the coevolutionary germ-soma conflict an unprecedented dynamic. Coevolving systems have significantly higher levels of heterozygosity and allelic diversity (Buckling and Rainey, 2002a; Duncan and Little, 2007; Duffy MA et al., 2008; Koskella and Lively, 2009; Béréanos et al., 2011) that correlates with their evolutionary potential (Fisher, 1930; Falk and Holsinger, 1991; Frankham, 1995; Falconer and Mackay, 1996; Franklin and Frankham, 1998; Reed and Frankham, 2003; Johnson et al., 2006; Leimu et al., 2006). Both the coevolutionary engine of the germ-soma conflict in bilateria and oxidative stress, the effector of mutagenesis and cellular selection and ultimate tool of the SMSCs (see chapter 10) gave animal evolution a kick-start during the Cambrian radiation. With these processes, sexual reproduction succeeded to accelerate evolution substantially, creating in the last 600 million years a wealth of taxa and species (Stanley, 1975). Thus, the CE was enabled by a multifactorial process. Abiotic and biotic factors that originated some 1.5 billion years apart were integrated into a highly efficient evolutionary vehicle.

19.8 The Darwinian-Lamarckian evolution controversy

*In my opinion, the greatest error which I have committed, has been not allowing sufficient weight to the direct action of the environment, for example, food and climate, independently of natural selection. When I wrote *The Origin*, and for some years afterwards, I could find little good evidence of the direct action of the environment; now there is a large body of evidence.*

Charles Darwin (1876) in a letter to Moritz Wagner

Natural selection acts upon phenotypic variation of individuals that is determined by their (epi)genetic constitution, but also shaped by their specific environment (Jablonka and Lamb, 2005), developmental processes (Müller, 2007), and stochastic events (Huang, 2012). The process of evolution is thus a result of complex interactions between various intrinsic and extrinsic factors (Pigliucci, 2009). According to Bateson (2012), Lloyd Morgan (1896) "suggested that if a group of organisms respond adaptively to a change in environmental conditions, the modification will recur generation after generation in the changed conditions, but the modification will not be inherited. However, any variation in the ease of expression of the modified character which is due to genetic differences is liable to act in favor of those individuals that express the character most readily. As a consequence, an inherited disposition to express the modifications in question will tend to evolve. The longer the evolutionary process continues, the more marked will be such a disposition. Plastic modification within individuals might lead the process, and a change in genes that influence the character would follow; one paves the way for the other".

In contrast to Darwin, Lamarck thought that evolution proceeds by the inheritance of acquired traits. Acquired traits have been gained by means of phenotypic plasticity during an organism's lifetime in response to environmental perturbation. Thus, Lamarck advocated the transgenerational transmission of learned characters. Weismann (1891), based on his concept of the germ-plasm, rejected the inheritance of acquired characters on the grounds that changes to the soma cannot produce the kind of changes to the germ-plasm that would result in the altered character being transmitted to subsequent generations (Haig, 2007). Thus, in the tradition of the Modern Synthesis it is generally considered that direct and rapid feedback from the environment to the germline cannot happen.

During recent years a lively controversy concerning the relative significance of Darwinian and Lamarckian

modes of evolution took place (Hoenigsberg, 2002; Jablonka and Lamb, 2005; 2008b; Haig, 2007; Shapiro and Sober, 2007; West-Eberhard, 2007; Koonin and Wolf, 2009; 2012; Feinberg and Irizarry, 2010; Merlin, 2010; Gissis and Jablonka, 2011; Dickins and Rahman, 2012; Koonin, 2012). The question is, formulated in molecular terms: can (epi)mutations in genes of somatic cells of an animal possibly be transmitted to the genes of germ cells and passed on to offspring of future generations?

Plants and benthic aquatic animals (e.g. Porifera, Cnidaria) have no sequestered germline. The germline can form at any time in the organism's life from multipotent stem cells. Accordingly, somatically acquired mutations can be inherited in these organisms by asexual and sexual reproduction and this has been discussed in chapter 15.2. In unicellular prokaryotic and eukaryotic microorganisms, the same cell is both soma and germline and, of course, mutations that have been acquired can be transmitted to the next generation. Thus, Weismann's dogma only can apply to unitary organisms, mobile animals. However, particularly in discussions concerning the Darwinian-Lamarckian evolution controversy this distinction has been blurred and, particularly by proponents of Lamarckian-type inheritance, processes in bacteria and plants are taken to vindicate Lamarckian modes of evolution (Koonin and Wolf, 2009; 2012; Koonin, 2012).

Epigenetics was first suggested by Jablonka and Lamb (1995) to play a role in evolution through Lamarckian inheritance, that is, direct modification of the genome by the environment, which is then transmitted transgenerationally. As defined by Jablonka et al. (1998) "Acquired characters are the outcome of instructive processes, such as those seen in embryonic induction, transcriptional regulation, and learning, all of which involve highly specific and usually adaptive responses to factors external to the responding system." Feinberg and Irizarry (2010) questioned this concept, proposing a non-Lamarckian theory for a role of epigenetics in evolution. As direct evidence for stochastic epigenetic variation, they referred to (i) the high variability of DNA-methylated regions in mouse and human associated with development and morphogenesis and (ii) a heritable genetic mechanism for variable methylation, namely the loss or gain of CpG dinucleotides over evolutionary time.

