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Ageing Research Reviews
1 (2002) 481–536

ageing
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Review

Aging is a deprivation syndrome driven by a germ–soma conflict

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Received 21 December 2001; accepted 22 December 2001

Abstract

Evolution through natural selection can be described as driven by a perpetual conflict of individuals competing for limited resources. Recently, I postulated that the shortage of resources godfathered the evolutionary achievements of the differentiation-apoptosis programming [Rev. Neurosci. 12 (2001) 217]. Unicellular deprivation-induced differentiation into germ cell-like spores can be regarded as the archaic reproduction events which were fueled by the remains of the fratricided cells of the apoptotic fruiting body. Evidence has been accumulated suggesting that conserved through the ages as the evolutionary legacy of the germ–soma conflict, the somatic loss of immortality during the ontogenetic segregation of primordial germ cells recapitulates the archaic fate of the fruiting body. In this heritage, somatic death is a germ cell-triggered event and has been established as evolutionary-fixed default state following asymmetric reproduction in a world of finite resources. Aging, on the other hand, is the stress resistance-dependent phenotype of the somatic resilience that counteracts the germ cell-inflicted death pathway. Thus, aging is a survival response and, in contrast to current beliefs, is antagonistically linked to death that is not imposed by group selection but enforced upon the soma by the selfish genes of the "enemy within". Environmental conditions shape the trade-off solutions as compromise between the conflicting germ–soma interests. Mechanistically, the neuroendocrine system, particularly those components that control energy balance, reproduction and stress responses, orchestrate these events. The reproductive phase is a self-limited process that moulds onset and progress of senescence with germ cell-dependent factors, e.g. gonadal hormones. These degenerate the regulatory pacemakers of the pineal–hypothalamic–pituitary network and its peripheral, e.g. thymic, gonadal and adrenal targets thereby eroding the trophic milieu. The ensuing cellular metabolic stress engenders adaptive adjustments of the glucose–fatty acid cycle, responses that are adequate and thus fitness-boosting under fuel shortage (e.g. during caloric restriction) but become detrimental under fuel abundance. In a Janus-faced capacity, the cellular stress response apparatus expresses both tolerogenic and mutagenic features of the social and asocial deprivation responses [Rev. Neurosci. 12 (2001) 217]. Mediated by the derangement of the energy–Ca^{2+}–redox homeostatic triangle, a mosaic of dedifferentiation/apoptosis and mutagenic

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PII: S1568-1637(02)00015-6

responses actuates the gradual exhaustion of functional reserves and eventually results in a multitude of aging-related diseases. This scenario reconciles programmed and stochastic features of aging and resolves the major inconsistencies of current theories by linking ultimate and proximate causes of aging. Reproduction, differentiation, apoptosis, stress response and metabolism are merged into a coherent regulatory network that stages aging as a naturally selected, germ cell-triggered and reproductive phase-modulated deprivation response.

Keywords: Aging; Longevity; Deprivation syndrome; Evolution; Reproduction; Gonadal hormones; Stress resistance; Metabolism; Oxidative stress; Mitochondria; Caloric restriction; Hormesis; Metabolic syndrome; Mutagenesis; Glucocorticosteroids; Insulin; Leptin; NPY; Differentiation; Apoptosis; Cancer; Alzheimer's disease; Diabetes mellitus; Glucose–fatty acid cycle; Germ–soma conflict theory

1. Introduction

Aging is almost universal in all phyla but despite of intense scientific efforts its evolutionary rationale has not yet been convincingly defined. The enigma is highlighted by the fact that the waning of vigor is not a biological must, biological systems are able to maintain immortality at the cellular level as is evidenced by the billion of years' propagation of unicellular organisms and germ line cells of multicellular organisms. Theories of aging can be broadly grouped into two classes: programmed (intrinsic) and stochastic (extrinsic) theories. The former include a variety of genetic determinants while the latter embrace somatic and mitochondrial mutations, oxidative stress and protein glycation (Rose, 1991; Ricklefs and Finch, 1995; Austad, 1997; Arking, 1998). Theories need plausible mechanisms as persuasive vehicles (e.g. Darwin's evolution by natural selection). The wealth of aging theories, however, have been unable to link the proximate (mechanistic) and ultimate (causal) processes of aging. Data do not leave any doubt that aging is naturally selected and genetically programmed across all phyla (Finch, 1990; Rose, 1991; Ricklefs and Finch, 1995; Finch and Tanzi, 1997; Arking, 1998; Guarente and Kenyon, 2000; Finch and Ruvkun, 2001). Darwin's theory of natural selection requires that evolutionary changes be adaptive, that is, that they be useful to the organism and not degenerative. Therefore, aging theories have to reflect the fact that aging, despite its phylogenetic persistence and genetic programming, appears to have an adverse impact on Darwinian fitness of the individual (Ricklefs and Finch, 1995; Kirkwood, 1997). Conceptually, this contraintuitive dilemma has been approached by the currently advocated "evolutionary theories of ageing" assuming that aging is due to the declining force of natural selection at later ages (Finch, 1990; Rose, 1991; Ricklefs and Finch, 1995; Arking, 1998). The mutation accumulation hypothesis attributes senescence to the accumulation of deleterious mutations with late-life detrimental effects (Medawar, 1952). The antagonistic pleiotropy hypothesis postulates the selection for alleles trading early-life fitness with late-life costs (Williams, 1957). Extending these theories, the disposable soma theory holds that aging reflects an optimal fitness balance between investment in reproduction and maintenance of the soma (Kirkwood, 1977, 2001; Partridge and Barton, 1993; Draye and Lints, 1996). This balance is environmentally modulated (Austad, 1997; Draye and Lints, 1996).

Recently, I defined a deprivation syndrome which is a universal response pattern to environmental stress and has been programmed as prototypic response of organisms to metabolic

stress (Heininger, 2001). These processes evolved in unicellular organisms and serve to either resist or mutagenically adapt to environmental stressors and in a consecutive step were developed as key mechanisms of differentiation, apoptosis and reproductive behavior. These mechanisms have been fixed and programmed as life- and cell-cycle events in multicellular organisms and constitute the core of sexual reproduction and ontogenetic and oncogenetic events. The deprivation syndrome represents a proto-formula and driving force of life and was postulated to provide the molecular processes through which the environment created the phenomena of phylogenesis as outlined by Charles Darwin. Here, the notion is further elaborated that in a world of limited resources aging evolved as a somatic survival pathway in response to the death sentence imposed by evolutionary pressure and executed by the differentiation-arisen germ cells (Heininger, 2001). The germ–soma conflict, an evolutionary legacy of the asymmetric reproductive event and the archaic differentiation-apoptosis response, is modulated by environmental cues and stress response pathways. The integration of differentiation, apoptosis, reproduction, stress response and metabolism into the coherent regulatory network of aging may be regarded as the test of concept for the deprivation syndrome paradigm.

2. Determinants of longevity

Analysis of the determinants of longevity should give important clues about aging-related processes and their regulatory framework. In the nematode *Caenorhabditis elegans*, a popular model organism in aging studies, longevity is dependent on a multitude of genes that are also involved in the regulation of metabolism, reproduction, stress responses and antioxidant defences (Hekimi et al., 1998; Riddle, 1999; Johnson et al., 2000; Braeckman et al., 2001; Finch and Ruvkun, 2001). In addition, these regulatory pathways control diapause (dauer larva formation), a developmental adaptation characterized by metabolic dormancy and stress resistance in response to harsh conditions (Hekimi et al., 1998). A pattern of stress-related genes that are upregulated during dauer formation is also prevalent in long-lived, aged and starved adult nematodes (Cherkasova et al., 2000). Conversely, these regulatory pathways are themselves regulated by germline-dependent factor(s) (Hsin and Kenyon, 1999; Riddle, 1999; Lin et al., 2001a,b). These pathways are conserved throughout phylogeny from yeast, nematodes and flies to mammals (Lin et al., 1998; Longo, 1999; Finch and Ruvkun, 2001; Jazwinski, 2001). The expression of longevity depends on gene-environment interactions (Clare and Luckinbill, 1985). In a variety of model systems, exposure to a multitude of stressors increases longevity (Braeckman and Vanfleteren, 1999; Johnson et al., 2000). Thus, senescence appears to be modulated by environmental cues that are relayed by sensory perception (Apfeld and Kenyon, 1999). A putative integrative site for these regulatory actions is the neurosecretory system, particularly the hypothalamic–pituitary–gonadal (HPG) axis (Boulianne, 2001; Braeckman et al., 2001; Finch and Ruvkun, 2001). From nematodes to mammals, interspecies and interstrain comparisons confirm multiple variables of oxidative stress exposure as determinants of lifespan. Genetic or therapeutic manipulations causing or attenuating oxidative stress shorten or prolong lifespan, respectively (Munkres et al., 1984; Larsen, 1993; Orr and Sohal, 1994; Sohal and Weindruch, 1996; Ishii, 2000; Golden and Melov, 2001). Independent lines of

evidence point at mitochondria as cellular pacemakers of aging (Sohal and Weindruch, 1996; Barja, 2000; Salvioli et al., 2001). Mitochondrial respiratory activity, energy homeostasis and mtDNA mutations are involved in determining aging in animals as diverse as *C. elegans* and mouse (Melov et al., 1999; Kayser et al., 2001; Tsang et al., 2001). Compatible with the non-Mendelian maternal heritage of mitochondria, longevity is an, at least in part, maternally inherited feature in a variety of species (Da Cunha and Oliveira, 1996; Vandenbroucke, 1998; Korpelainen, 1999). Discrete mtDNA haplogroups are associated with longevity and resistance to aging-related diseases (Tanaka et al., 2000; De Benedictis et al., 2001). From an analysis of determinants of longevity, aging can be tentatively characterized as the composite result of a gene-environment interaction, regulated by stress, metabolic factors and reproduction.

3. The evolutionary roots of aging

According to the Gompertz demographic model, aging and mortality are deterministically linked. However, while death is inevitable in almost all Metazoa, aging trajectories may differ widely, ranging from catastrophic (Lee and Cockburn, 1985; Finch, 1990; Wilson, 1997) to negligible aging (Finch, 1990, 1998). Paradoxically, much can be learned about the evolutionary roots of aging by looking at organisms who, in principle (with few exceptions), do not die, the prokaryotes. Death would be an evolutionary dead end street in these germ cell-like organisms which proliferate by replication and in which the original organism goes up in its descendants. The distinction between germ line and soma, as recognized by Weismann (1889), is at the core of the evolution of aging in multicellular organisms (Bell, 1984). Germ cells are principally immortal and constantly rejuvenated (Medvedev, 1981). In contrast, somatic aging and death as a constitutive element of life in an evolutive system (Wallace, 1967; Theodoridis et al., 1996) could only evolve and persist with the advent of asymmetric and sexual reproduction (Partridge and Barton, 1993; Stearns, 2000) leading to age-structured populations (Charlesworth, 1994). Death would not have been an evolutionary necessity in a world of unlimited resources. The pervasive nature of the limited resources paradigm can be easily illustrated. The unrestrained growth of a bacterial culture for 14 days would yield a biomass exceeding the actual biomass on earth. After 200 generations, the number of bacteria would even exceed the total number of atoms in the universe (Dawkins, 1995). Reproduction itself drives the organisms to constantly outgrow the available resources and thus is the imperative force behind the persistent shortage. Therefore, the elimination of the aged, redundant ancestors and their competition for food should have conferred an evolutionary advantage to the genes of the progeny.

Aging is an evolutionary achievement of unicellular organisms. By asymmetric division, some yeast and fungi strains generate daughter cells which, in contrast to symmetrically dividing bacteria, leave the mother cell intact (Horvitz and Herskowitz, 1992). Yeast senescence is characterized by increased cell size, slower cell cycles and loss of fertility. Both a strong genetic component (Jazwinski, 1993, 2000, 2001) and modulation by environmental factors such as stressors (Braeckman and Vanfleteren, 1999; Jazwinski, 2001) are features of yeast aging. Asymmetric division being associated with reproductive aging has even been demonstrated in a prokaryote, the bacterium *Caulobacter crescentus* (Pennisi, 2000).

Key to the etiological appreciation of aging is the fact that aging has its phenomenological counterpart in bacteria which enter stationary phase following nutrient deprivation according to their "feast and famine" lifestyle (Kolter et al., 1993; Heininger, 2001). "Aging" of bacterial cultures under limiting fuel conditions displays the elementary features of cells in an aging organism, characterized by hypometabolism, increased energy storage, oxidative stress, heat shock protein (HSP) expression and effective or defective DNA repair, the latter resulting in mutagenesis (Longo, 1999; Nyström, 1999; Heininger, 2001). Phenotypic similarities are suspects of shared evolutionary roots (Heininger, 2001); but how may the evolutionary step have been accomplished, converting a facultative response to nutrient stress into a phylogenetically fixed, constitutive disposal of the old? A variety of regulatory interactions between the stationary phase survival response and aging are encountered in yeasts and fungi. During stationary phase, a famine response, mitochondrial oxidative stress (Longo et al., 1996) exhausts antioxidant defence (Jakubowski et al., 2000) and decreases respiratory function followed by death (Longo et al., 1996). In line with these findings, lack of antioxidant enzymes deteriorates yeast stationary phase survival (Longo et al., 1996; Jakubowski et al., 2000) and accelerates aging (Barker et al., 1999; Nestelbacher et al., 2000), an effect which can be reversed by antioxidants (Nestelbacher et al., 2000). As response to DNA damage, DNA repair is up-regulated in stationary phase (Siede and Friedberg, 1990; Sweet et al., 1997) and DNA damage appears also to be a feature of yeast aging as evidenced by the shortened lifespan of DNA repair gene mutants (Park et al., 1999). On the other hand, a variety of mutants, selected on the basis of extended survival under starvation conditions, had extended replicative lifespans (Kennedy et al., 1995). As another link between aging and stationary phase adaptation, cellular energy utilization and glucose metabolism are also altered during aging mediated by regulatory pathways which play a role in global responses to glucose starvation, stationary phase survival (Ashrafi et al., 2000; Lin et al., 2001a,b) and oxidative stress (Godon et al., 1998). The yeast starvation response itself appears to be progeroid, since it accelerates poststationary-phase aging (Ashrafi et al., 1999).

