Reviews in the Neurosciences, 12, 217-287 (2001)

The Deprivation Syndrome is the Driving Force of Phylogeny, Ontogeny and Oncogeny

Kurt Heininger

Department of Neurology, Heinrich Heine Universität, Düsseldorf, Germany

CONTENTS

Accepted: 22 September, 2000

Reprint address:
Prof. Dr. Kurt Heininger
Hildener Str. 77
40597 Düsseldorf, Germany
e-mail: kurt.heininger@web.de

SYNOPSIS

Energy is the motor of life. Energy ensures the organism's survival and competitive advantage for reproductive success. For almost 3 billion years, unicellular organisms were the only life form on earth. Competition for limited energy resources and raw materials exerted an incessant selective pressure on organisms. In the adverse environment and due to their 'feast and famine' life style, hardiness to a variety of stressors, particularly to nutrient deprivation, was the selection principle. Both resistance and mutagenic adaptation to stressors were established as survival strategies by means of context-specific processes creating stability or variability of DNA sequence. The conservation of transduction pathways and functional homology of effector molecules clearly bear witness that the principles of life established during prokaryotic and eukaryotic unicellular evolution, although later diversified, have been unshakably cast to persist during metazoan phylogenesis. A wealth of evidence suggests that unicellular organisms evolved the phenomena of differentiation and apoptosis, sexual reproduction, and even aging, as responses to environmental challenges. These evolutionary accomplishments were elaborated from the dichotomous resistance/mutagenesis

Abbreviations: amyloid β-protein = Aβ; apoptosis inhibitory proteins = IAP; differentiation-inducing factor = DIF; general adaptation syndrome = GAS; glucocorticosteroid = GC; glucose-regulated protein = GRP; glyceraldehyde-3-phosphate dehydrogenase = GAPDH; heat shock proteins = HSPs; low-density lipoprotein = LDL; mitogen-activated protein kinase = MAPK; nitric oxide = NO; peroxisome proliferator activated receptor = PPAR; poly(ADP-ribose) polymerase = PARP; reactive nitrogen species = RNS; reactive oxygen species = ROS; retinoic acid = RA; superoxide dismutase = SOD; transforming growth factor = TGF; tricarboxylic acid = TCA; tumor necrosis factor = TNF.

response and sophisticated the capacity of cells to tune their genetic information to changing environmental conditions. Notably, the social deprivation responses, differentiation and apoptosis, evolved as intercellularly coordinated events: a multitude of differentiation processes were elaborated from sporulation, the prototypic stress resistance response, while apoptosis, contrary to current concepts, is no altruistic cell suicide but was programmed as a mutagenic survival response; this response, however, is socially thwarted leading into mutagenic error catastrophe. In the hybrid differentiation-apoptosis process, cytocide and cannibalism of apoptotic cells thus serve the purpose of fueling the survival of the selfish genes in the differentiating cells. However, successful mutagenesis, although repressed, persisted in the asocial stress response of carcinogenesis as a regression to primitive unicellular behavior following failure of intercellular communication. While somatic mutagenesis was largely prevented, Metazoa elaborated germ cell mutagenesis as an evolutionary vehicle. Genetic competence, a primitive, stress-induced mating behavior, evolved into sexual reproduction which harnessed mutagenesis by subjecting highly mutable germ cells to a rigid viability selection. These processes were programmatically fixed as life- and cell-cycle events but retained their deprivation response phenotypes. Thus, the differentiation-apoptosis tandem evolved as the 'clay' to mold the specialized structures and functions of a multicellular organism while sexual reproduction elaborated the principle of quality-checked mutagenesis to create the immense diversity of Metazoa following the Cambrian explosion. Throughout these events, reactive oxygen and nitrogen species, which are regulated by energy homeostasis, shape the genetic information in a regulated but random, uncoded process providing the fitness-related feedback of phenotype to genotype. The interplay of genes and environment establishes a dynamic stimulus-response feedback cycle which, in animate nature, may be the organizing principle to contrive the reciprocal duality of energy and matter.

KEY WORDS

deprivation syndrome, stress, evolution, phylogenesis, ontogenesis, oncogenesis, cancer, mutagenesis, stress tolerance, oxidative stress, calcium, energy metabolism, DNA repair, glucose-fatty acid cycle, differentiation, apoptosis, cytocide, intercellular communication, SOS, sexual reproduction, aging, mitochondria, central dogma of molecular biology, Alzheimer's disease