I think the discussions and insights presented in various chapters of this work provided the insights on the basis of which we can revisit the Darwinian-Lamarckian controversy:

Chapter 8.1: Natural selection is only the proverbial tip of the iceberg of Darwinian selection processes. On all levels of development and sexual reproduction, cellular competition, fuelled by variation created by stochastic processes, results in cellular selection.

Chapter 18.1.2: The myriad of molecular processes that determine an individual's phenotype have no inbuilt sensor that informs about the selective value of an action. These processes are totally blind with regard to their fitness-relevance. In addition, the degeneracy, although a source of robustness and evolvability, is so pervasive that no fitness-relevant result can be pinpointed to a certain process.

Chapters 12 and 17: Evolution is a cybernetic process. Reinforcement learning enables organisms to learn from past "experiences" (in the sense that survival/reproduction is the evolutionary feedback loop enabling reinforcement learning), making "educated guesses" to face new, unpredictable challenges. Bet-hedging is the ESS in a capricious environment.

Chapter 16: Transgenerational epigenetic inheritance is an evolutionary reality. Germ granules are the carriers of transgenerational messages.

Chapter 17: Apart from selection, stochasticity is an organizing principle of evolution. Various processes, perfectly designed as they may appear have inherently stochastic elements.

Environmental stressors are the most relevant triggers of transgenerational information transfer. The metabolic and energetic stress is sensed by the mitochondria and can be relayed to the nucleus (see chapter 21) where it elicits epigenetic and genetic changes (see chapter 10.3). Close contact between the somatic gonads and germline cells are used to transmit these messages via autocrine, paracrine and endocrine messengers and ncRNAs. These messengers may induce both changes of the gametogenic mutagenesis-selection equilibrium and more directed sequence changes due to transcription-associated mutagenesis and epigenetic changes affecting gene expression. Most importantly, the several genetic and epigenetic tools have a constitutively stochastic character that allows a large sampling of the (epi)genetic search space and degeneracy that may yield functionally equivalent results. Selective sampling from this quasispecies cloud makes the process Darwinian. Missing this Darwinian aspect of the SMSC, created the impression of a Lamarckian-type evolutionary process. With few exceptions (Feinberg and Irizarry, 2010), this aspect has been consistently overlooked in the many

discussions surrounding the Darwinian-Lamarckian issue.

The non-randomness of TE insertions (see chapter 12.4) has been taken as evidence for a (quasi)Lamarckian modality of evolution (Martienssen, 2008; Koonin and Wolf, 2009; Zhang Z et al., 2013). That TE insertion is largely irrespective of its adaptive nature can be inferred from circumstantial evidence. It has been estimated that 80% of the spontaneous mutations seen in *Drosophila* genetics result from TEs (Ashburner, 1992) that constitute 7–8% of the genome (Smith et al., 2007). Do mobile DNA insertions similarly create 80% of evolutionary changes in this species? Without question, they do not (Brookfield, 2004). Those mutations that survive over long periods of evolutionary time are expected to be a very small subsample of newly induced mutations (Kidwell and Lisch, 1997). The most revealing observation is the almost complete absence of fixed sites of mobile DNAs in *D. melanogaster* (Charlesworth and Langley, 1989). A mobile DNA insertion that created an advantageous phenotype would be expected to spread to fixation in the species by natural selection. This would create a site fixed for the element throughout the species. Such sites are very rare, although they have recently been detected for the S element family in heat shock protein genes (Maside et al., 2002).

The processes of adaptation in a multi-agent system consist of two complementary phases: 1) learning, occurring within each agent's individual lifetime, and 2) evolution, occurring over successive generations of the population. The key conceptual point in a couple of mathematical models was: mutations in genes of somatic cells of an animal can possibly be transmitted to the genes of germ cells and passed on to offspring of future generations. These models suggest that Lamarckian evolution would speed up the adaptation process and promote the early independence of the offspring from the parents by providing more explicit information about the environment in the genotype (Sendhoff and Kreutz, 1999; Arita and Suzuki, 2000). However, by evaluating the characteristics of two different mechanisms of genetic inheritance, i.e. Darwinian and Lamarckian, Sasaki and Tokoro (1997) showed that while the Lamarckian mechanism is far more effective than the Darwinian one under static environments, it is found to be unstable and performs quite poorly under dynamic environments. In contrast, even under dynamic environments, a Darwinian population is not only more stable than a Lamarckian one, but also maintains its adaptability with respect to such dynamic environments and only Darwinian

populations can adapt to the new world (Sasaki and Tokoro, 1997; 1999; Yamamoto et al., 1999). These models highlight the fundamental differences between the Lamarckian and Darwinian modes of evolution. In a world of uncertainty, organisms have to bet-hedge and cover all bases. Learning can limit the search space and increase the likelihood that some of the generated variations will be useful (Jablonka and Lamb, 2007) (see chapter 12). But unable to estimate the fitness value of (epi-)mutations in a given environment, the features of the Baldwin effect such as stress- and transcription-associated mutagenesis and phenotypic plasticity are nested within the Darwinian principles of quasi-stochastically generated variation and selection.