Like all microorganisms, colonies of asymmetrically reproducing eukaryotes, feeding on a carbon source in their natural habitat, experience intermittent nutrient deprivations (de Winde et al., 1997). Repetitive "feast and famine" cycles may have curbed the investments in somatic maintenance as suggested by the disposable soma theory (Kirkwood, 1977, 2001). According to this concept, in response to environmental hazards organisms are programmed to balance their investment in both the maintenance of the soma and reproduction (Kirkwood, 1977, 2001; Stearns, 2000). The progeroid action of the yeast starvation response (Ashrafi et al., 1999) is evidence for this adaptive behavior. Conserved throughout phylogenesis, the acceleration of aging due to increased extrinsic mortality has been demonstrated in asymmetrically dividing bacteria (Pennisi, 2000), zooplankton (Dudycha and Tessier, 1999), fruit flies (Stearns et al., 2000), fish (Reznick et al., 2001), birds (Ricklefs, 1998) and mammals (Austad, 1993). Investment in somatic maintenance is also determined by adult mortality in plants (Franco and Silvertown, 1996). Importantly, the relationship between extrinsic mortality and the reproduction-somatic maintenance balance is density-dependent as has been predicted theoretically (Abrams, 1993) and shown experimentally (Graves and Mueller, 1993; Gage, 1995; Riha and Luckinbill, 1996; Tucic et al., 1997). In terms of population dynamics, density determines the availability of resources to the individual.

The density dependence of germ–soma trade-off thus mirrors the deprivation rationale of senescence.

A multitude of abnormalities emphasizes the causal involvement of mitochondria in protozoan replicative aging. Aging-related decrement of antioxidant capacity (Grzelak et al., 2001) and increased mitochondrial generation of reactive oxygen species (ROS) (Laun et al., 2001) may underlie the accumulation of deleterious mutations, particularly of mitochondrial DNA (mtDNA) (Thacker and Parker, 1976). It should be stressed that mtDNA has only limited repair mechanisms, is not protected by histones and is close to the inner membrane where ROS are produced (Heininger, 1999a, 2001). Since mtDNA is more vulnerable to oxidative stress than nuclear (n)DNA, the age-related increase of oxidative damage of DNA is more prevalent in mt than nDNA (Hudson et al., 1998) and mtDNA has evolved more rapidly than nDNA (Vawter and Brown, 1986). Metabolism, mitochondrial oxidative stress, mitochondrial membrane potential and mtDNA rearrangements are linked to each other in a progeroid cascade of events (Koll et al., 2001; Osiewacz and Stumpferl, 2001). Mutants of *Neurospora crassa* display constitutive aging and death, characterized by oxidative stress (Munkres et al., 1984) and mtDNA instability (Bertrand et al., 1993). Corroborating the key role of oxidative stress, the lifespan of the protozoan *Paramecium tetraurelia* can be extended by the antioxidant melatonin (Thomas and Smith-Sonneborn, 1997). Yeast and fungal aging is modulated by retrograde signalling-effector loops between mitochondria and nucleus (Osiewacz and Kimpel, 1999; Jazwinski, 2000, 2001). This signalling pathways impart information about the mitochondrial efficiency and result in the expression of nuclear-coded mitochondrial proteins (Jazwinski, 2000, 2001; Heininger, 2001). A mechanism underlying the replicative clock and, hence, lifespan determination may depend on the asymmetric distribution of mitochondria between yeast mother and daughter cells which is caused by a cytoskeleton-dependent polarized movement of mitochondria (Simon et al., 1997; Yang et al., 1999).

4. Cellular and somatic aging

During evolution, cellular stressors, particularly shortage of nutrients and building blocks, have given rise to multiple adaptive behaviors, such as stress resistance and mutagenesis (Storz and Hengge-Aronis, 2000; Heininger, 2001). The advent of cellular cooperativity and multicellularity widened the spectrum allowing the elaboration of the social differentiation/apoptosis responses (Heininger, 2001). Under nutrient shortage, social bacteria and Protozoa (e.g. *Streptomyces*, *Dictyostelium*) differentiate into a dying fruiting body and germ cell-like spores. In a continued heritage, Metazoa segregated immortal germ cells from the mortal soma by an early differentiation event, thereby, reproducing asymmetrically in a specialized tissue. This asymmetry-generating event can be regarded as the evolutionary origin of metazoan constitutive aging/mortality. In the process of metazoan aging, cellular and somatic deprivation responses are intertwined in an intriguing cascade of events. Cellular features like resistance to stress (Kirkwood et al., 2000), DNA repair capacity (Hall et al., 1984) and replicative potential (Juckett, 1987; Hayflick, 1994; Arking, 1998) correlate with animal lifespan, highlighting the interdependence of cellular and somatic aging.

4.1. Cellular replicative senescence

By means of asymmetric division, metazoan somatic cells create daughter cells with different developmental potentials, which is of fundamental significance for the generation of cell diversity (Horvitz and Herskowitz, 1992). These cells have a limited replicative potential and undergo a variety of aging-related changes. Replicative senescence of cells is associated with oxidative stress, DNA damage and downregulated DNA repair (Chen et al., 1995; Norwood and Gray, 1996; Gilchrest and Bohr, 1997; Serrano and Blasco, 2001). Premature cellular senescence is also elicited by energetic stress and a variety of other stressors (Corbisier and Remacle, 1993; Toussaint et al., 2000; Serrano and Blasco, 2001). On the other hand, repeated mild stressors are able to delay the onset of various cellular senescence-related changes (Verbeke et al., 2000), mimicking the hormesis phenomenon (Section 10). Cellular stress responses in bacteria, including the stationary phase adaptations, are controlled by the so-called SOS system (Storz and Hengge-Aronis, 2000). Reflecting the phylogenetic continuity of the stationary phase/aging response, cellular senescence in metazoan cells is regulated by p53 (Wynford-Thomas, 1996; Itahana et al., 2001), a homologue of the bacterial SOS system (Heininger, 2001). The central role of mitochondria in the generation of cellular senescence is indicated by a variety of circumstantial evidences. For instance, mitochondrially generated ROS are the predominant effectors of cellular senescence (Sohal and Weindruch, 1996). Members of a mitochondrial HSP family are involved in cellular senescence and immortalization (Wadhwa et al., 2000). Like stationary phase and differentiation (Heininger, 2001), cellular senescence may be associated with a state of tolerance that characterizes specialized survivors (Wang, 1995; Yeo et al., 2000).

The role of specialized nucleoprotein complexes that protect the chromosome extreme ends and function as mitotic clocks, the telomeres, in cellular senescence has been recognized (von Zglinicki, 2000). Their role in somatic aging, however, is discussed controversely (Campisi, 2001; Kipling, 2001; Klapper et al., 2001). At any rate, the loss of telomere maintenance may affect cellular replicative senescence in renewable tissues with adverse consequences, e.g. for immunosenescence and carcinogenesis (Rudolph et al., 1999; Campisi, 2001).

4.2. Differentiation, apoptosis and somatic aging

In unicellular organisms, differentiation events were programmed as responses, e.g. to nutrient shortage and served to ensure the survival of extremely resilient germ-like cells as spores. The building blocks and nutrients to fuel this complex metamorphosis, however, are depleted in the environment and hence, have to be provided by dead siblings (Heininger, 2001). By segregating immortal germ cell-like spores from a mortal body, e.g. a fruiting body in *Myxococcus* or *Dictyostelium* (Heininger, 2001), these differentiation events evolved as another, a metazoan, type of asymmetric reproduction. Key for the understanding of the death/aging riddle is the notion that mortality and potency are controlled by differentiation events. In higher Metazoa somatic cells, totipotency and immortality is lost with the first differentiation events following the blastula stage (Clark, 1999). Cellular retrodifferentiation or plasticity of differentiation in primitive Metazoa, e.g. the hydra (Bode et al., 1986; Piraino et al., 1996), on the other hand, may prevent the persistent loss of totipotency and immortality

(Piraino et al., 1996; Martinez, 1998). Cellular immortality can also be recovered in Metazoa by regression to unicellular life forms during malignant transformation (Heininger, 2001). In plants, dedifferentiation of somatic cells in localized regions, the meristems (Nagata et al., 1994; Sugiyama, 1999), leads to clonal growth and potential immortalization. Likewise, asexually reproducing lower metazoa may achieve continuous rejuvenation and immortalization by vegetative differentiation/dedifferentiation cycles (Balser, 1998; Kawamura and Fujiwara, 2000) which appear to be fueled by apoptotic events (Balser, 1998). Thus, senescence of the mother soma and vegetative reproduction in plants and animals due to circumscribed dedifferentiation of somatic cells are not mutually exclusive events (Martinez and Levinton, 1992) but highlight the role of differentiation for the loss of totipotency and immortality.

The whole range of differentiation/apoptosis features that segregates immortal germ cells and mortal somatic cells is phylogenetically conserved in *Xenopus* (Hensey and Gautier, 1998), avian (Sanders et al., 1997) and mammalian embryogenesis (Tam and Behringer, 1997; Manova et al., 1998), particularly during gastrulation when primordial germ cell specification occurs (Tam and Behringer, 1997; Pesce and Scholer, 2000). Evidence that includes the finding of an increased vulnerability of these cells to ionizing radiation (Heyer et al., 2000), toxic agents (Pampfer, 2000) and TNF-α (Sanders et al., 1997) suggests the effector role of oxidative stress and thus the deprivation legacy of the germ cell specification event (Heininger, 2001). Asymmetric division is a prerequisite of germ cell specification in the multicellular alga *Volvox* (Miller and Kirk, 1999). A variety of genetic markers of germline specification are conserved throughout the animal kingdom (Gavis, 1997; Saffman and Lasko, 1999; Wylie, 1999) as witnesses of the inherited potency–mortality regulation. Vasa-related genes, a marker of totipotency, are expressed in germline cells of *C. elegans*, *Drosophila*, *Xenopus* (Ikenishi, 1998), planarians (Shibata et al., 1999), fishes (Knaut et al., 2000), birds (Tsunekawa et al., 2000), rodents (Toyooka et al., 2000) and humans (Castrillon et al., 2000). Planarian somatic cells, called neoblasts, have retained a strong regenerative potential and express a vasa-like gene (Agata and Watanabe, 1999; Shibata et al., 1999). Upon differentiation the neoblasts lose their vasa expression and totipotency (Shibata et al., 1999). The specification of germ cells occurs very early by asymmetric distribution of germ plasma. The vasa gene product is a cytoplasmic component that is segregated in germ cell precursors at the late blastula stage before gastrulation (Ikenishi, 1998; Knaut et al., 2000; Tsunekawa et al., 2000). Intriguingly, vasa encodes an RNA helicase and RNA helicases have been found to be essential for sexual development and G1 arrest in yeast (Maekawa et al., 1994), social development in *Dictyostelium* resulting in spore/fruiting body formation (Machesky et al., 1998) and germ cell determination in nematodes (Roussell et al., 1994). Mitochondrial ribosomal RNA is an indispensable factor of germ cell determination (Iida and Kobayashi, 1998; Kashikawa et al., 1999). Thus, mitochondrial translation machinery (Kashikawa et al., 1999) and respiratory activity (Akiyama and Okada, 1992) appear to be phylogenetically conserved determinants of spore (germ cell) formation in Protozoa (Maekawa et al., 1994; Machesky et al., 1998) and primordial germ cell specification in Metazoa (Iida and Kobayashi, 1998; Kashikawa et al., 1999). Remarkably, mitochondria undergo a prespore-specific functional and structural transformation in *Dictyostelium* (Matsuyama and Maeda, 1998; Inazu et al., 1999) which may be a predecessor of the metazoan primordial germ cell-defining nuage/sponge-like formation (Gavis, 1997;

Wilsch-Brauninger et al., 1997). The importance of germ cell cytosolic factor(s) for the rejuvenation of the genome has been demonstrated recently. Nuclear transfer from senescent bovine fibroblasts into oocytes rejuvenated the replicative lifespan and telomere lengths in the cloned animals (Lanza et al., 2000). A mammal transcription factor, Oct-4, is expressed in totipotent embryonic stem cells, is down-regulated during differentiation into somatic tissues but maintained in postgastrulation primordial germ cells and appears to be essential for their totipotency (Pesce and Scholer, 2000). Intriguingly, different viruses have evolved oncoproteins that target Oct-4 and in this stem cell-specific activity may play a role in malignant transformation (Brehm et al., 1999).

5. Aging is the somatic struggle for survival in response to the germ cell-imposed death pathway: the "germ–soma conflict" theory

The time course of postreproductive death is the result of a complex interplay between investment into reproduction, individual fitness and environmental challenges (Fig. 1). Catastrophic death of the postreproductive soma as it occurred during the archaic reproductive events is the evolutionary default state (Clark, 1999). In semelparous Metazoa, environmental conditions limit reproduction to a singular event (e.g. annual plants cannot survive winter, Pacific salmon are unable to return to spawning grounds). Postreproductive survival did not pay off evolutionarily and was selected against in favor of reproductive investment (the r strategy; MacArthur and Wilson, 1967). Through natural selection, however, death could be delayed in organisms in which the relationship between the investment in reproduction, extrinsic mortality and resistance to environmental stressors allowed postreproductive survival either for parental care or repetitive reproductive cycles. The carrying capacity of the environment places a constraint on the reproduction of these species (K strategy; MacArthur and Wilson, 1967).

Central to the understanding of aging is the role of stress resistance for the aging process. Increased stress resistance favors survival (a key component of fitness) in a variety of adverse conditions and it extends longevity, slows aging and delays death (Parsons, 1995; Draye and Lints, 1996; Johnson et al., 2000). This notion has several implications that are now formulated and will be later elaborated on

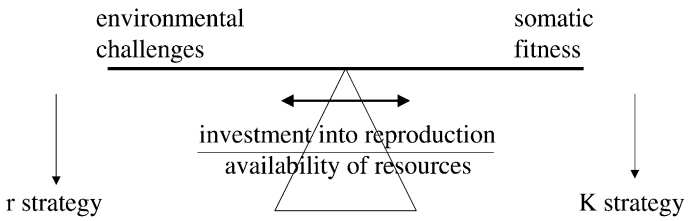

Fig. 1. The balance of r–K strategies. The interplay of environmental challenges and somatic stress resistance determines the evolutionary selection of either r or K reproductive strategies. The relationship between the investment into reproduction and the availability of resources affects the leverage of the hazard-fitness balance on r–K trajectories.

1. Long-lived species are fitter, e.g. efficiently can avoid death due to predation or other environmental hazards thanks to evolutionary achievements such as homeothermy (birds, mammals), wings (birds), shells (turtles), size (whales, elephants) and brain size which facilitates learning and problem solving (primates). Many of the genes that extend lifespan regulate processes necessary to protect the organism against stressful conditions. In consequence, less stress resistant somas succumb earlier to postreproductive death than more stress resistant organisms.
2. Slowed aging is the feature of a more stress resistant phenotype. Programmed by the same regulatory networks like stress responses, aging is a stress response itself. Accordingly, extended postreproductive survival is an adaptive behavior and can be expected to have been naturally selected.
3. As a corollary of this notion, aging counteracts death, aging and death are linked antagonistically.