1. INTRODUCTION: STRESS AND THE DEPRIVATION SYNDROME

Energy is the basic requirement of life. According to Aristotle, a body only moves when a force drives it. Hence, an organism which has abundant resources has no reason to move or evolve. On the other hand, lack of resources or other stressors should be powerful "movers". Since the dawn of life, nature rarely provided optimal conditions for growth, and when it did, this growth depleted the resources and bore the seed for privation. This constant cycling between "feast and famine" /507/ favored the selection of organisms which were able to program deprivation responses that allowed them to survive nutritional duress and other adversities. Once fixed, an environmental challenge, such as shortage of oxidative fuels or vital raw materials, or temperature stress, elicited a programmed response which, although dependent on the nature and intensity of the adverse situation and the evolutionary stage of the responder, became elementary and widely uniform in all phyla. Hans Selye (1975) /899/ was the first to appreciate the basic uniformity of stress responses in his general adaptation syndrome (GAS). Stress responses are ubiquitous in life. It should be emphasized that in addition to general stress responses stressor-specific features exist and have been described as early as at the level of bacteria /76,964/. The stress-specific responses do not bring into question the GAS as a core principle and indeed have been taken into account in Selye's original concept. In fact, diversification of stress responses is simply another feature of the evolution of biological complexity /2/. A comparison between *Bacillus subtilis* and *Escherichia coli* regarding the degree

of integration of stress responses suggests that the interdependence of stress signaling pathways may crucially depend on the environmental pressures of their natural habitat /693/. Environmental stressors have been suggested as a driving force in evolution /574,629,758/ leading to the conclusion that genetic variation and stress resistance resulted from this evolutionary pressure. This was a central element of Darwin's evolution theory /203/ that populations tend to outgrow the resources available to them and the ensuing competition among individuals is the driving force leading to the survival of the fittest.

Recently, I defined a deprivation syndrome which is a prototypic response of organisms to metabolic stress and encompasses such diverse processes as sporulation, hibernation, ischemia, aging, and aging-related diseases (hypertension, diabetes mellitus, atherosclerosis, Alzheimer's disease). Programmed at the evolutionary level of microorganisms, a deprivation syndrome is characterized by hypometabolism, adaptations of the glucose-fatty acid cycle (which due to the lack of substantial fat stores shows in microorganisms as catabolite repression/derepression circuits), oxidative stress and modulation of DNA repair /389/. Here, I elaborate the concept that these processes evolved in unicellular organisms and serve either to resist or to adapt mutagenically to environmental stressors; in a consecutive step such processes were developed as key mechanisms of differentiation, apoptosis and mating behavior. These mechanisms have been fixed and programmed as life- and cell-cycle events in multicellular organisms and they constitute the core of sexual reproduction and ontogenic and oncogenic events. The deprivation syndrome represents a proto-formula and driving force of life and provides the molecular processes through which the environment created the phenomena of evolution and natural selection as outlined by Charles Darwin /203/.

2. THE PROTOTYPIC DEPRIVATION RESPONSES OF PROKARYOTES: RESIST OR MUTATE

Evolution of unicellular organisms may have gone through several energy crises due to atmospheric constraints on fuel availability /1051/. In addition, low aquatic phosphorus concentrations appear to have constrained microbial growth /211, 401/. Thereafter, metazoan evolution was set back by several minor and at least five major mass extinctions in which as many as 80% of species became extinct /190,238/. Whatever may have been the putative causes, e.g. persistent volcanic activity /190/, an asteroid impact which deprived the earth of sunlight for several years /16/, climatic changes /405/ or reduction of habitat areas /238/, these eras exposed all phyla to extreme deprivation in which only those species survived which were best equipped to cope with austerity. Thus, evolution repeatedly selected for organisms best adapting to a variety of environmental deprivations. For instance, evidence from fossils and molecular phylogenetics argues for a putative evolution of Metazoa earlier than or around 1 billion years ago /157,1082/. These organisms, however, were subject to extreme environmental stress and became largely extinct during Neoproterozoic repetitive cycles of global glaciation ('snowball earth') /405/. However, the Metazoa made a fulminant comeback during the Cambrian explosion, and a causal relationship between the extreme selection pressure favoring adaptive mutagenic organisms and the accelerated rate of evolution has been suspected /406/. However, mass extinctions, spectacular as they may be, represent only the tip of the iceberg exaggerating apocalyptically a general principle that runs through the history of life. In fact, limited resources were a persistent leitmotif of evolutionary selection. Unicellular organisms are too small to contain environmental challenges. Unable to store significant amounts of nutrients and/or to economize on the use of nutrients during excess, replication of bacteria in their natural habitat inevitably cycles between exponential growth in log phase and growth arrest in stationary phase /507/. Thus, the natural lifestyle of these microbes is characterized by an inherent "feast and famine" cycle, limiting amounts of nutrients being rather the rule than the exception, and long periods of nutritional deprivation punctuated by short periods that allow fast growth. To survive the challenges of nutrient shortage and of other environmental stressors, such as heat, cold, desiccation, or irradiation, populations of microorganisms evolved a battery of adaptive responses. These entail the