20. The resource-stress dimensions and ecological window of sexual/asexual reproduction

The key remaining questions of evolutionary biology are more ecological than genetic in nature.

Edward O. Wilson, 1987

The goal of science is to discover patterns of relations among recorded phenomena, so that a few principles can explain a large number of propositions concerning these phenomena.

Ayala (1968c)

Summary

Available resources build the framework for a variety of life history traits and strategies. Both reproduction and stress have energetic and metabolic costs. Threshold traits are phenotypically discrete but are causally related to a continuously distributed condition, called the liability. Individuals above the threshold display one morph and individuals below the threshold display the alternate morph. Sexual/asexual reproduction can be another threshold trait, e.g. in cyclical parthenogens where resource availability and environmental stress intensity are liabilities that often jointly, sometimes individually, determine reproduction strategies. In almost all organisms, reproductive mode is fixed as a result of long-standing selective pressures. Stress intensity (moderate or harsh) and resource availability (r- and K-selected environments) define

the four quadrants of the ecological window of sexual/asexual reproduction. The ratio between resource availability and resource investment into mature individuals (that determines the relative costs of a reproductively competent individual, i.e. a lottery ticket in the raffle of life) and the habitat's stress intensity are species-specific parameters. Importantly, in most animals with a larger-than-microscopic body size, ecological conditions favor sexual reproduction with its pre-selection of viable zygotes. Only by investing little into (epi)mutagenic gametes/zygotes and pre-selecting them before natural selection exerts the final "quality control", a bet-hedging strategy in the face of unpredictable environments was a viable option in these animals.

20.1 The resource-stress dimensions

MacArthur (1972b) argued that the goal of community ecology (as of all science) is to find general rules. We have now reached the point where the wealth of information can be shaped into a general pattern. Available resources build the framework for a variety of life history traits and strategies. Both reproduction and stress (Parsons, 1994; 2005; 2007; Krebs and Loeschcke, 1994; Davis and Schreck, 1997; Sloman et al., 2000; Fisher, 2007; O'Connor et al., 2011; Johnstone et al., 2012) have energetic and metabolic costs. In a multitude of trade-offs, resources have to be partitioned between these energetic demands (Krebs and Loeschcke, 1994; Wang Y et al., 2004; Huang LH et al., 2007).

One attempt to construct a predictive framework for the relationships between habitat and species characteristics is the habitat templet theory (Southwood, 1977; 1988, Townsend and Hildrew 1994, Korfiatis and Stamou, 1999). This theory assumes that the habitat provides the templet on which evolution forges characteristic morphologies and life history strategies, being at the same time a "filter" resulting in the ecological sorting of the species able to occupy them (Ribera et al., 2001). The influence of habitat is epitomized in a small set of a priori defined axes that are hypothesized to summarize the environmental constraints acting on the populations. These axes are normally related to disturbance and adversity or stress (Southwood, 1977; 1988); habitat predictability and adversity (Greenslade, 1983); or to temporal and spatial heterogeneity, which can be taken as a measure of disturbance and availability of refugia, respectively (Townsend and Hildrew 1994, Korfiatis and Stamou, 1999). An equivalent hypothesis for plants is that of Grime (1977), with ecological strategies (with their respective morphological

adaptations) accommodating to stress, disturbance, and biological competition (Grime, 1977; Grime et al., 1997).

Frequently in biology there are so-called threshold traits (Roff, 1996; 1998). These traits are phenotypically discrete but causally related to a continuously distributed condition, called the liability. Both are linked by a threshold of response: individuals above the threshold display one morph and individuals below the threshold display the alternate morph. For instance, reproductive mode such as semelparity/iteroparity, is a threshold trait (Roff, 1996; 1998; Lesica and Young, 2005; Heininger, 2012). I argue that sexual/asexual reproduction can be another threshold trait, e.g. in cyclical parthenogens (Rispe and Pierre, 1998; Serra and King, 1999). Both resource availability and environmental stress intensity are liabilities that often jointly, sometimes individually, are causally related to sexual or asexual reproduction strategies.

One possibility for the persistence of asex is that competition (with sexual species) would be lower, as there are simply fewer species occurring in such highly fluctuating and extreme habitats. Another reason could be that asexuals are able to survive in very low densities over many generations, since they do not need to find a mate to reproduce (Burt, 2000; Van Dijk, 2007, Hörandl, 2008). For all sexual populations, there is a density threshold (that is a proxy of resource availability and is mediated by size and mobility of animals, amongst other biological characteristics) below which the probability of finding a mate is too low to ensure sufficient reproduction for the population to remain viable. In marginal habitats, such as semi-terrestrial ones, conditions may vary widely and asexuals would have the advantage over sexuals.