The foregoing implicates that the soma tries to evade death that is forced upon it. But what is the evolutionary rationale behind this force? Certainly, it is not an altruistic suicide of individuals for the benefit of the species; at the level of species or populations, the processes of selection are weak (Williams, 1966; Dawkins, 1989; Rose, 1991). Survival of the individual is the evolutionary blueprint; resilience is a trait of the selfish gene (Dawkins, 1989). Apoptosis, for instance is no altruistic cell suicide but is the attempted survival of cells in response to the cytocide committed by differentiating cells (Heininger, 2001). Thus, the differentiating spores inflict death upon their kin ensuring the provision of resources in the deprived habitat. For instance in *Dictyostelium*, the prespores secrete so-called morphogens that kill prestalk cells (Heininger, 2001). As discussed earlier, spores evolved into germ cells and the dying fruiting body into the mortal soma of a metazoan organism, handing down their antagonistic interrelationship. This source and sink principle is evident both during primordial germ cell specification and later reproductive activities. A *Volvox* gene locus, regA, controls germ–soma differentiation and, putatively regulated by a pheromone from germ cells, acts in somatic cells to suppress all their germ cell functions. By preventing chloroplast biogenesis, regA determines the apoptotic fate of somatic cells (Kirk, 1997; Meissner et al., 1999) whose remains nurse the maturation of the hatching gonidia and increase their chance of survival (Koufopanou and Bell, 1993). Evolutionarily conserved, the differentiation/apoptosis events during mammalian primordial germ cell specification involve fratricide (Parchment, 1993) and cannibalism (Kumazawa et al., 1998). Ingestion of the apoptotic cell contents ensures also the survival of vertebrate embryo cells (Endrich et al., 1996). Like in *Dictyostelium*, the embryonic differentiation/apoptosis balance and germ cell specification is regulated by autocrine/paracrine antiapoptotic (Morales et al., 1997; Manova et al., 1998) and proapoptotic (Sanders et al., 1997) signals. Likewise during adult life, the survival of growing ovarian follicles appears to be ensured by granulosa cell apoptosis (Vaskivuo et al., 2001). The survival-sustaining function of apoptosis is well preserved in egg-laying animals and plant seed development but apoptosis execution and consumption of its remains may be temporally separated. Engulfment of apoptotic bodies has been demonstrated to sustain the proliferation and differentiation of oocytes in *Drosophila* (McCall and Steller, 1998; Buszczak and Cooley, 2000). Instigated by the developing oocytes (Miller et al., 2000a,b), nurse cells of a variety of species transfer their

cytoplasmic contents and DNA fragments to maturing oocytes and then die (McCall and Steller, 1998; Buszczak and Cooley, 2000; Miller et al., 2000a,b). Premature death of nurse cells, on the other hand, impairs the viability of *Drosophila* germ cells (Tran et al., 2001). During plant endosperm development, cellular apoptosis provides the starch and storage proteins which later fuel the seeds' germination (Young and Gallie, 2000).

With increasing and persistent nutrient resources supplied by the metazoan soma and its fuel stores, fitness in critical events, e.g. reproduction, could be augmented (Gatto and Ghezzi, 1996) and reproductive investment increased, reproduction eventually repeated and thus reproductive phase prolonged. Death, the fate of the fruiting body, could be delayed by many cell generations and evolved into the somatic death that is regulated by endocrine signals of the gonads (Section 6). Phenomenologically, similar evolutionary mechanisms appear to determine apoptosis/aging trajectories in asymmetrically dividing prokaryotes: under nutrient stress the soil bacteria *Bacillus subtilis* are restricted to a singular reproductive event in which an apoptosing mother nurses a single, very resistant spore (Stragier and Losick, 1996); in contrast, the aging *C. crescentus* (Pennisi, 2000), exposed to more abundant resources in its aquatic habitat, is able to reproduce repeatedly, generating as many as 13–19 swarmers (Poindexter et al., 2000). Likewise, in wild populations of simple Metazoa, e.g. zooplankton (Dudycha and Tessier, 1999), sponges (Ereskovsky, 2000) and nematodes (Gems, 2000), the balance between reproductive investment, resource availability and environmental hazards determines the life-history trade-off and aging/death pathways. Throughout evolution, the soma as the evolutionary legatee of the apoptosing fruiting body supports the morphogenesis and dissemination of the germ cells but is disposed of thereafter. The source and sink relationship between soma and germ cells (Koufopanou and Bell, 1993) is maintained in an antagonistic trade-off between reproductive effort and somatic maintenance (Kirkwood, 2001; Van Voorhies, 2001) and is linked to energy homeostasis (Nelson et al., 1995; Hart et al., 1999; Burks et al., 2000; Van Voorhies, 2001). The soma and germ cells antagonize each others' influence on metabolic pathways (Hsin and Kenyon, 1999; Riddle, 1999). In a particularly pure form of this source-sink relationship, some insect offspring devour their living mother from the inside (Gould, 1977). Pleiotropic trade-off are phenotypes suggesting molecular mechanistic compromises that reconcile conflicting interests. Multiple trade-off between reproduction and aging/death have been demonstrated (Rose, 1991; Kirkwood, 2001). In fact, a wealth of data suggests that, in a world of limited resources, germ cells and soma have conflicting interests that require continuous compromise solutions which are shaped by the arbiter of the evolutionary/environmental framework. Thus, the concept is advocated that death is no altruistic suicide but is imposed on the soma by the "enemy within", the germ cells (Fig. 2). Circumstantial evidence of these divergent interests are a variety of trade-off that link fecundity, the success of germ cells, with the longevity of the soma (Rose, 1991; Kirkwood, 1997, 2001; Stearns, 2000).

6. Reproductive phase and aging

As highlighted by the polychaete *Nereis*, the Pacific salmon and marsupial mice, the reproductive phase determines the timing and execution of somatic catastrophic death (Finch, 1990; Rose, 1991; Arking, 1998). Likewise, many plants die after first

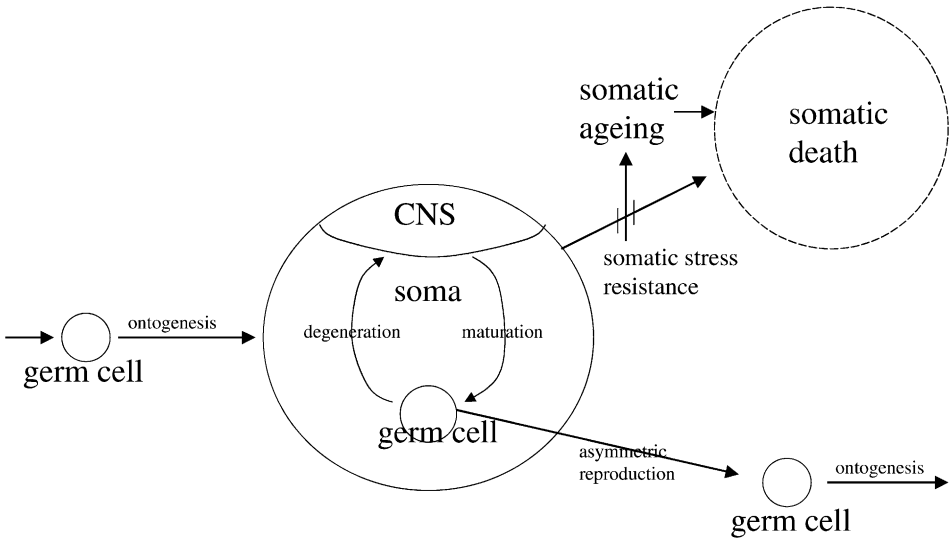

Fig. 2. Schematic representation of the germ–soma conflict theory. Soma and germ cells are linked by a source and sink relationship. Like the apoptosing fruiting body, the soma nurses the germ cells and promotes their dissemination. In the legacy of the fratricide executed by the differentiating spores, the germ cells, by means of Janus-faced agents, degenerate somatic regulatory pacemakers, e.g. of the neuroendocrine system and thereby erode the trophic milieu. Postreproductive somatic death, the evolutionary default state, may be delayed stress resistance-dependently resulting in the somatic aging process. Importantly, all processes (depicted by arrows) and their trade-off balances are modulated by the availability of resources.

reproduction as if committing suicide (Wilson, 1997). Abundant evidence suggests that reproductive activity is a major pacemaker of aging and death. Removal of all flowers and fruits substantially prolongs life of soybean plants (Leopold, 1961) and sterile mutants of the monocarpic plant *Arabidopsis thaliana* are also longer-lived (Noodén and Penney, 2001). Sterile mutants of *S. cerevisiae* (Kennedy et al., 1995) and *C. elegans* (Van Voorhies, 1992) have an increased lifespan. Delay of sexual maturation or reproductive phase in *Nereis* and *C. elegans* slows aging (Johnson et al., 1984). Similarly, ablation of the germline precursor cells in *C. elegans* slows the aging process which argues for signals from germline cells limiting the parents' lifespan (Hsin and Kenyon, 1999). Starvation of a mature specimen of a flatworm leads to regression to an immature stage and extension of lifespan (Kozloff, 2000). Sterile *Drosophila* mutants live longer (Maynard Smith, 1958; Sgro and Partridge, 1999). Delayed reproductive maturation and reduced fecundity due to reduction-of-function mutants in the insulin/IGF signalling pathway extend the lifespan of *Drosophila* (Clancy et al., 2001; Tatar et al., 2001). Pharmacological acceleration of reproductive maturation, on the other hand, normalizes longevity in these mutants (Tatar et al., 2001). Reproductive diapause in a variety of adult insects slows aging (Tatar and Yin, 2001). The removal of the corpora allata, source of the juvenile hormone that controls ovary maturation, doubles adult insect longevity (Tatar and Yin, 2001). Castration also doubles the lifespan of salmon (Robertson, 1961). Semelparous marsupial male mice, when castrated, survive more than one breeding season (Lee and Cockburn, 1985). Following castration, both female and male

cats and dogs live several years longer than their intact counterparts (Bronson, 1981). Castration also extends life in male humans (Hamilton and Mestler, 1969) all of which argues for the phylogenetic conservation of these mechanisms.

Signals from the brain modulate reproductive maturation and aging in animals (Golding and Yuwono, 1994; Boulianne, 2001; Braeckman et al., 2001; Finch and Ruvkun, 2001). Thus, an interplay between gonads and brain drives the dynamics of both reproductive phase and aging (Nelson et al., 1995; Wise et al., 1997) and elicits reproductive cessation as aging-related feature (Packer et al., 1998). In higher Metazoa, the reproductive phase/aging balance is controlled by hormones of the HPG axis (Kalra et al., 1993; Nelson et al., 1995; Wise et al., 1997).

In addition to their reproductive actions, gonadal hormones appear to mediate both somatic maintenance and aging, dependent on intricately balanced, Janus-faced modes of action (Nathan and Chaudhuri, 1998). Thus, both estrogens (E) and testosterone (T) are cytotrophic/protective in a variety of tissues, e.g. heart and central nervous system (CNS) (Heininger, 1999a), supporting the maintenance of tissue capacity during the reproductive period. On the other hand, the involution of the thymus and degeneration of various brain structures (e.g. distinct hypothalamic nuclei), tissues that have a pacemaker function in aging, is advanced by cytotoxic actions of E and T. Specifically, E, although neuroprotective at short term (Heininger, 1999a), induce degenerative changes in cholinergic basal forebrain neurons upon chronic replacement (Gibbs, 1997). The neurotrophic/neuroinhibitory dualism of E 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 engenders the aging of the somatotropic, thyrotropic and gonadotropic axes (Meites, 1990; Wise et al., 1997). Evidence indicates that E contribute to the derangement of hypothalamic catecholaminergic rhythmicity and function (Wise et al., 1997; Legan and Callahan, 1999). Moreover, E are cytotoxic in a variety of hypothalamic nuclei (Brawer et al., 1993; Yang et al., 1993), incite loss of arcuate nucleus synapses (Leedom et al., 1994), actuate the oxidative stress-mediated degeneration of β-endorphin neurons in the arcuate nucleus (Brawer et al., 1993; Desjardins et al., 1995) and elicit neuronal and glial stress reactions (Seifer et al., 1994; Mydlarski et al., 1995; Krebs et al., 1999). As a result, E induce aging-like dysfunctions in the regulation of estrous cycles and E-induced LH surges (Mobbs and Finch, 1992; Desjardins et al., 1995; Tsai and Legan, 2001). These neurotoxic actions may be ultimately related to the loss of sexual functions (Brawer et al., 1993; Desjardins et al., 1995) as is evidenced by the restoration of sexual behavior by fetal hypothalamic transplants in aged (Huang et al., 1987; Hung et al., 1997) and medial preoptic area-lesioned rats (Giordano et al., 2001). Conversely, the reproductive senescence can be delayed by ovariectomy (Mobbs and Finch, 1992). The neurotoxic actions may depend on repetitive cycles of gonadotropin surges following excitatory/inhibitory imbalances due to E-mediated increased glutamatergic transmission (Brann, 1995; Ping et al., 1997) and reduced inhibitory GABAergic input (Parducz et al., 1993). These imbalances may be causally related to the aging-associated decreased HPG responsiveness (Leedom et al., 1994; Zuo et al., 1996; Bonavera et al., 1998). E and other ovarian factor(s) may also play a role in aging-related pituitary changes (Pasqualini et al., 1986; Telford et al., 1987). Oxidative stress, at least

in part mediated by gonadal hormones, is a hallmark of sexual reproduction-related events (Heininger, 2001). 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). In male reproductive senescence, Leydig cells, the testicular cells responsible for T production, become steroidogenically hypofunctional (Zirkin et al., 1997). Oxidative stress which is requisite for steroidogenesis may play a causal role (Myers and Abney, 1988; Zirkin et al., 1997) as evidenced by the prevention of Leydig cell aging following the suppression of Leydig cell steroidogenesis (Chen and Zirkin, 1999). Thus, T-induced oxidative stress in the testes, although indispensable for spermatogenesis (Chainy et al., 1997), may advance the aging of the male reproductive organ. On the other hand, the increased length of male reproductive phase may, at least in part, depend on the protective action of T against the neurotoxic action of E 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 on the HPG axis. Thus, the rate of reproductive aging appears to be determined by the lifetime number of ovulatory cycles, cumulatively determined by the length of menstrual cycles and pregnancy-related anovulation (Packer et al., 1998; Harlow and Signorello, 2000; Thomas et al., 2001). Similar to mammals, *C. elegans* and *Drosophila* germ cells regulate somatic longevity via steroid or sex hormone-like signals (Hsin and Kenyon, 1999; Lin et al., 2001a,b; Tatar et al., 2001).