20.2 The ecological window of asexual and sexual reproduction

...understanding the evolution of sex requires the synthesis of every important process in evolutionary biology.

Otto and Lenormand, 2002

The sexual-asexual reproduction balance is determined by the availability of resources that can be used to sample genotypic search space by trial-and-error reproductive entities. Stress intensity is the other liability that delimitates the framework for the distribution of reproduction strategies. In r-selected environments the organisms with the highest growth rates, i.e. asexually reproducing organisms, are favored. K-selected environments favor competitive

organisms. Since Weismann, various authors advocated the idea that the generation of genetic variation underlies the evolutionary rationale of sexual reproduction (Weismann, 1889; 1904; Barton and Charlesworth, 1998; Burt, 2000). Traditionally, the benefits of sex by generating genetic diversity have been considered to become only visible in the long-term, but cannot offset the short-term, two-fold cost of sex compared to asexuality (Maynard Smith, 1978a). However, the SMSC can act at the individual level to create short-term, even immediate, effects and at the population or species level long-term effects. Without any doubt, the shuffling of genes by meiotic recombination and segregation increases genetic variance but the fitness-related consequences of genetic mixing may rather be detrimental than beneficial. Asexually reproducing organisms are able to generate a high amount of genetic variation (Loxdale and Lushai, 2003; Lushai et al., 2003) without having to pay the cost of recombination load (Fisher, 1930; Feldman et al., 1980; Charlesworth and Barton, 1996). In *Chlamydomonas*, for example, sex resulted in increased fitness variance in sexual relative to asexual lines, and despite an initial decrease in mean fitness in the generations immediately subsequent to sex (recombination load), long-term fitness increased at a faster rate when there were larger increases in variance (Kaltz and Bell, 2002). This work supports some Weismann–Fisher–Muller models of a short-term cost to sex accompanied by a long-term benefit due to increased variance (Colegrave et al., 2002b; Kaltz and Bell, 2002).

Figure 3 represents graphically the various reproduction domains. Moderate stress and K-selected environments define the sexual reproduction domain. Asexual reproduction is prevalent in high stress/K-selected environments (e.g. geographical parthenogenesis) and moderate stress/r-selected environments. Importantly, what is perceived as stressful by the various species is also dependent on their evolutionary history and various constraints. Likewise, whether the domain is r- or K-selected depends on the species-specific ratio between resource availability and investment into mature organisms. Thus environments that are resource-limited for species with a large body mass, may offer abundant resources allowing large population sizes for species with a small body mass. Cyclical parthenogens like *Daphnia* cycle between asexual and sexual domains, e.g. caused by population density/crowding and/or seasonal cycles.

21. Extension of Crick's central dogma of molecular biology

....it is quite wrong to think of the environment as just a selector of heritable variation. The environment has a dual role in evolution – it does not just select among heritable phenotypic variations, it also induces them.

Jablonka and Lamb, 1995

In essence, Francis Crick's (1958; 1970) central dogma of molecular biology conveys that the flow of coded information is unidirectional, i.e. from DNA to protein and never in reverse (see Judson, 1979). Crick worded the Central Dogma thus: "This states that once 'information' has passed into protein it cannot get out again. In more detail, the transfer of information from nucleic acid to nucleic acid, or from nucleic acid to protein may be possible, but transfer from protein to protein, or from protein to nucleic acid is impossible. Information means here the precise determination of sequence, either of bases in the nucleic acid or of amino acid residues in the protein" (Crick, 1958). Over the years, the central dogma has come under criticism (Shapiro, 2009; 2011). The discovery of reverse transcriptase (Baltimore, 1970; Temin and Mizutani, 1970) and prions (Prusiner, 1991), allegedly questioned Crick's central dogma (Hunter, 1999). However, as Keyes (1999) pointed out, these discoveries did not refute Crick's original formulation but clearly violated James Watson's later interpretation which claimed that the flow of genetic information was 'unidirectional' and that 'RNA never acts as a template for DNA' (Watson, 1965, p. 298). Genome sequencing has revealed abundant evidence of the importance of reverse transcription in genome evolution (Brosius, 1999; 2003; Betrán et al., 2002). Indeed, over one third of our own genomes comes from DNA copies of RNA (International Human Genome Consortium, 2001). The vision of the Central Dogma has resisted the many different challenges it has faced, including the role of chaperones in protein folding, and phenomena occurring in the transfer of information from DNA to proteins (epigenetic modifications of DNA, RNA interference, RNA splicing and RNA editing) (Morange, 2008). As Wilkins (2012), in response to Shapiro (2011) asserted, Crick's specific conclusion is still valid: nucleic acid sequence information can be read into proteins or copied into each other (DNA → RNA or RNA → DNA) but protein sequences cannot be reverse-read into nucleic acid sequences. The degeneracy of the genetic code (there is more than one way to specify an amino acid) and of the protein

code (very different amino acid sequences can form similar protein structures) clinches the argument.