Gonadal hormones may also exert progeroid actions on other neuroendocrine axes. The pineal–hypothalamic–pituitary axis appears as a pacemaker of mammal aging. E and T downregulate the secretory activity of the pineal gland, M synthesis (Pablos et al., 1993; Alonso-Solis et al., 1996; Okatani et al., 1998; Redins et al., 1999) and M receptor-mediated effector functions (Seltzer et al., 1992). These effects may be mediated both by catecholaminergic and opioidergic mechanisms (Yie and Brown, 1995; Alonso-Solis et al., 1996) and iron released by the action of E (Pablos et al., 1993) and may underlie the aging-related pineal calcification and loss of secretory activity (Schmid, 1993). Conversely, M treatment delays reproductive aging in rats involving the central opioid system (Trentini et al., 1992; Pierpaoli et al., 1997). Grafting of pineals from young mice prolongs survival and delays reproductive senescence in aging mice (Pierpaoli et al., 1997). Conversely, grafting of old pineals accelerates aging in young mice (Pierpaoli and Bulian, 2001). Apart from M, other pineal factors appear to have a role in the geroprotector activity of the pineal gland (Anisimov et al., 2001). Thus, pinealectomy increases various indices of oxidative protein, lipid and DNA damage in aged rodents (Berker et al., 1996; Reiter et al., 1999) and accelerates collagen aging, a marker of biological age (Berker et al., 1996; Sell et al., 2000). Both E exposure and M decline may add up to generate the hypothalamic (Lin et al., 1990) and pineal (Lan et al., 2001) morphological changes.

The reproductive phase is also related to the development of immune senescence. Thymus involution as marker of immune senescence is initiated and perpetuated following sexual maturation (Goya, 1992; Hirokawa et al., 1992) under the control of the hypothalamus (Hirokawa et al., 2001). T and progesterone are immunosuppressive while E, possibly dose-, target-, age- and time-dependently, can both stimulate and inhibit immune functions (Van Vollenhoven and McGuire, 1994). E inhibits lymphopoiesis in the thymus and bone

marrow and induces thymic involution (Kincade et al., 1994; Okasha et al., 2001). Conversely, gonadectomy enhances thymic growth and 'rejuvenation' of T-cell populations and prevents aging-associated thymic involution (Kendall et al., 1990; Olsen et al., 1991; Windmill and Lee, 1998). Gonadectomy-associated thymic and T-cell rejuvenation is reversed by T replacement (Olsen et al., 1991). In aged male rats, castration may even result in reappearance of the thymic tissue (Kendall et al., 1990).

Throughout phylogenesis, reproductively active individuals appear to age more rapidly (Partridge, 1986; Van Voorhies, 1992; Reznick, 1997). Conversely, experimental inhibition of reproductive activity in *Nereis*, *C. elegans*, salmon or soybean delays aging (this section). Along the same line, human longevity appears to be negatively correlated with reproductive success (Kirkwood, 2001). The adverse effects of reproductive activity on somatic stress resistance (Salmon et al., 2001; Wang et al., 2001) and immune functions (Deerenberg et al., 1997; Nordling et al., 1998; McKean and Nunney, 2001) may mediate the cost of reproduction, e.g. in male marsupials and Pacific salmon.

7. Differential life expectancy of men and women

Females have a higher life expectancy than males in virtually all human societies (Austad, 1997; Arking, 1998; Guralnik et al., 2000). However, this is no general rule in other species (Morley, 2000). The epidemiological finding can be explained primarily by a higher female survival probability in the older age intervals (Guralnik et al., 2000). It stands in contrast to the earlier reproductive senescence of females (Velde et al., 1998) which has not been delayed despite a substantial increase of female longevity in recent years (Brody et al., 2000), findings that suggest that both phenomena are controlled by different mechanisms. Again, the pattern of tissue-specific protective/degenerative actions of E may provide an explanation for this conundrum. According to this pattern, organs which are protected by E, e.g. heart and brain, should suffer from the postmenopausal loss of its protective actions. In fact, morbidity and mortality particularly for cardiovascular diseases rise sharply in postmenopausal females (Hammond et al., 2000). Hormone replacement therapy (HRT) decreases the risk for these diseases (Hammond et al., 2000) but does not seem to influence life expectancy (Grady et al., 1992). The contra-intuitive finding that the delay of lifespan limiting diseases does not extend lifespan indicates that the beneficial effects may be compensated by adverse effects. Apart from a slightly increased risk for endometrial and breast cancer (Grady et al., 1992), these effects of HRT may depend on the progeroid actions of E on pacemakers of the neuroendocrine-immune axis, as alluded to earlier. The postmenopausal cessation of these deteriorating actions, on the other hand, may have a lifespan-extending effect. A similar phenomenon is observed in men which have been castrated, the younger the men at the time of castration the more pronounced was its life-extending effects (Hamilton and Mestler, 1969). On the other hand, the persistence of the gonadal hormones' progeroid actions (Waters et al., 2000) may have a key role in the shorter male life expectancy.

A variety of so far patchy neuroendocrinological findings may provide mechanistic clues. Neurokinin B, a neuroprotective tachykinin (Raffa, 1998) is upregulated in discrete hypothalamic nuclei of postmenopausal women (Zhou and Swaab, 1999). This increase

is secondary to ovarian failure as these changes are mimicked by gonadectomy (Danzer et al., 1999) and suppressed by E replacement therapy (Abel et al., 1999). DHEAS levels, another neuroprotective hormone (Heininger, 1999a), are higher in aged female than male brains (Lanthier and Patwardhan, 1986). Female CSF DHEAS levels are maintained after menopause while the serum levels decline, resulting in an increased CSF/serum ratio (Murakami et al., 1999); in aged males CSF levels appear to decline (Azuma et al., 1993). The abrupt perimenopausal cessation of ovarian E production is accompanied by an increased pineal M synthesis (Okatani et al., 2000) which may further promote the female antiaging milieu. The progeroid action of testicular agents, on the other hand, is evidenced by the finding that orchidectomy can reduce DNA damage in elderly male dog brain (Waters et al., 2000).

Mortality deceleration at advanced ages (Vaupel et al., 1998) may be another consequence of the waning of detrimental gonadal hormone effects. Evolutionary theories of aging fall short in explaining this phenomenon: the postreproductive lifespan should be short because there is no selection against mutations that are not expressed until reproductive activity has ceased (Curtsinger et al., 1995; Pletcher and Curtsinger, 1998).

Both the nervous and immune systems are pacemakers of organismal aging. Neurobehavioral and immunological senescent decline proceed in a coordinated fashion (Goya, 1992; Viveros et al., 2001) as evidence of a pleiotropic homeostatic network which is controlled by the hypothalamus (Hirokawa et al., 2001). The synergy of sex-specific differential decline of gonadal hormones, DHEA and M in aging individuals and their impact on immune system functions may play a primary role in female superior survival (Aspinall, 2000) and may account for the higher male susceptibility to infection- and cancer-associated morbidity and mortality (Lang et al., 1994; Aspinall, 2000). In fact, immune responsiveness in rodents (Doria and Frasca, 2000) and humans (Pawelec and Solana, 2001), MHC loci in mice (Goya, 1992; Dubey et al., 2000) and HLA haplotypes in humans (Goya, 1992; Caruso et al., 2001; De Benedictis et al., 2001) are associated with longevity. Aging men display a less active cellular and humoral immune system (Oyeyinka, 1984; Huppert et al., 1998; Aspinall, 2000) which may predict senescent morbidity and mortality (Aspinall, 2000; Caruso et al., 2001). Thymic involution, the marker of immune senescence which also adversely affects bone marrow lymphopoiesis is promoted by androgen (Olsen et al., 1991). These processes still operate in aged male rats since castration even results in reappearance of the thymus (Kendall et al., 1990). The intrathymic aromatization of T, thus conversion to estradiol, appears to be a central pathomechanistic process since aromatase inhibitors also restore the thymus in aging rats (Greenstein et al., 1992). Importantly, the immunosuppressive action of E is more pronounced in aged compared to young mice (Smith and Holladay, 1997).

8. Stress and aging

The gonadal hormone-mediated deterioration of the somatic trophic milieu elicits a systemic and cellular metabolic stress response (Heininger, 1999a). Programmed at the evolutionary level of microorganisms and conserved from bacteria to mammals, the response to metabolic stress is characterized by hypometabolism, adaptations of fuel utilization, oxidative stress and modulation of DNA repair creating either fidelility or infidelity of

genomic information transmission. The response in Metazoa is regulated via the reciprocal glucose–fatty acid (FA) cycle (Heininger, 2000, 2001). Glucose, due to its ready mobilization and utilization is predestined as abundance fuel, allowing an active life style while FAs because of their high energy density but bad solubility in water and relative inertness of the C–C bonds are the optimal storage fuel which is mobilized during deprivation. Perceived or anticipated conditions of increased energy demand due to stressful events activate the regulatory agents of this metabolic cycle, hormones and neurotransmitters. Both the control of energy balance at the systemic level and the cellular adaptation to the changing fuel supply is primarily achieved by the insulin/glucocorticosteroid (GC) system (Dallman et al., 1993, 1995). In principle, eutrophic insulin is opposed by the metabolic stress-induced, dystrophic GC system. GCs induce food intake and weight gain while insulin acts reciprocally. With regard to time course and fuel availability two main stress reactions can be distinguished: the acute fight/flight reaction and the chronic starvation response. In the acute reaction with abundant glucose supply, GCs increase blood glucose and insulin, but not FA/ketone bodies (KB) (Heininger, 2000), responding to the suddenly increased, stress-related demand for fuel and allowing fast action. In conditions of glucose deprivation or insulin deficiency such as fasting and diabetes, however, GC induce a reduced systemic and cerebral glucose utilization (to save glucose as substrate for anabolic pathways) and increased FA/KB concentration and utilization (Dallman et al., 1993, 1995; Heininger, 2000), allowing energy economization and long-term endurance. Systemic markers of this adaptive response are activation of the hypothalamic–pituitary–adrenal (HPA) axis, insulin resistance and dyslipidemia.

Evolved from an unicellular stress response, aging has conserved its stress response phenotype, displaying a multitude of neuroendocrinological, metabolic and cell biological features which are characteristic of stress responses. These stress-related alterations are also reflected at the level of the gene expression profile (Papaconstantinou et al., 1996; Lee et al., 1999; Zou et al., 2000; Weindruch et al., 2001). Abundant evidence suggests that aging is selected in a phenotypic cluster with stress resistance characters (Parsons, 1995; Draye and Lints, 1996; Johnson et al., 2000). This feature indicates that aging is dependent on and regulated by, an efficient stress response machinery. Increased resistance to a variety of stressors is associated with longevity in various metazoan models. Conversely, long-lived species and strains are more resistant to stressors (Section 10): Yeast lifespan is determined by the ability to mount a stress response and to recover from stress (Jazwinski, 2001). Lifespan extension mutants of *C. elegans* have an increased resistance to oxidative stress, heat shock and UV radiation (Johnson et al., 2000). In all phyla, susceptibility to oxidative stress is inversely correlated with lifespan (Larsen, 1993; Sohal and Weindruch, 1996; Golden and Melov, 2001). Increased expression of HSPs, universal stress-protective agents, is associated with increased stress tolerance and longevity (Tatar, 1999; Cherkasova et al., 2000). Following the multitude of correlations between stress resistance and longevity, a stress theory of aging has been formulated (Parsons, 1995).

Responses of the aging organism to stressors, however, tend to be blunted and prolonged (Heydari et al., 1993; Darr and Fridovich, 1995; Heininger, 1999a) and stress resistance attenuated (Drapeau et al., 2000). The life-sustaining antioxidative systems shut down during normal aging in yeast (Kale and Jazwinski, 1996), worms (Larsen et al., 1995) and flies (Arking, 1998), increasing the vulnerability to stressors. Hence, oxidative stress elicits an upregulation of antioxidant defences in young but not aged *C. elegans* (Darr and

Fridovich, 1995). Likewise, HSP expression following a variety of stressors is blunted in aged human cells (Volloch and Rits, 1999). The deficiency of stress pathways is exemplified by the NF-κB stress transduction pathway. NF-κB is constitutively activated in senescence but its stimulation by stressors is attenuated (Ponnappan, 1998; Helenius et al., 1999). These data indicate that the functional reserves are strained and exhausted by the aging-associated adaptations leaving the organism defenseless and more vulnerable to additional stressors (Azhar et al., 1999; Volloch and Rits, 1999).

9. Neuroendocrine stress markers of aging

The reproductive phase-modulated perturbation of the hormonal balance creates cellular nutrient deprivation and drives the loss of Ca^{2+}–energy–redox homeostasis during cellular aging (Heininger, 1999a, 2001). At the systemic level the adaptive responses of the glucose–FA cycle are activated. In species with slow aging processes the changes may be too gradual and discrete to be detected, particularly in outbred species where differential speeds of aging may increase the variability of findings and blur the underlying pathogenetic principles. Hence, to get clues about the nature of this conserved process it may be instructive to study species with rapid senescence where an overwhelming process sweeps aside all counterregulatory adaptations. Such examples are the spawning Pacific salmon and male marsupial mice. In both species, rapid senescence ensues after sexual reproduction characterized by a more or less dramatic decline of gonadal steroids and a concomitant surge of GCs (Lee and Cockburn, 1985; Finch, 1990). The same pattern of declining gonadal hormones and increasing GCs is encountered in aging humans, primates and rodents as well. Yet, the evidence that GCs are associated with aging mechanisms in the gradual senescence characteristic of most vertebrate species is not robust (Masoro, 1995; Finch, 1997). As for human plasma GCs, the changes are modest and large cohorts are needed to verify these elevations. More conspicuous is an aging-related deterioration of HPA axis feedback regulation (Heininger, 1999a). These subtle changes are compatible with the protracted course of aging in these mammals. However, they may not be sufficient to cause death as in catastrophic senescence. Another clue comes from the notion that aging does not develop uniformly in a given organism but that, similar to interindividual differences, intraindividual differences and predilections exist (Hayflick, 1994; Arking, 1998). Different organs may be affected differentially by the aging process (Arking, 1998). Hence, nonsystemic changes localized in vital organs may be pacemakers of aging.