It has been argued that the central dogma is of the profoundest import, for it illuminates the physiological necessity for the rejection of Lamarckism, the inheritance of acquired traits (Judson, 2004) (at least in organisms without a sequestered germline, see chapter 19.8). However, accepting the universal validity of Crick's central dogma, we are left with a dilemma. Evidence is accumulating that the environment is able to shape the phenotype of organisms not only by the action of natural selection but also by transgenerational processes (Jablonka and Lamb, 1995; 2005; 2007; Caporale, 1999; 2003a; b; 2009; Radman et al., 1999; Shapiro, 2011). How is this compatible with the central dogma?

Extending an earlier model (Heininger, 2001), I suggest that the phenotype of an organism as result of the coded information transfer DNA/RNA → protein signals back to the (epi)genome via condition-dependent but uncoded signals of the bioenergy-redox-Ca²⁺ triangle (figure 4). This feedback loop is another manifestation of the dual stochasticity-selection balance.

Tight coordination between the nucleus and mitochondria is required for proper mitochondrial functioning and includes both anterograde (nucleus to mitochondria) and retrograde (mitochondria to nucleus) signals (Allen, 2003; Butow and Avadhani, 2004; Cannino et al., 2007; Pesaresi et al., 2007; Woodson and Chory, 2008). Growth and replication of the nucleus are limited by mitochondrial energy production and thus calorie availability. The regulation of nuclear replication, gene expression and mutagenesis is mediated by mitochondrial energetics. Mitochondria are the cellular sensors for substrate supply, oxygen, bioenergetics, and redox balance (Duchen, 1999; Carrasco et al., 2001; Dzeja et al., 2002; Lane, 2005; Wright et al., 2009). Mitochondria are the key components and conductors orchestrating the cellular stress responses (Biswas et al., 2005; Manoli et al., 2007). The metabolic condition of organisms determines the adaptive stress in a given environment. The vulnerability of organellar genomes to replicative and especially oxidative damage could provide quality-control functions for detecting, correcting or removing cells with long-term or cumulative damage to both genomes, which could otherwise go undetected and compromise the survival of an organism (Wright et al., 2009). In this capacity, mitochondria are long-term redox damage sensors (Wright et al., 2009). Such signalling is presumed to occur via tonic organelle-to-nucleus (retrograde) signaling systems

(Butow and Avadhani, 2004; Janssen-Heininger et al., 2008; Woodson and Chory, 2008). These enable the nuclear compartment to respond by setting a new tonic level of nucleus-to-organelle (anterograde) signaling (Butow and Avadhani, 2004; Woodson and Chory, 2008).

Mitochondria take up calcium, and the high capacity mitochondrial calcium uptake pathway provides a mechanism that couples energy demand to increased ATP production through the calcium-dependent upregulation of mitochondrial enzyme activity (Duchen, 1999). Metabolic stress due to stress and maladaptation leads to dysregulation of the Ca^{2+} -energy-redox triangle (Brookes et al., 2004; Camello-Almaraz et al., 2006; Feissner et al., 2009; Peng and Jou, 2010). Both Ca^{2+} and redox balance mediate the mutagenetic pressure exerted by energy homeostasis. In metazoans, cellular Ca^{2+} homeostasis is under control of a highly organized reticulum formed by mitochondria and endoplasmic reticulum (Rutter and Rizzuto 2000; Csordás and Hajnóczky, 2009). Mitochondrial Ca^{2+} signalling has a profound impact on nuclear Ca^{2+} homeostasis (Faulk et al., 1995). Thus Ca^{2+} changes are relayed to the nucleus to evoke specific changes in gene expression (Roche and Prentki, 1994; Chawla and Bading, 1998; Hardingham and Bading, 1998) and via regulation of DNA repair (Gaftner et al., 1997; Korzets et al., 1999) also affect mutagenesis (Seetharam and Seidman, 1992).

ROS and RNS are the mediators of metabolic stress adaptations in all phyla. Nuclear redox systems are controlled independent of the cytoplasmic counterparts (Go and Jones, 2010). Superoxide anion, H_2O_2 and NO as relatively inert RONS have long-range signaling properties (Hancock, 1997; Rhee, 1999) and qualify as signal transducers and primary mitochondrial-nuclear messengers for gene expression (Burdon, 1995; Sen and Packer, 1996; Cimino et al., 1997; Lander, 1997; Dalton et al., 1999; Pfeilschifter et al., 2001; Turpaev, 2002; Shapiguzov et al., 2012). Proteins with oxidizable thiols are essential to many functions of cell nuclei, including transcription, chromatin stability, nuclear protein import and export, DNA replication and repair (Go and Jones, 2010). Redox regulation has been shown to play an important role in modulating the DNA binding activity of a number of transcription factors including AP-1, $\text{NF}\kappa\text{B}$, HIF-1 α , HLF, CREB, PAX, p53, Egr-1, and others (Abate et al., 1990; Xanthoudakis and Curran, 1992; Xanthoudakis et al., 1992; 1994; Huang and Adamson, 1993; Yao et al., 1994; Huang et al., 1996; Sun and Oberley, 1996; Akamatsu et al., 1997; Jayaraman et al., 1997; Ema et al., 1999;

Gaiddon et al., 1999; Evans et al., 2000; Lando et al., 2000; Hanson et al., 2005). The thiol groups of the cysteines involved in the zinc-finger motif as part of the metal-binding, DNA-intercalating fingers (Kadonaga et al., 1987; Desjarlais and Berg, 1992) confer gene regulation by ROS (Cimino et al., 1997). These zinc finger structures are potentially very sensitive redox targets in DNA binding motifs of many DNA transcription factors and DNA repair enzymes (Berg, 1992; Rhodes and Klug, 1993; Wu et al., 1996). Through Fenton-type reactions transition metals, e.g. iron and copper (Pierre and Fontecave, 1999), may displace zinc ions in zinc-finger motifs located at the DNA target sites and convert RONS into more aggressive radicals, e.g. hydroxyl radical (Wink et al., 1994; Pecci et al., 1997) or peroxynitrite, which dose-dependently (Martin and Barrett, 2002) control gene expression of stress response systems and cell cycle events (O'Halloran, 1993; Cimino et al., 1997; Boldt, 1999), induce DNA breaks (Mello-Filho and Meneghini, 1984; Kazakov et al., 1988; Tachon, 1989; Bertocini and Meneghini, 1995; Spear and Aust, 1995; Meneghini, 1997; Rodriguez et al., 1999), epimutagenesis (see chapter 10.3) and mutagenesis (see chapter 10.1) and mediate a variety of cell cycle events including differentiation (see chapter 6.1), apoptosis (see chapter 10.5) and carcinogenesis (Cerutti, 1985; Babbs, 1990; Lutz, 1990; Dreher and Junod, 1996; Tamir and Tannenbaum, 1996; Marnett, 2000; Klaunig and Kamendulis, 2004; Matés et al., 2008; Toyokuni, 2008; Klaunig et al., 2010; Liou and Storz, 2010; Sosa et al., 2013). Thus, the cellular energy flow, Ca^{2+} homeostasis and redox balance determine cellular-context and dose-dependent events like proliferation, differentiation, apoptosis, necrosis and oncosis.

This flow of information is not coded and specific as from gene to protein but code-free and stochastic. The randomness of the feedback process from environment to the genome process relies on the simple, codeless messenger agents ATP, Ca^{2+} and free radicals (Saran et al., 1998) both regulated by and regulating cellular and organismal homeostasis in a feedback triangle (Brookes et al., 2004; Camello-Almaraz et al., 2006; Yan Y et al., 2006; Feissner et al., 2009; Kowaltowski et al., 2009). Cellular oxidative stress-dependent responses, although undoubtedly programmed, are also highly variable (Heininger, 2012), at least in part based on the stochasticity of mitochondrial bioenergetic/oxidative events (Hüser et al., 1998; Genova et al., 2003; Passos et al., 2007; Wang W et al., 2008). In addition to cellular processes, these agents regulate organismal life history events like

development and aging (Heininger, 2012) in response to environmental cues. The regulated stochastic nature of the effectors and the degeneracy of (epi)mutagenic tools that may act both as a source of robustness and evolvability (see chapter 13) allows multiple solutions for a given problem (Lenski and Travisano, 1994; Rosenzweig et al., 1994; Finkel and Kolter, 1999) and therefore has given rise to the huge diversity of evolution with an ever increasing complexity (Adami et al., 2000).

22. Conclusions

What is utterly baffling to me is why one cannot be a reductionist and a holist at the same time.

John Tyler Bonner, *The Evolution of Complexity*, 1988

Simplification may indeed be necessary for news articles, but it can distort the more complex and subtle realities of evolutionary patterns and mechanisms

Carroll (2005) *Endless Forms Most Beautiful*

Of all forms of mental activity, the most difficult ... is the art of handling the same bundle of data as before, but placing them in a new system of relations with one another by giving them a different framework.

Thomas Kuhn, 1962

I attempted to decipher the evolutionary success of sexual reproduction by a Herschelian approach (Herschel, 1830). As Gildenhuys (2004) wrote: "For Herschel, scientific inquiry is a two-step process, beginning with the explanation of phenomena, through the exposure of their often hidden causes, and ending with the generalization of these causal processes to form laws of nature (1987, p. 144; first published 1830). Causal explanation involves decomposing a phenomenon into its component causes, a process Herschel calls 'analysis', comparing it to the decomposition of substances performed by chemists. During the analysis phase of inquiry, the researcher must discover the hidden operations that are responsible for outwardly sensible phenomena (ibid., p. 92)."