The CNS as the site of neuroendocrine control is a prime candidate for such an aging clock. In fact, a wealth of data point at the CNS as decisive site of control for life and death (Boulianne, 2001; Braeckman et al., 2001; Finch and Ruvkun, 2001). Mature adults of the segmented worm *Nereis* stop to feed and die soon after spawning. Transplantation of cerebral ganglia from immature donors into adults can postpone these changes and after another transplantation the lifespan of the recipient could be doubled (Golding and Yuwono, 1994). Sensory perception (Apfeld and Kenyon, 1999) and CNS-resident insulin/IGF-signalling also determine longevity in *C. elegans* (Boulianne, 2001; Braeckman et al., 2001; Finch and Ruvkun, 2001). The increased expression of antioxidant enzymes, confined to the CNS, extended the lifespan of *Drosophila* by approx. 40% (Orr and Sohal, 1994). Lesion of

distinct hypothalamic areas and hypophysectomy retard a variety of aging-related markers (Wyndham et al., 1987; Bernardis and Bellinger, 1998). Congenital deficiencies in pituitary function result in remarkably prolonged longevity of dwarf mice (Bartke et al., 1998). Conversely, ablation of the hypothalamic ventromedial nucleus is associated with subsequent accelerated appearance of aging-associated markers (Bernardis and Bellinger, 1998). Consistent with both progeroid and antigeroid effects of hypothalamic lesions, the aged hypothalamus exhibits both activation and degeneration phenomena (Zhou and Swaab, 1999). As a general principle, nuclei involved in the regulation of the HPA axis, e.g. by secreting corticotropin-releasing hormone and vasopressin, appear preserved or even activated while nuclei involved in the HPG axis control, e.g. the sex-dimorphic nucleus, degenerate. The neurohypophysis also degenerates during aging (Schultz et al., 1997). In view of the putative pacemaker function of basal brain structures, particularly the hypothalamus, these may be strategically located targets of aging-related hormonal effectors. According to recent findings (Swaab et al., 1994; Murakami et al., 1999), human aging is associated with increased CSF, particularly ventricular, cortisol levels. Due to an at best mild concomitant increase of serum cortisol levels the cortisol CSF/serum ratio is elevated (Murakami et al., 1999) suggesting an intrathecal accumulation of GC. Conversion of inactive precursors into active agents at the level of target structures appears to be the underlying principle (Heininger, 2000). Overall, as evidence of a metabolic stress response aging is associated with an increased HPA axis activity exerting particularly CNS-targeted effects.

10. Stress resistance (e.g. as achieved by caloric restriction) and aging

Many forms of stress when experienced at mild-to-moderate preconditioning intensities create tolerances, e.g. thermotolerance, radiation tolerance, ischaemic tolerance (Heininger, 2000, 2001). The tolerogenic mechanisms include increase of antioxidant defences, upregulation of HSP expression and DNA repair. The common denominator of tolerance induction in eukaryotes appears to be oxidative stress. Stress tolerance is also a primary modulator of aging processes. Across phylogeny, animals which have been exposed to or are resistant against a variety of low-dose stressors (e.g. radiation, methanol, heat, gravity, repetitive injury) exhibit lifespan extension (the hormesis phenomenon) (Parsons, 1995; Martinez, 1996; Masoro, 1998; Lin et al., 1998; Longo, 1999; Johnson et al., 2000; Minois, 2000; Jazwinski, 2001). Conversely, long-lived animals are more resistant to stress/oxidative stress (Lin et al., 1998; Kirkwood et al., 2000; Braeckman et al., 2001; Jazwinski, 2001). Consistent with the dual aging/stress resistance concept, both nDNA and mtDNA repair activity as marker of stress tolerance correlate well with species and strain longevity (Bürkle, 2000; Vijg, 2000; Zahn et al., 2000).

Reduced caloric intake is a special case of a chronic stressor and inducer of stress resistance (Hart et al., 1999) which has gained wide attention in gerontology. Caloric restriction (CR) consistently retards aging and prolongs life in yeast (Lin et al., 2000), nematodes (Hosono et al., 1989) and rodents (Weindruch and Walford, 1988; Masoro, 1998) and may also reduce a variety of aging-related changes in nonhuman primates and humans (Wanagat and Weindruch, 2000). CR attenuates aging-associated and stress-related systemic and brain gene expression profiles (Lee et al., 1999; Weindruch et al., 2001). Markers of pituitary

(Han et al., 2001), hypothalamic (Meites, 1990; Nichols et al., 1995) and pineal gland aging (Henden et al., 1992) are retarded. At the cellular level, CR inhibits the aging-related increase of mitochondrial ROS release (Gabbita et al., 1997) and level of oxidative stress and damage (Gabbita et al., 1997; Risby et al., 1999), attenuates the decrease of antioxidant defences (Rao et al., 1990) and augments the resistance of mitochondria against oxidant stress-mediated inhibition of transcription and induction of permeability transition (Kristal and Yu, 1998). The metabolic alterations of CR are substantial, indicating a downregulation of energy metabolism and increased energy efficiency paralleled by a reduced mean body temperature (Duffy et al., 1997; Hart et al., 1999). Both serum levels of nutrients and glycolytic and lipolytic metabolism per cell are attenuated (Masoro, 1992; Scrofano et al., 1998). The energetic stress elicits adaptive responses of the glucose–FA cycle. The increased respiratory quotient suggests the preferential combustion of FA and KB (McCarter and Palmer, 1992; Duffy et al., 1997). The substantial decrease in fat mass and extramitochondrial metabolism of FA may have a hitherto underestimated impact on CR-related cellular pathology, neuroendocrine control of fuel homeostasis and life extension (Gabriely and Barzilai, 2001; Unger and Orci, 2001). Insulin/IGF-1 levels and glycemia are decreased and insulin sensitivity increased (Masoro, 1992; Sohal and Weindruch, 1996; Sonntag et al., 1999). Intriguingly, a multitude of features of metabolic control of CR are mimicked by lifespan-extended insulin/IGF signalling pathway-mutants of *C. elegans* and mice (Bartke et al., 1998; Lane, 2000; Han et al., 2001). Reduction-of-function mutants of the *Drosophila* and mouse insulin/IGF signalling pathway also exhibit adaptive responses of the glucose–FA cycle with increased plasma triglycerides (Bohni et al., 1999; Brüning et al., 2000; Tatar et al., 2001). A reduced metabolic rate per weight unit does not appear to be the cause of lifespan extension (McCarter and Palmer, 1992) while organ metabolic rate and energy expenditure may be a more valid determinant of aging rate and its slowing by CR (Greenberg et al., 2000; Ramsey et al., 2000a).

In addition to insulin, other hormonal systems are affected by CR. A relevant argument against a detrimental role of GC in aging comes from CR research, in fact corroborating the adaptive and protective rationale of HPA activation during aging (Sabatino et al., 1991; Masoro, 1995; Nelson et al., 1995). CR induces a hyperadrenocorticism with elevated GC levels (Sabatino et al., 1991; Nelson et al., 1995; Duffy et al., 1997) which appears to be causally related to the attenuated inflammation (Klebanov et al., 1995) and prevention of cancer (Schwartz and Pashko, 1994). Compared to controls, the aged CR animals, however, exhibit a reduced basal GC level and a blunted GC response to stress (Stewart et al., 1988) arguing for a retarded HPA axis aging. Moreover, reproductive lifespan is prolonged by CR-related delayed maturation and aging of the HPG axis (Nelson et al., 1995). Estrogen levels, signal transduction and responsiveness are reduced leading to delayed puberty, while amplitudes of LH surge are preserved and reproductive senescence delayed (Li et al., 1994; Wise et al., 1997). Thus, the neuroendocrine pattern of aging, i.e. hyperadrenocorticism and gonadal hypoactivity is elicited by CR but is associated with a delay of aging. The lifespan extension achieved by CR has been interpreted as a redirection of resources from reproduction toward somatic maintenance in adaptation to uncertain food supplies (Nelson et al., 1995; Hart et al., 1999; Shanley and Kirkwood, 2000).

The germ–soma conflict in relation to energy homeostasis is integrated at the neuropeptide Y (NPY)-leptin level, both opposing each other in the channeling of resources (Aubert

et al., 1998; Rohner-Jeanrenaud, 1999). Hypothalamic NPY is the deprivation hormone that controls stress-dependent somatic maintenance by mediating the central regulation of appetite, energy storage, HPA axis activity and insulin resistance (Dallman et al., 1995; Rohner-Jeanrenaud, 1999) and induces undernutrition-dependent downregulation of reproductive activity (Kalra and Kalra, 1996; Aubert et al., 1998; Judd, 1998). Peripheral adipose tissue-derived leptin is the abundance hormone which favors fuel oxidation at the expense of storage (Rohner-Jeanrenaud, 1999; Harris, 2000), stimulates the activity of the reproductive system and induces fertility (Aubert et al., 1998; Judd, 1998; Cunningham et al., 1999; Harris, 2000). The brain, particularly the hypothalamus, appears to be the central mediator of these leptin actions (Cohen et al., 2001). NPY and leptin have also opposing effects on the hypothalamic–pituitary–somatotropic axis (Aubert et al., 1998). GC mediate the effects of NPY and antagonize leptin effects (Rohner-Jeanrenaud, 1999). Gonadal steroids modulate the NPY-leptin loop in the control of energy homeostasis (Judd, 1998; Mystkowski and Schwartz, 2000). Hypothalamic NPY is increased following CR (Kalra and Kalra, 1996; Schwartz et al., 1999), whereby diminished insulin levels may be causally involved (Malabu et al., 1992; Schwartz et al., 1999). In contrast, leptin levels are reduced by CR (Aubert et al., 1998; Cunningham et al., 1999; Shimokawa and Higami, 2001). Both alterations may add up to decrease the activity of the reproductive axis (Aubert et al., 1998; Judd, 1998; Cunningham et al., 1999). In consequence, leptin/NPY may be critically involved in the antiaging action of CR (Gabriely and Barzilai, 2001; Shimokawa and Higami, 2001). Hypogonadism may be the centrepiece of this action by delaying the gonadal steroid-mediated degeneration of the hypothalamic arcuate nucleus (Brawer et al., 1993; Leedom et al., 1994; Desjardins et al., 1995). This nucleus appears to be the brain's blood-brain-barrier-free window to systemic circulation and, well endowed with receptors for insulin and leptin and NPY synthesizing neurons, could be critical to the regulation of food intake and energy balance (Malabu et al., 1992; Schwartz et al., 1999; Havel et al., 2000). Moreover, these neurons project to the paraventricular nucleus and both nuclei, in a feedback loop, regulate the somatotropic and reproductive axes (Aubert et al., 1998; Judd, 1998; Schwartz et al., 1999). These nuclei are also components of the stress-mediating neural circuits (Stratakis and Chrousos, 1995; Lopez et al., 1999) and, with these multiple inputs, may be the integrative relay station of metabolism-stress-reproduction-senescence regulation. The effects of CR on reproductive function appear to be modulated by insulin/IGF signalling. Both at the gonadal and hypothalamic level, the insulin/IGF system is involved in germ cell maturation and reproductive functions in all metazoan phyla (Hsin and Kenyon, 1999; Wang and Chard, 1999; Brüning et al., 2000; Burks et al., 2000; Lackey et al., 2000). CR downregulates the gonadal insulin pathway which results in decreased, even impaired, reproductive activity, functions which are resumed following realimentation (Bossis et al., 2000). Likewise, hypofunction of the HPG axis is reversed after refeeding (Temple and Rissman, 2000). CR activates the secretory activity of the pineal gland and increases serum M levels, features that appear to be causally involved, at least in part, in the observed suppression of the reproductive axis (Chik et al., 1989; Wilamowska et al., 1992; Everitt et al., 1995; Cunningham et al., 1999).

Like other stressors (Heininger, 2001), CR confers cross-tolerance to other challenges (Frame et al., 1998; Masoro, 1998; Prolla and Matson, 2001). CRs tolerogenic mechanisms include HSP expression (Heydari et al., 1993), improved mitochondrial efficiency (Gabbita

et al., 1997; Lass et al., 1999), reduced mitochondrial ROS leakage and increased antioxidant defences resulting in decreased oxidative stress (Sohal and Weindruch, 1996; Gabbita et al., 1997; Kristal and Yu, 1998) and upregulation of DNA repair (Haley-Zitlin and Richardson, 1993; Spencer, 1993).

Another clue for the relationship between longevity, stressors and fuel availability comes from the analyses of exercise and longevity. Exercise prolongs life (Lee et al., 1997; Kujala et al., 1998; Blair et al., 2001) and delays aging-related changes (Lee et al., 1997; Blair et al., 2001) dependent on the intensity (Andersen et al., 2000; Drygas et al., 2000; Lee and Paffenbarger, 2000) and continuity of the activity (Kujala et al., 1998; Skalicky and Viidik, 1999). The antiaging effects of physical activity may be mediated by CR-like adaptations of the NPY–leptin loop (Judd, 1998; Koistinen et al., 1998). In a well-nourished human population, exercise may bring about only modest lifespan increases (Lee et al., 1995). The lack of leptin decrease in well-fed, exercising humans (Koistinen et al., 1998) may play a role in this phenomenon. Exercise, on the other hand, has no substantial additive effect on CR-induced longevity (McCarter et al., 1997). Combining physical activity with mild CR in rats, however, may have additive effects on redox balance (Kim et al., 1996; Ikeno et al., 1997), aging-related variables (Ikeno et al., 1997; Ichikawa et al., 2000) and lifespan extension (McCarter et al., 1996; Ikeno et al., 1997). Expression of HSPs and antioxidant enzymes following exercise in various organs including the brain (Mattson, 2000; McArdle and Jackson, 2000) are cellular markers of physical activity-related stress resistance and life prolongation. These adaptive responses may possibly be due to an exercise-related increased oxidative stress (Bejma and Ji, 1999; Yan and Sohal, 2000) that sustains tolerance phenomena.

11. Metabolic rate, nutrients and aging

The rate-of-living theory of aging postulates that longevity is inversely proportional to metabolic rate (Austad, 1997; Arking, 1998; Hulbert and Else, 2000). Although the theory, is flawed in its strict sense (Austad, 1997; Arking, 1998) its circumstantial features reflect some important implications of the oxidative damage and mitochondrial theories of aging (Arking, 1998; Van Voorhies, 2001). There is no doubt that a variety of metabolism-related features have an impact on aging-dependent processes. Both environmental conditions, e.g. nutrient deprivation or low temperature and mutations which lead to increased longevity are associated with an enhanced metabolic efficiency and decreased metabolic rate (Jazwinski, 2000; Van Voorhies, 2001). In worms, flies and mammals, metabolism regulation mediated by insulin-like signal transduction pathways is at the core of lifespan control (Bartke et al., 1998; Braeckman et al., 2001; Flurkey et al., 2001; Tatar et al., 2001). In *Drosophila*, substrate flow of the Krebs cycle is a key determinant of lifespan (Da Cunha and Oliveira, 1996; Regina et al., 2000). The lifetime oxygen consumption of longer-lived, lighter, food-restricted animals is about equal to that of their shorter-lived ad libitum fed siblings (Harman, 1983) arguing for a role of mitochondrial oxygen exposure. Accordingly, an increased metabolic rate and respiratory activity is associated with a higher mitochondrial ROS generation and lipid peroxidation potential (Sohal and Weindruch, 1996; Gabbita et al., 1997; Barja, 2000). Whole-body metabolic rate may be a key variable of aging-related oxidative DNA damage and protein glycation (Greenberg et al., 2000). A wealth of

studies have shown that caloric intake and body weight determine occurrence of degenerative diseases and lifespan (Hart et al., 1999).

Displaying the pattern of a prototypic deprivation response, aging prokaryotic and eukaryotic microorganisms engage in both hypometabolism and increased energy storage (Heininger, 2001; Lin et al., 2001a,b). Likewise, the adaptive reponse in CR is characterized by hypometabolism and an altered energy consumption/storage balance regulated by the leptin–NPY system. The cells of an aging metazoan organism are also deprived of nutrients due to hormone and growth factor deficiencies/resistances (Heininger, 1999a). Responding to the cellular nutrient stress, aging organisms downregulate metabolic rate (Piers et al., 1998; Greenberg et al., 2000) while nutrient storage is favored above oxidation (Calle-Sescandon et al., 1995; Blaak et al., 2001; Lin et al., 2001a,b). Accumulation of fat stores before and consumption of these stores during, environmental nutrient shortage is a common feature of bacterial stationary phase (Heininger, 2001), *C. elegans* dauers (Larsen et al., 1995; Van Voorhies, 2001), insect diapause (Ohtsu et al., 1993) and mammal hibernation (Heininger, 2000). In contrast to CR, aging ad libitum-fed organisms store the fuel surplus and the median-age individual becomes obese (Andres, 1984; Vardi and Pinhas-Hamiel, 2000). The visceral fat mass that is regulated by neuroendocrine signals (Dallman et al., 1995) appears to play an important role in the generation of the metabolic syndrome (Kissebah and Krakower, 1994; Gabriely and Barzilai, 2001).

Economization of nutrient utilization is a hallmark of chronic deprivation responses. To this end, the aging organism develops, as a feature of systemic adaptation, a variety of hormone resistances of e.g. insulin and leptin. Nutrient abundance that determines the mismatch between extracellular and intracellular carbon source availability and between supply and utilization, however, decides the well- or mal-aptitude of these changes. The Janus-faced actions of fuel sources mediate this ambiguity. Glucose alters the mitochondrial redox balance and can generate ROS (Hunt and Wolff, 1991; Du et al., 1999). Generation of ROS appears to be a trophic signal elicited by glucose (Ha and Lee, 2000) and as such is physiologically essential for growth and proliferation (Heininger, 2001). On the other hand, hyperglycemia is a systemic oxidative stress-provoking condition (Ceriello, 1997) and causal agent for a multifaceted metabolic-haemodynamic complex, the metabolic syndrome X (Porte, 1999; Reaven, 1999). Mitochondrial generation of oxidative stress may be causally involved in the pathophysiological pathways of systemic hyperglycemic damage (Du et al., 1999; Nishikawa et al., 2000). Like aging, hyperglycemia induces mtDNA mutations (Fukagawa et al., 1999) and aged individuals with impaired glucose tolerance exhibit an increased level of mtDNA mutations (Liang et al., 1997). Hyperglycemia-associated glycation reactions impair protein and DNA functions (Masoro, 1998) and initiate an autocatalytic cascade resulting in oxidative stress (Hunt and Wolff, 1991; Thorpe and Baynes, 1996). These sequelae make glycation a biomarker of aging and confirm the pacemaker role of glucose intolerance (Sell et al., 2000). Chronic hyperglycemia elicits aging-like impairments of the ventromedial hypothalamus and hyperinsulinaemia followed by insulin resistance (Mobbs, 1993). Increased insulin exposure resulting from this ‘vicious circle’ may also control the rate of mammalian aging and aging-related diseases due to its pro-oxidant effects, also independent from its effects on glucose metabolism (Parr, 1999; Facchini et al., 2000). Based on these multifaceted mechanisms, high glucose intake shortens the lifespan (Mlekusch et al., 1996). On the other hand, pharmacological insulin sensitization increases lifespan (McCarty, 1994).

The starvation-induced switch from glucose utilization to FA/KB utilization has a variety of protective effects (Heininger, 2000). The increased FA fulfil important roles as uncoupler of mitochondrial respiration from ATP synthesis thus preventing formation of superoxide (Woitczak and Schönfeld, 1993; Skulachev, 1998). Uncoupling proteins, upregulated by FAs (Samec et al., 1999), oxidative stress (Pecqueur et al., 2001) and leptin (Scarpace et al., 2000a), mediate these uncoupling actions and are regulators of energy and redox homeostasis (Kagawa et al., 1999; Boss et al., 2000), FA oxidation (Boss et al., 2000) and insulin sensitivity and secretion (Kagawa et al., 1999; Samec et al., 1999). As another marker of the adaptive response of the glucose–FA cycle, uncoupling proteins are increased during aging (Barazzoni and Nair, 2001). FA delivery to tissues, however, may exceed their oxidative utilization, particularly in the absence of leptin action due to leptin resistance (Unger and Orci, 2001). In a Janus-faced capacity, higher LDL and triglyceride levels increase oxidation susceptibility and compromise antioxidant defences (Araujo et al., 1995; Mosinger, 1999). The resulting increase in non-β-oxidative metabolism may lead to ceramide formation (Unger and Orci, 2001), lipid peroxidation (Das, 1999) and cellular dysfunction and apoptosis (Unger and Orci, 2001). FA modulate signal transduction pathways, particularly activate the HPA axis (Widmaier et al., 1995; Tannenbaum et al., 1997) and reduce plasma corticosteroid binding globulin (Haourigui et al., 1994), resulting in an overall increase of free GC.

The links between nutrient availability, longevity and resource allocation to growth and reproduction have been investigated in *Drosophila*. Fruit flies selected for starvation resistance exhibited increased storage of carbon fuels, particularly lipids, longer development and increased longevity (Graves, 1993; Chippindale et al., 1996). Increased nutrient availability, on the other hand, resulted in increased metabolic activity and fecundity, decreased storage of fuels, starvation resistance and longevity (Simmons and Bradley, 1997). In mammals, similar phenomena may be linked to both the basal activity and responsivity of the stress system and its metabolic implications (Esposito-Del Puente et al., 1994; Surwit and Williams, 1996) and mediated by nutrient- (Zimmet et al., 1999; El-Haschimi et al., 2000) and GC-induced insulin and leptin resistance (Björntorp and Rosmond, 1999; Rohner-Jeanrenaud, 1999; Solano and Jacobson, 1999).

Vital stress is associated with a depletion of fuels which are consumed e.g. during starvation, for fight or flight. Psychosocial stressors, however, differ from these stressors in terms of a mismatch of nutrient supply and consumption. Psychosocial stress, particularly if chronic, gives contradictory signals to cells: supplied with plentiful of nutrients by the action of catecholamines and GC, the cells do not consume these fuels, e.g. by physical activity and in protracted, stressfully perceived conditions even shut down metabolism. Consequently, the nutrients may unfold their detrimental effects. Thus, psychosocial stress promotes a variety of aging-associated functional deficits and shortens life expectancy (Björntorp, 1995; Nilsson, 1996; Kaplan et al., 1996). Likewise, hyper-reactivity to stressors is genetically linked to a reduced lifespan and accelerated brain aging (Gilad and Gilad, 1995), putatively actuated by increased oxidative stress (Liu and Mori, 1999). The reproductive phase modulates stress susceptibilities. In rats, HPA activity is attenuated by gonadal hormones (Mizoguchi et al., 1992; Taylor et al., 1993) and accordingly, young age protects against, while castration aggravates, the stress/GC-induced deficits (Mizoguchi et al., 1992). Through these mechanisms, aging and psychosocial stress add up to unfold the toxic, oxidative stress-promoting action of fuels.

12. Aging and aging-related morbidity

As pointed out earlier (Heininger, 2000) aging, according to Selye's stress theory (1975), corresponds to stage 2, the stage of resistance, while aging-related diseases, e.g. Alzheimer's disease (AD), noninsulin dependent diabetes mellitus (NIDDM), are stage 3, the stage of exhaustion of a stress response. Conserved from bacteria to man, the deprivation responses, stress tolerance, differentiation, apoptosis and mutagenesis, are regulated by a continuum of energy–Ca^{2+}–redox homeostatic network derangements (Heininger, 2001). Similar to interindividual differences in the progression of the aging clock, intraindividually a host of tissue-specific and use- and lifestyle-dependent resistancies/vulnerabilities may result in a mosaic of tolerogenic and degenerative/mutagenic changes. Successful aging, e.g. mediated by CR, activates a variety of tolerogenic mechanisms. In a variety of species, aging leads to an upregulation of cytoprotective proteins, e.g. HSPs (Maiello et al., 1998; Wheeler et al., 1995) and Bcl-2 (Warner, 1997; Kaufmann et al., 2001). In comparison with normal aged individuals, healthy aged animals and human nonagenarians/centenarians exhibit reduced oxidative stress, increased antioxidant defences, particularly antioxidant vitamins (Paolisso et al., 1998; Mecocci et al., 2000), glucose tolerance, metabolic efficiency (Paolisso et al., 2000), cellular proliferative vigor (Franceschi et al., 1999) and repair of nuclear (Bürkle, 2000) and mtDNA (Souza-Pinto et al., 1999).

The neuroendocrine changes follow a stereotypic pattern in aging. In general, cytoprotective and proglycolytic hormones like insulin, gonadal steroids, melatonin and thyroid hormones decline (Heininger, 1999a; Veldhuis, 2000). In response to the metabolic stress, the aging organism displays the adaptive adjustments of the glucose–FA cycle and the primary tolerogenic rationale of this adaption has been emphasized (Heininger, 2000, 2001). However, what is intended as a protective adaptation turns into a destructive cascade during a sequence of events that, as outlined above, is promoted by the abundance of nutrients. Epidemiologically, the systemic features of the adaptation response, particularly the multiple phenomea of the metabolic syndrome, manifest as risk factors for a variety of aging-related diseases. At the cellular level, Janus-faced phenomena with a primary cytoprotective rationale, i.e. stress resistance, elicit the processes of dedifferentiation/apoptosis and mutagenesis which are routed following increased derangements of the homeostatic network and either result in loss of function and tissue degeneration or malignant transformation (Heininger, 2001).

A variety of independent evidences suggests that aging-related diseases are inherent, although exaggerated, features of biological aging and that both are linked by threshold phenomena and controlled by common pathways (Heininger, 2000). The more than temporal relationship of aging and aging-associated diseases is highlighted by the protective action of CR for a variety of disease susceptibilities and vulnerabilities (Weindruch and Walford, 1988; Masoro, 2000) and slowing of immune senescence (Pahlavani, 2000). Likewise, the congruous impact of loss-of-function mutations in the insulin/IGF signalling pathway on aging-related morbidity and mortality in a variety of species indicates the dual progeroid/morbogenic pacemaker role of this pathway (Bartke et al., 1998; Braeckman et al., 2001; Flurkey et al., 2001; Tatar et al., 2001). In humans, development of disease and longevity are also controlled in parallel (De Benedictis et al., 2001). Aging is routinely associated with a deterioration of insulin sensitivity, glucose tolerance (Rowe et al.,

1983) and leptin sensitivity (Scarpace et al., 2000b) which appear to be common denominators of the metabolic syndrome X (Reaven, 1999; Zimmet et al., 1999). The leptin resistance and HPA dysregulation play essential roles in the dyslipidemia and insulin resistance syndrome (Dallman et al., 1995; Zimmet et al., 1999; Cohen, 2001; Unger and Orci, 2001), suggesting GC-elicited leptin resistance (Rohner-Jeanrenaud, 1999; Solano and Jacobson, 1999) as integrative link. These networks illustrate the strategic dimension of the localized GC increase (Swaab et al., 1994) at the hypothalamic pacemaker of the metabolic syndrome (Björntorp and Rosmond, 1999). The aging-related decline of gonadal hormones has a key role in the dysregulation of the HPA/leptin/insulin network (Chu et al., 1999; Ferrini et al., 1999; Mystkowski and Schwartz, 2000; Cohen, 2001; Kastin et al., 2001). The metabolic syndrome contributes significantly to premature morbidity and mortality, particularly from atherosclerosis and other cardiovascular diseases (Hansen, 1999; Ginsberg, 2000). Epidemiological (Hansen, 1990; Moore et al., 1998) and molecular-biological evidences (Trosko and Chang, 1980; Hamet, 1997; Volkers, 2000) indicate that pathophysiological events of aging-related diseases, i.e. NIDDM, hypertension, atherosclerosis and cancer, unfold at a continuum of shared risk factors, vulnerabilities and molecular processes linked to oxidative stress, mutability and insulin/growth factor exposure.

The aging-related derangement of hormonal balances (Heininger, 1999a) further deteriorates in metabolic syndrome individuals and in a variety of aging-related diseases. Trophic hormones, e.g. DHEAS and M are decreased (O'Brien et al., 1986; Herrington, 1995; Brugger and Herold, 1998; Heininger, 1999b; Suzuki et al., 1999). In contrast, the HPA axis is activated in comparison to healthy age-matched controls (Troxler et al., 1977; Dullaart et al., 1995; Brugger and Herold, 1998; Kelly et al., 1998; Björntorp and Rosmond, 1999; Heininger, 1999b). More pronounced than in normal aging (Heininger, 1999a), the immune system displays a primitive response pattern in metabolic syndrome X, NIDDM, atherosclerosis and AD (Pickup and Crook, 1998; Heininger, 1999b; Curtiss et al., 2000; Festa et al., 2000). A multitude of factors which favour carcinogenesis are also increased during aging, e.g. loss of intercellular communication, cellular energetic stress and down-regulation of DNA repair (Heininger, 1999a, 2000, 2001). A scenario can be drafted in which these factors with or without genetic disposition and exogenous stressors create a milieu in which the social, antimutagenic surveillance is lost, particularly in rapidly renewable but also in terminally differentiated tissues, leading to the manifestation of cancer (Turker, 2000; Heininger, 2001). Working in unison with aging, chronic psychosocial stress appears to contribute to hypertension, NIDDM, atherosclerosis and cancer (Baltrusch et al., 1988; Surwit and Williams, 1996; Björntorp, 1995; Nilsson, 1996; Kaplan et al., 1996). Mitochondrial dysfunction may be the common denominator of these pathophysiological pathways (Liang et al., 1997; Heininger, 2001).