When embarking on the mission to elucidate the workings of a clock you can make two fundamental mistakes: the holist and reductionist mistake. The former was described by Feldman and Lewontin (1975) when they wrote: "There is a vast loss of information in going from a complex machine to a few descriptive parameters. Therefore, there is immense indeterminacy in trying to infer the structure of the

machine from those few descriptive variables, themselves subject to error. It is rather like trying to infer the structure of a clock by listening to it tick and watching the hands." Reductionists, on the other hand, may devote a whole scientific life to the study of a gearwheel in the clockwork, describe its size, the alloy it is made from, the number and form of its teeth, infer its function in the whole system from the effects of slowing-down and accelerating its movement and it is easily comprehensible that they finally may come to the conclusion that the gearwheel is the centerpiece and moves the clockwork. But the gearwheel may be only one amongst many and it is questionable whether the workings of the whole clockwork can be understood from its action. Yet, the reductionist approach is the only feasible method to understand the functioning of the clockwork as a whole. But there is no shortcut to study ALL gearwheels and their interactions. Conventional concepts of sexual reproduction considered a multitude of design features (most often from a population genetics approach) but they failed to apply an eminent principle: a systemic approach taking all nuts and bolts of the problem into account. A systemic approach is required to solve the Kuhnian puzzle. The insight that drives systems biology is that a full understanding of the role played by any one component in a biological process can be achieved only by considering it in its appropriate context in the whole system. In this sense, systems biology goes beyond a reductionist paradigm in which the properties of system components are considered in isolation (Bennett and Monk, 2008).

P. Kitcher (1981) advanced the idea that "...the natural sciences do not merely pile up unrelated items of knowledge of more or less practical significance, but that they increase our understanding of the world" (p. 508). And: "By using a few patterns of argument in the derivation of many beliefs we minimize the number of types of premises we must take as underived. That is, we reduce, in so far as possible, the number of types of facts we must accept as brute" (p. 529). Kitcher elaborated on earlier thoughts of Hempel: "What scientific explanation, especially theoretical explanation, aims at is not [an] intuitive and highly subjective kind of understanding, but an objective kind of insight that is achieved by a systematic unification, by exhibiting the phenomena as manifestations of common, underlying structures and processes that conform to specific, testable, basic principles" (Hempel 1966, p. 83; see also Hempel 1965, pp. 345, 444); and Feigl: "The aim of scientific explanation throughout the ages has been unification, i.e., the comprehending of a maximum of facts and regularities in terms of a minimum of theoretical concepts and assumptions"

(Feigl 1970, p. 12).

In 1982, Graham Bell wrote: "Sex is the queen of problems in evolutionary biology". Obviously, he coined this sentence for the issue of understanding the evolutionary rationale for the success of sexual reproduction. However, since genetic transmission by sexual reproduction is so pervasive in nature, the sentence has its connotation. A multitude of issues in evolutionary biology and population genetics have been virtually intractable without an in-depth understanding of the molecular mechanisms underlying sexual reproduction.

This and my previous work (Heininger, 2012) mark a fundamental change of paradigm. Both should not be seen independent of each other. In fact, they draw a huge coherent scenario within which reproduction and death unfold, both coselected and orchestrated by stochasticity and selection as the two general organizing principles of evolution.

These insights should have a major impact on the entire biomedical sciences, and particularly evolutionary theory.

23. Abbreviations

8 - oxoG: 8-oxoguanine
 APE1: apurinic/aprimidinic endonuclease 1
 AQP: aquaporin
 BER: base excision repair
 CE: Cambrian explosion
 CRH: corticotropin-releasing hormone
 EGT: evolutionary game theory
 eIF2: eukaryotic translation initiation factor 2
 ESS: evolutionarily stable strategy
 GA: Genetic Algorithm
 GPG: General Purpose Genotype
 HIF: hypoxia-inducible factor
 HO: heme oxygenase
 HR: homologous recombination
 HPA: hypothalamic-pituitary-adrenal
 HPG: hypothalamic-pituitary-gonadal
 HSP: heat shock protein
 MMR: mismatch repair
 NER: nucleotide excision repair
 NHEJ: non-homologous end joining
 PAE: paternal age effect

PGCs: primordial germ cells
 RONS: reactive oxygen nitrogen species
 ROS: reactive oxygen species
 SAM: S-adenosyl-L-methionine
 SNPs: single nucleotide polymorphisms
 SGs: stress granules
 SMSC: sexual mutagenesis selection cascade
 TAM: transcription-associated mutagenesis
 TAR: transcription-associated recombination
 TCA: tricarboxylic acid
 TE: transposable element
 Tet: ten eleven translocation
 VEGF: vascular endothelial growth factor