13. The proximate cause of aging

During metazoan phylogenesis, a hierarchy of aging-related events evolved at the systemic, organismal and cellular level, events that determine the 'how' of aging.

13.1. Organic and organismal level

The evolutionary advent of multicellularity afforded a coordination of an increasingly complex regulatory network in the internal milieu. A variety of signalling molecules organized in a hierarchy of regulatory axes evolved. The neuroendocrine system and its central control, the hypothalamus, monitor and integrate the vital processes of energy homeostasis, reproduction and stress responses. As such it is optimally equipped to function as pacemaker of somatic aging. Modulated by signals from energy stores, the neuroendocrine system regulates the reproductive phase that due to the ambiguous effects of gonadal hormones, is self-limited. The selective degenerative actions of gonadal hormones on the central regulators of energy homeostasis result in the gradual deterioration of the trophic milieu (Heininger, 1999a). At the first hierarchical level of the metazoan metabolic stress response, adaptations of the glucose–FA cycle tap the systemic resources of the fuel stores leading to the phenotype of the metabolic syndrome. The increasing cellular stress, accentuated by mismatch of fuel supply and utilization, actuates the social and asocial deprivation responses (Heininger, 2001) which may eventually lead to the functional collapse, manifesting as aging-associated diseases.

Longitudinal studies suggest that, although trajectories of aging may differ between individuals of the same species such as pathological and successful aging (Vaillant and Mukamal, 2001), markers of functional decline, despite a different time course, are consistently expressed (Seeman et al., 2001) indicating the basic uniformity of aging processes. Apart from this uniformity, intraindividual heterogeneity with regard to affected body systems (Hayflick, 1994; Arking, 1998) reflects (in addition to genetic disposition and lifestyle factors) a stochastic element of aging (Finch and Kirkwood, 2000).

13.2. Cellular events

The role of mitochondria in stress responses has recently emerged (Heininger, 2001; Salvioli et al., 2001). Oxidative stress generated by mitochondria is a means of phenotype–genotype feedback control to engender a variety of cellular stress responses such as stress resistance and mutagenesis (Heininger, 2001). Mitochondria as major source and target of oxidative stress play a key role in aging and the progeroid action of a variety of environmental stressors (Sohal and Weindruch, 1996; Ozawa, 1999; Kowald, 1999; Golden and Melov, 2001). Mitochondrial oxygen exposure has been found a determinant of lifespan in a variety of species and experimental systems (Harman, 1983; Yan and Sohal, 2000). With aging, the mitochondrial membrane potential, activity of the electron transport chain and aerobic efficiency decline, ROS generation is increased and permeability transition susceptibility is enhanced (Sohal and Weindruch, 1996; Gabbita et al., 1997; Wei et al., 1998). Conserved from fungi (Osiewacz and Stumpferl, 2001), a cascade of events links derangements of energy and redox homeostasis with mtDNA rearrangements (Kopsidas et al., 1998; Melov et al., 1999). The oxidative stress is causal to mitochondrial mutations (Wei et al., 1998; Ozawa, 1999; Barja, 2000; but see Mott et al., 2001) and thus the oxidative stress and mitochondrial aging theories highlight different features of the same pathophysiological cascade (Sohal and Weindruch, 1996; Miquel, 1998). The functional relevance of the mtDNA mutations, however, has been questioned (Sohal and Weindruch, 1996; Rustin et al., 2000).

Particularly, mtDNA mutations may induce a tolerogenic cytoprotective response with increased levels of antioxidant enzymes (Ohkoshi et al., 1995; Esposito et al., 1999) and bcl-2 (Mott et al., 2001). On the other hand, in some tissues mutations and functional deterioration may correlate (Hsieh et al., 1994; Brierley et al., 1998; Mott et al., 1999). Conspicuously, there is a substantial mosaicism of mtDNA rearrangements (Hsieh et al., 1994; Kadenbach et al., 1995; Melov et al., 1999). Thus a single mutant type may rarely exceed 0.1%, whereas $<5\%$ of the mtDNA in aged human skeletal muscle may be still in the form of full length mtDNA, the rest made up of both different deletion products and oversized rearrangements (Linnane et al., 1998). The focus on mtDNA mutations neglected the functionally equally important silencing of mitochondrial gene transcription and translation (Kristal and Yu, 1998; Schwarze et al., 1998; Barazzoni et al., 2000), altered mitochondrial turnover of mitochondria bearing mutations (Gershon, 1999; Kowald, 1999), post-translational oxidative and glycational modifications of proteins (Agarwal and Sohal, 1995; Sohal and Weindruch, 1996; Yan and Sohal, 1998) and loss of activity of enzymes involved in energy transduction (Hsieh et al., 1994; Fannin et al., 1999). Oxidative stress appears to be the common denominator underlying a multitude of these abnormalities (Shigenaga et al., 1994; Kristal and Yu, 1998; Schwarze et al., 1998; Esposito et al., 1999). An intriguing finding links the aging-related accumulation of mtDNA mutations in a segment that controls mitochondrial replication with the organelles' reduced turnover (Michikawa et al., 1999). In humans, a longevity-associated mitochondrial genotype suppresses mtDNA mutations (Tanaka et al., 2000) thus linking mitochondrial oxidative stress/mutagenesis with aging. Similar to yeast retrograde regulation, Metazoa appear to entertain a mitochondrial-nuclear signalling loop which controls somatic aging (De Benedictis et al., 2000; Heininger, 2001; Salvioli et al., 2001). Processes which may be intuitively regarded as stochastic such as oxidative stress in fact are targeted and, due to intrinsic vulnerabilities, affect preferentially specific DNA sequences and mutational hot spots (Clarke and Johnston, 1976; Hollstein et al., 1991; Burdon et al., 1996, Michikawa et al., 1999) or rate-limiting enzymes of mitochondrial TCA cycle, energy homeostasis and permeability transition both at the functional and transcriptional level (Yan and Sohal, 1998; Sharma et al., 1998; Tretter and Adam-Vizi, 2000; Nulton-Persson and Szweda, 2001; Vieira et al., 2001). Accordingly, aging impacts preferentially key enzymes of energy homeostasis (Agarwal and Sohal, 1995; Nicoletti et al., 1998; Schwarze et al., 1998; Sharma et al., 1998). Moreover, oxidative stress and aging target key enzymes of antioxidant defence. Catalase, Mn-SOD and Cu-, Zn-SOD inactivation is achieved by preferential oxidation, nitration and glycation (Yan and Harding, 1997; Heininger, 1999b; MacMillan-Crow et al., 1999) possibly resulting in an oxidative stress vicious circle. By this type of "regulated randomness", analogously to other evolutionary processes (Heininger, 2001), the huge diversity of aging-related changes is achieved. The causal role of mitochondrial aging for cellular senescence has been suggested by the observation that microinjected mitochondria from old cells induce senescence and degeneration in recipient young cells (Corbisier and Remacle, 1993). On the other hand, cells without mtDNA that lack oxidative phosphorylation-dependent ROS formation may be virtually immortal (Kagawa et al., 1999). Thus, genetically programmed processes combine with random, yet targeted, processes that are driven by selective vulnerabilities to actuate the adaptive regulation of the energy–redox homeostasis in the phylogenetically archaic deprivation response (Heininger, 2001). In this response, the aging cells accumulate DNA

damage and mutations (Randerath et al., 1996; Vijg, 2000). Mutagenesis is facilitated by the permissiveness of a downregulated DNA repair (Gilchrest and Bohr, 1997; Doria and Frasca, 2000; Heininger, 2001; Zahn et al., 2000). As result of this random process, mutagenesis creates a mosaic of genetically heterogeneous cells (Pla et al., 2000). Thus, oxidative stress and accumulation of mutations are not the causes of aging but the secondary adaptive responses of the cells to the aging-related metabolic deprivation (Heininger, 2001).

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 (Heininger, 2001) and thus rejuvenation and essential immortality of germ cell lines. The importance of oocyte cytosolic factor(s), putatively the mitochondria, also for the rejuvenation of the genome has been demonstrated recently. Nuclear transfer of senescent fibroblasts extended the replicative lifespan and telomere lengths in the cloned animals (Lanza et al., 2000). Importantly, oxidative stress and mutagenesis of nuclear and mtDNA are not only effectors of cellular aging but also of cellular immortalization during cancerogenesis (Heininger, 2001). Critically, it is determined by the intracellular energy–redox context and intercellular communication which of these pathways are routed. A network of tumor suppressors, e.g. p53, PTEN, Rb, c-myc, $p19^{ARF}$ and $p16^{INK4a}$ regulates cell fate decisions including cellular senescence and immortalization (Derventzi et al., 1996; Serrano and Blasco, 2001) and, modulating and being modulated by insulin/IGF signalling pathways (Neuberg et al., 1997; Mihaylova et al., 1999; Simpson and Parsons, 2001), may be involved in the integration of cellular and somatic aging (Mihaylova et al., 1999). Linking aging and cancer, the same pathophysiological mechanisms may associate a mutator phenotype with progeroid features (Heininger, 2001). Thus, the same signalling pathways and agents can give rise to opposite outcomes, immortality or mortality, a notion that emphasizes the importance of the ambiguity of cell fate programming (Heininger, 2001).

14. The ultimate cause of aging

What is the evolutionary rationale of aging? Limited resources of energy and building blocks put a constant selection pressure on organisms (Heininger, 2001). Aging and death evolved when the reproductive life histories of the individuals of a colony of microorganisms differed due to asymmetric reproduction (Partridge and Barton, 1993; Charlesworth, 1994) giving a selective advantage to species which discarded the less fit, aged organisms for the benefit of the progeny (Wallace, 1967; Theodoridis et al., 1996). Along this line, A.R. Wallace, the co-discoverer of natural selection, was the first to put forward an evolutionary explanation of aging (written between 1865 and 1870, but only quoted as a footnote in Weismann, 1889). His theory, however, interpreted as one of group selection, was rejected following the insight that group selection forces are weak (Williams, 1966; Dawkins, 1989; Rose, 1991). Replacing an interindividual (group) selective force by an intraindividual force, the intraindividual conflict of selfish genes, would be a way out of the impasse. Yet, it may appear difficult to envisage an intraindividual conflict that creates an antagonism between germ and soma cells (both springing from the same genome), ensuring the immortality of the former and mortality of the latter. At the evolutionary roots of the deprivation-dependent segregation of soma and germ cells, bacterial or protozoan cells, the prospective germ

cell-like spores, doom the fruiting body-building cells and exploit, in a source and sink relationship, their remains for their own survival, metamorphosis and dispersion (Heininger, 2001). Bacterial or protozoan colonies tend to be the clonal progeny of a founder individual; colonies behave like "super-organisms" that cover themselves with surface films and adjacent colonies usually do not merge (Tetz et al., 1993; Lewis, 2000). And yet, the individual cells act as distinct organisms that are poised to enforce their selfish survival, even against their kin (Heininger, 2001). At the next level of evolution, following the intensification of intercellular communication and sociability in primitive Metazoa (Heininger, 2001) the clonal progeny of a founder (germ) cell built a distinct organism with soma and germ cells. Although in a distinct organism, the fundamentally different fates of the segregated soma and germ cells and their source and sink relationship persisted. The appreciation of the intraindividual germ–soma conflict depends on the realization that it is the evolutionary legacy of the interindividual conflict between distinct individuals. Thus, the step from interindividually regulated, environmentally determined stress responses to intraindividually programmed, hormonally controlled life and cell cycle processes is a leitmotif of protozoan-metazoan evolution (Heininger, 2001). Like cancerogenesis, the germ–soma conflict is a witness of the persistent unicellular heritage which is only poorly harnessed in a metazoan organism (Heininger, 2001) and of the unrestricted vitality of the selfish gene (Dawkins, 1989).

The notion that ontogenesis recapitulates phylogenesis (Gould, 1992) implicates that archaic evolutionary events are iterated during metazoan development. The metazoan ontogenesis conserved the differentiation/apoptosis-dependent life/death dichotomy that was established during protozoan development. The loss of immortality and totipotency of soma cells (the initiation of the death pathway) occurs following the specification of germ cells. In the further plot of the germ–soma conflict, the germ cell-triggered and reproductive phase-modulated death of the somatic "host" is an endocrinally mediated event whose timing and execution, like the death of the apoptosing fruiting body, is regulated by germ cell-dependent factors that actuate the degeneration of somatic pacemakers.

A wealth of data suggests that somatic aging is the result of continuous compromise solutions which are shaped by the arbiter of the evolutionary framework. The modest heritability of aging (Curtsinger et al., 1995; Finch and Tanzi, 1997; De Benedictis et al., 2001) has been regarded as argument against its genetic regulation. Adaptation of the life-history traits to a variable environment during the lifetime of an individual (Ergon et al., 2001), however, should have a strong selective advantage. Hence, the genetic control for reproduction–aging trajectories is plastic (Finch, 1990, 1997; Scheiner, 1993), subject to environmental modulation (Clare and Luckinbill, 1985) and mediated, at least in part, through stress resistance (Buck et al., 1993; Krebs and Loeschcke, 1999). Extended longevity is associated with improved metabolic capacity and response to stress. The plasticity of aging trajectories is an adaptive advantage under a variety of short-term environmental changes (e.g. nutrient availability, temperature changes). Consequently, slowing metabolism, delaying sexual maturation or reproductive activity, e.g. by dauer formation, diapause, hibernation or CR, slows aging of the soma. Extrinsic mortality and resource availability may give rise to widely differing longevities programmed by the same genome in social insects (Carey and Gruenfelder, 1997) or similar genomes in nematodes (Gems, 2000), sponges (Ereskovsky, 2000) and zooplankton (Dudycha and Tessier, 1999). Thus, aging is a key paradigm for a gene-environment interaction and, mediated by the phenotype–genotype feedback loop

(Heininger, 2001), can be added to a growing list of phenomena regulated by a nature-nurture interdependence (Meaney, 2001).