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Illustrations

Illustration 1

Figure 1

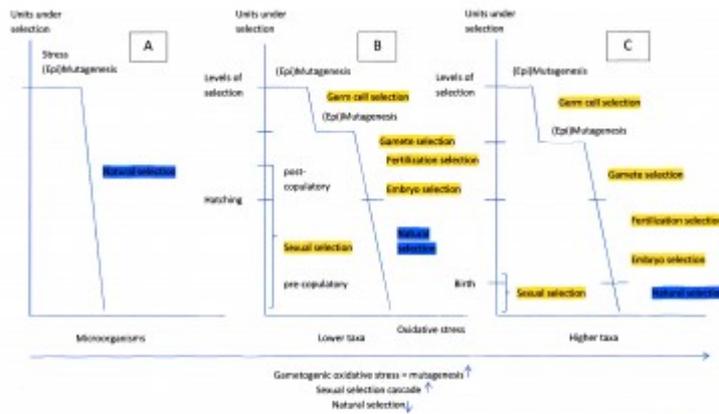


Figure 1: Figure 1A: Category 1; B: Category 2; C: Category 3 (see chapter 31.2 for category features). The sexual selection cascades are highlighted yellow. The population size subject to natural selection is highlighted blue. From category 1 to 3 the gametogenic oxidative stress and stringency of sexual selection cascades (quality control) increases while the importance of natural selection (= population size under natural selection) decreases.

Illustration 2

Figure 2

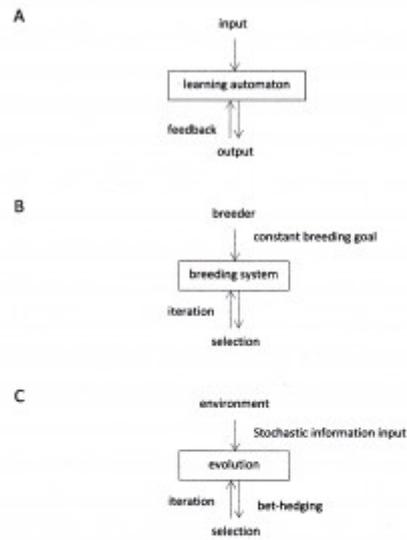


Figure 2.

A: Cybernetic systems are characterized by feedback control. They are a special class of cause-and-effect (input-output) systems. Learning automata are adaptive decision-making devices operating on unknown random environments. Iteration is required for feedback control.

B: In artificial selection, the breeder determines the constant direction of the breeding goal and selects the individuals for the next round of breeding.

C: In evolution, the direction and regime of selection are established by the environment. However, the target, adaptation to varying biotic and abiotic environmental conditions, is a moving target and selection can be highly fluctuating. Bet-hedging is the adaptive response to environmental stochasticity.

Illustration 3

Figure 3

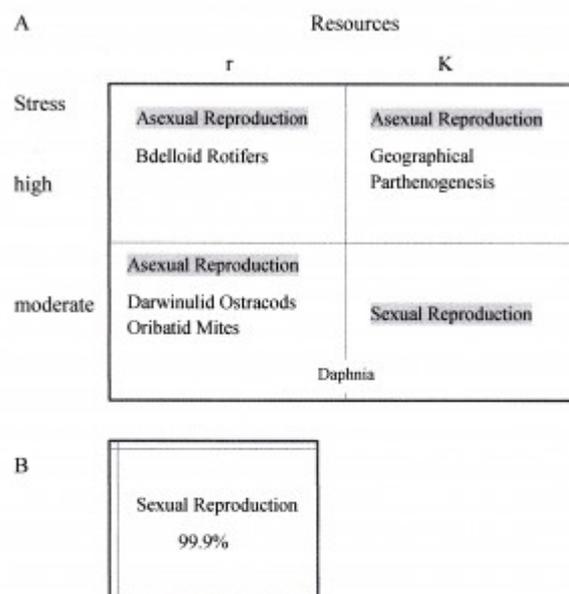


Figure 3.

Ecological window of asexual and sexual reproduction in unitary organisms. A: Stress intensity (moderate or harsh) and resource availability (r- and K-selected environments) relative to resource investment define the four quadrants of the window. B: Skewed window reflecting more realistically the ecological distribution of sexual and asexual reproduction. Importantly, in most organisms with a larger body mass, ecological conditions favor sexual reproduction with its pre-selection of viable zygotes.

Illustration 4

Figure 4

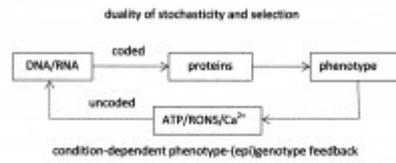


Figure 4. Extension of Crick's central dogma of molecular biology. The flow of **coded** information is unidirectional, i.e. from DNA/RNA to protein and never in reverse. The **phenotype** signals back to the (epi)genome via condition-dependent but **uncoded** signals of the energy-redox- Ca^{2+} triangle. The feedback occurs via stochastic signals that promote either conservation (DNA repair) or innovation (mutagenesis) of the (epi)genomic information. The duality of stochasticity and selection acts both at the subcellular, cellular, organismal and group level.

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