Given the complexity of the aging process virtually any gene which is involved in reproduction, metabolism and stress responses can be expected to have a role in the aging process. This multisite regulation, however, does not rule out the existence of master genes (Puca et al., 2001). There exist target profiles for candidates of such master genes that should be involved in the control of traffic junctions of regulatory pathways. Conserved from yeast to human, the networks that regulate cell cycle events converge at the genetic level through the control of transcriptional activity (Guarente, 1999; Gartenberg, 2000). The regulation of yeast and metazoan cell replicative lifespan by silent information regulator (SIR) genes (Kennedy et al., 1995; Kaeberlein et al., 1999; Gartenberg, 2000; Roy and Runge, 2000) witnesses the evolutionary roots of lifespan control that is reflected by the complex interweaving of SIRs in various events like transcriptional silencing of DNA and regulation of stress responses, cell cycle check points, DNA repair and in yeast mating-type loci and sporulation (Guarente, 1999; Gartenberg, 2000; Lin et al., 2000; Luo et al., 2001). The dependence of SIR proteins in yeast on energy and redox homeostasis (Shei and Broach, 1995, Imai et al., 2000; Lin et al., 2000) appears to be established by a link to the insulin/IGF signalling system in Metazoa (Tissenbaum et al., 2000).

Death has been evolutionarily introduced at the unicellular level in conjunction with reproductive behavior in response to deprivation stress. Limitation of resources in a variable environment rendered the involved periodic turnover of adaptable individuals an evolutionary stable strategy, critically orchestrating an interconnected homeostatic triangle of stress, reproduction and aging/death. In this triangle, stress responses as link between reproduction and aging/death provide the evolutionary continuity between ultimate and proximate causes of aging. Energy homeostasis and oxidative stress link reproduction and aging/death and their mutual compromises. Pleiotropic reproduction-longevity trade-off have been described as r (large numbers of offspring coupled with high extrinsic mortality) and K (small numbers of offspring coupled with lower mortality) strategies (Curtis, 1963; MacArthur and Wilson, 1967). These alternative strategies reflect the trade-off between individual fitness and environmental resource limitation. Fitter (K) organisms are constrained by the resource-dependent carrying capacity of their environment; in contrast the less fit, more vulnerable, r strategists rely on large numbers of progeny that due to their low survival prospects do not strain the environmental capacity to its limits. Oxidative stress is the effector of biotic and abiotic stressors (Heininger, 2001) and the ambiguous arbiter of the pleiotropic trade-off. Established as a means to increase diversity and fitness, sexual reproduction has evolved as "quality-checked mutagenesis" which constitutively engages oxidative stress as its diversity-generating tool (Heininger, 2001). Oxidative stress, however, advances aging. Therefore, redox balance can be expected to have opposing consequences for reproductive functions and aging. In fact, stress resistance as established by increased antioxidant defence and stress proteins is a cellular and organismal marker of extended longevity (Sharma et al., 1997; Lin et al., 1998; Tatar, 1999; Cherkasova et al., 2000; Tower, 2000; Braeckman et al., 2001) and reduced reproductivity (Sharma et al., 1997; Sorensen et al., 1999; Silbermann and Tatar, 2000). On the other hand, reproductive activity increases stress and oxidative stress susceptibility in *Drosophila* (Salmon et al., 2001; Wang et al., 2001), a finding that provides a mechanism for the adverse effects of reproductive activity on somatic

fitness and longevity. Stress resistance as both a heritable and environmentally adaptive response is negatively linked to reproductive activity and positively to longevity and is posited to be the cellular and organismal regulator of r and K strategies and their pleiotropic trade-off.

As a prime example of self-organized criticality, metabolism is plastically tuned in an area of conflict between current availability of environmental resources and individual somatic fitness (in part determined by the economic use of these resources as a component of stress resistance) that determines both reproductive success and resilience against external (parasites, predators) and internal (germ cells) challenges, but also the future access to resources. The phylogenetically ancient insulin/IGF system (Chan and Steiner, 2000) is a key player at the metabolic level of the antagonistic germ–soma regulation. By shared signal transduction and transcription factors, this pathway is regulatory linked to stress response systems (Larsen, 1993; Lithgow, 1996; Johnson et al., 2000; Lin et al., 2001a,b) and antioxidant defence (Larsen, 1993; Taub et al., 1999; Clancy et al., 2001; Tatar et al., 2001). As signal of resource availability, it also integrates energy homeostasis and reproduction (Burks et al., 2000). Reproductive functions are dependent on the functional activity of the insulin/IGF system (see above). In a feedback loop, germ cells regulate somatic longevity via sex or steroid hormone-like signals that modulate the insulin/IGF pathway (Hsin and Kenyon, 1999; Lin et al., 2001a,b; Tatar et al., 2001). Cumulative evidence suggests that somatic insulin/IGF exposure is causally related to aging and aging-associated morbidity (Parr, 1999; Facchini et al., 2000; Flurkey et al., 2001). Growth hormone excess results in reduced lifespan (Bartke et al., 1998). Body size as a function of IGF exposure and signalling (Bohni et al., 1999; Clancy et al., 2001) is negatively correlated with longevity in mice, dogs and possibly humans (Bartke et al., 1998; Miller et al., 2000a,b). Reduction-of-function mutations in the insulin/IGF pathway impair reproductive functions and extend lifespan in nematodes (Braeckman et al., 2001; Finch and Ruvkun, 2001), fruit flies (Clancy et al., 2001; Tatar et al., 2001) and rodents (Bartke et al., 1998; Brüning et al., 2000; Burks et al., 2000; Flurkey et al., 2001). The somatic and gonadal influences on the insulin/IGF pathway appear to counteract each other (Hsin and Kenyon, 1999; Riddle, 1999). Of note, fertility and longevity may be differentially susceptible to genetic and environmental modulation of insulin/IGF signalling (Guarente and Kenyon, 2000; Clancy et al., 2001). Differential effects on reproduction and lifespan controlled by other genetic loci and transduction pathways (Lithgow, 1996; Johnson and Shook, 1997) indicate that additional regulatory levels exist, e.g. leptin/NPY (Shimokawa and Higami, 2001).

That the germ–soma conflict, although at the evolutionary roots of aging, is not the only pacemaker of aging is illustrated by social insects with germ cell-bearing long-lived queens and short-lived sterile workers (Carey and Gruenfelder, 1997). In fact, aging is regulated by a hierarchy of aging clocks (Comfort, 1979). Like extrinsic mortality, the reproduction-driven, intrinsic mortality shapes the limited somatic investment. In addition, circadian rhythms exert a modulating effect. During metazoan phylogeny a biological clock evolved which is synchronized with the ambient photoperiod (due to the earth's rotation) and transmitted to the organism via neuroendocrine signals (Korf, 1994). This physicochemical clock modulates the turnover in populations living in niches with a fixed carrying capacity determined by its resources (Kloeden et al., 1994). Light regimes affect the reproduction-senescence trade-off in *Drosophila* (Sheeba et al., 2000). Pineal degeneration may be the aging clock

in vertebrates (Schmid, 1993; Pierpaoli et al., 1997; Pierpaoli and Bulian, 2001), advanced by inputs from pineal photoreceptors (in lampreys, fish, amphibians, reptiles and birds) or the suprachiasmatic nuclei (SCN), the mammalian circadian pacemaker (Schmid, 1993; Kennaway, 1997) and the HPG axis (Pablos et al., 1993; Alonso-Solis et al., 1996; Okatani et al., 1998; Redins et al., 1999). This aging clock is modulated by gonadal hormones and, via M, links into the insulin/IGF and leptin regulator systems both at the gonadal (Schaeffer and Sirotkin, 1997) and systemic/hypothalamic level (Vriend et al., 1990; Rasmussen et al., 2001). The loss of the antioxidant and antiaging pineal hormones may actuate detrimental sequelae leading to aging related-morbidity, immune senescence and cancer susceptibility (Giraldi et al., 1994; Pahlavani, 1997; Maestroni, 2001).

Two proposed evolutionary mechanisms of aging, the mutation accumulation and antagonistic pleiotropy theory hold that aging is due to a decline in the force of natural selection at later ages (Medawar, 1952; Williams, 1957). The antagonistic pleiotropy hypothesis postulates the selection for alleles trading early life fitness with late life costs. The mutation accumulation hypothesis attributes senescence to the accumulation of deleterious mutations which only manifest late in life. However, from yeast to mammals, aging is determined by processes which are timed early during ontogeny (Jazwinski, 1993; Miller et al., 2000a,b). *C. elegans* longevity is under the control of genes which also regulate developmental stages (Larsen et al., 1995; Malone et al., 1996; Morris et al., 1996). *Drosophila* longevity is also regulated by ontogenetic processes (Buck et al., 1993; Arking, 1998). The expression of antioxidant enzymes which already takes place during *Drosophila* larval development determines the rate of aging. Aging-related loss-of-function of these enzymes ensues following sexual maturation (Arking, 1998). Metabolic flux in larvae, interacting with larval density, affects adult lifespan (Riha and Luckinbill, 1996). In many species including humans, the senescent process proceeds in middle-aged individuals while they are still reproductively active (Arking, 1998; Sehl and Yates, 2001). Menopause is not the starting signal for senescence but is itself already a feature of senescence (Packer et al., 1998; Wise et al., 1997). There seem to be hierarchically turned-on aging systems (Comfort, 1979; Arking, 1998). Particularly, thymus involution as marker of immune system aging is initiated and perpetuated after puberty (Goya, 1992; Hirokawa et al., 1992). Metabolic adjustments can already be detected in middle-aged organisms. Middle-aged CR rats and monkeys differ from their ad libitum fed controls in the manifestation of features of the metabolic syndrome (Ramsey et al., 2000b). Aging-related changes in postmitotic tissues, e.g. the heart and brain, can be demonstrated in middle-aged individuals (Masliah et al., 1993; Adler et al., 2001; Grachev and Apkarian, 2001; Tuzcu et al., 2001).

Semelpary/monocarpy-linked aging trajectories contradict the concept of a postreproductively reduced investment in soma maintenance due to declining selective forces. In monocarpic plants (reproducing only once), there is little or no postreproductive life implicating that plant senescence is not post but perireproductive (Noodén and Guiamét, 1996). Also in salmon and male marsupials, aging occurs already during the reproductive period (Finch, 1990; Maldonado et al., 2000). The rarity of senescence in wild animal populations is due to the waning vigor in middle age particularly of the neuromuscular, sensory and immune systems (Arking, 1998) which renders animals more vulnerable to famine, predation and infection. Thus, the assumption that aging is due to a decline in the force of natural selection at later ages is inconsistent with both the early, sexual maturation-related initiation

of aging processes and the deceleration of aging at advanced age (Curtsinger et al., 1995; Vaupel et al., 1998; Pletcher and Curtsinger, 1998).

Most importantly, the stress-response dependency of aging is not compatible with the so-called evolutionary theories of aging. The fundamental misconception underlying the flaws of these theories is the concept that aging and death are agonistically linked, that aging paves the way for death. Quite the opposite, aging is the phenotype of somatic resistance against death that is caused by signals from the germ cells. Thus, the lack of natural selection in postreproductive individuals does not result in senescence but in catastrophic death. Semelparous/monocarpous species, in which reproduction requires a large investment which cannot be repeated (e.g. bamboo or Pacific salmon), suffer a catastrophic postreproductive death. In these species natural selection was unable to work on postreproductive individuals and thus aging as resilient behaviour could not evolve. Thus, aging is not the consequence of a loss of selective forces but a naturally selected, stress resistance-dependent phenomenon which allows individuals to resist, at least for some time, the germ cell-enforced death sentence.

According to the neo-Darwinian synthesis, evolution by natural selection favours genotypes dependent on their fitness phenotype and eventually carries them to fixation. To turn the argument on its head, the genetic programming of a feature, e.g. aging, lets infer the work of selective forces (genetic drift as evolutionary force behind the phenomenon of aging can be precluded). The near ubiquity of aging reveals that there are powerful selective forces at work that render aging/death an evolutionarily stable phenomenon. That aging is programmed similar to embryonic development and is subject to regulation by a multitude of genes is incompatible with the theory that aging is caused by the waning of selective forces at later ages. For too long, our thinking has been prejudiced by the bias that aging is maladaptive or detrimental (Arking, 1998). Trusting into the correctness of the neo-Darwinian principles it should be assumed that a phenomenon that has been evolutionarily selected and genetically programmed is adaptive. Concluding that aging is adaptive and yet, paradoxically, finally leads into death only leaves one solution to this riddle: as has been established by the archaic reproduction events, postreproductive death is the evolutionarily selected default state; aging, on the other hand, is the phenotype of a resilient soma that responds to this lethal threat to which, however, it finally has to succumb. Extrinsic mortality (Austad, 1993; Ricklefs, 1998; Pennisi, 2000, Stearns et al., 2000), shapes the investment in the maintenance of the soma (Kirkwood, 1977, 2001; Partridge and Barton, 1993; Draye and Lints, 1996). Death being the inevitable fate of the reproducing soma, the intrinsic mortality inflicted by the "enemy within" can be expected to have analogous consequences. Evolution provides countless examples of semelparous/monocarpic organisms which, due to a critical balance between investment into reproduction, fitness and available resources, are unable to survive a single reproductive effort and appear to resign into their fate imposed by putative "death hormones" (Denckla, 1975; Wilson, 1997). Only when fitter organisms can cope with environmental hazards and can accumulate the resources necessary for repetitive reproductive events or care for the brood, selection against catastrophic death can occur and aging can delay death. Whenever postreproductive death is delayed the imprint of selective forces can be inferred, e.g. when female marsupial mice survive reproduction to provide parental care while males die shortly after the mating period; or in iteroparous Atlantic salmons that are able to return to their spawning grounds. The timing of catastrophic death

gives the unequivocal answer to the question for the trigger of this event: the new life ensures that the limited resources are not consumed by the now redundant ancestors or that, even nearer to the archaic differentiation/apoptosis event, their remains fuel the hatching life (Gould, 1977; Koufopanou and Bell, 1993). Thus, postreproductive death is no group- but a selfish gene-selected feature.

In its last consequence, programming of death was linked to the motor of life, the production of energy related to the use of oxygen and organic fuels and, by engaging nonenzymatic oxidative reactions, makes chemistry the ultimate winner over biology (Baynes, 2000).

Note added in proof

Recently, it was demonstrated that *C. elegans* germ cells regulate the lifespan of the adult animal [Arantes-Oliveira et al., Science 295 (2002) 502; Patel et al., Proc. Natl. Acad. Sci. USA 99 (2002) 769]. These findings add substantial support to the validity of the germ-soma conflict theory of aging.

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