development of stress resistance, mutagenesis and genetic competence (a primitive variant of mating behavior). Key to the understanding of these processes is the appreciation that they are regulated by promiscuous signaling pathways which elicit context-specific ambiguous effector mechanisms leading to dichotomous stress resistance/mutagenesis responses. Bacterial and protozoan populations appear to have "learned" not to rely on a single survival strategy but to keep a variety of options open. Many of the deprivation responses are only pursued by discrete subpopulations of cells in a given bacterial community and are regulated as mutually exclusive events coordinated by integrated molecular switches and threshold phenomena. Thus, stationary phase adaptive responses engage a highly interconnected network of signal transduction pathways which regulate motility (to exploit other carbon sources, flight), antibiotic production (cytocide), competence for DNA uptake (mating responses), stress resistance, sporulation (differentiation), and mutagenesis /598,693,1093/.

2.1 Stress resistance

In response to nutrient deprivation and other stressors, bacteria engage a highly coordinated stress response system /392/. The cells enter stationary phase or sporulation programs and become more resistant to a variety of stressors /643,722,1065/. The expression of these stress responses is controlled by the same regulons /283,721/ indicating their interdependence. The programs lead to the upregulation of heat shock proteins (HSPs) /283,578/, oxidative defense /261,283/ and DNA repair enzymes /218, 773/ and confer increased metabolic efficiency /251, 723/. A multitude of direct and circumstantial evidence indicates that oxidative stress has both regulatory and effector capacity in this adaptive response /106,283,721/. In replicating *E. coli,* an adaptive response to DNA damage has been characterized, called the 'SOS response' /306/, which is also functional in stationary phase bacteria /656,965/. The system orchestrates cellular survival responses to a variety of stressors, mediates growth arrest and resistance or mutagenesis. Mutants which lack components of the SOS regulon are more sensitive to a variety of damaging agents /306/. In the absence of DNA damage the genes controlled by the regulon are transcriptionally repressed by the LexA protein. Autocleavage and thus inactivation of the LexA repressor is promoted by RecA which is activated by DNA damage. The system can also be activated by metabolic stressors /296,905/ and oxidative stress /261,435/ and in the absence of DNA damage /495/. The products of the derepressed SOS genes repair DNA lesions by various mechanisms including recombination and excision repair /306/. On the other hand, the SOS system is also functional in the expression of the HSP response /250/ and re-establishment of metabolic competence /135/. Members of the SOS-regulated DNA repair enzymes also function as prokaryotic cell cycle checkpoints /930/. Remarkably, deprivation provides cross-protection. For instance, starvation renders microbes more resistant to irradiation, acid, heat, and osmotic, hydrostatic and oxidative stress /71,73,376/, which is dependent on the expression of the antioxidant defense /435, 1100/, HSPs /845/ and the DNA repair response /435,1100/. This cross-protection is under control of the SOS regulon /38,376/, but other systems may also be involved /38,39/.

2.2 Mutagenesis

Mutagenesis is another unicellular strategy to avert the sequelae of deprivation. Experimenting with their genomes appears to make good sense for individuals in a deprived population. For instance, the existential threat of starvation drives the organisms into a highly dynamic response which increases their genetic variability and aims at improving their genetic fitness /294,560,931/. Thus, various environmental stressors, such as high temperature and nutrient shortage, can accelerate mutagenic changes /72,294,362,560,633,751,931/. In yeast, selective pressure exerted by nutrient limitation leads to adaptive shifts whereby approx. once every 50 generations fitter genetic variants replace one another over time /752/. These clones exhibit higher expression of enzymes of the TCA cycle, ATP generation and oxidative phosphorylation resulting in higher metabolic efficiency /107, 289/. Likewise, in experimental models, spontaneous reversion of mutations in essential amino acid-requiring mutants is enhanced under stationary

phase conditions induced by starvation with this amino acid (the stringent response) /633,1083/ or in mutant bacteria unable to use nutrients when exposed to this nutrient as sole carbon source /362,558,575,596/. These adaptations are favored in conditions of stress and oxidative stress /105,619, 967/. The reversions are not 'directed', but appear to be blind to the adaptive fitness of the mutant. Adaptive mutagenesis occurs stochastically in genomic 'hot' regions of transiently hypermutable subpopulations by a process involving recombination /105,558,575,596,619,967/. In addition, the transcriptional state of genes plays a role to direct mutagenesis (see below) /204,1083/. The randomly acquired mutations are rendered 'adaptive' by the selective pressure exerted by the stressful essential nutrient deprivation /558, 575,596/. Overall, this mutagenesis-prone state increases microbial diversity /294,751/ and enables subpopulations of deprived cells to acquire survival-promoting adaptations /73,560,596/. On the other hand, glucose represses these responses /619,620/ and abundance of nutrients in a chemostat decreases hypermutability /997/. Hence, replicating microorganisms are less mutable than growth-constrained or stressed populations.

As in stress tolerance, the various features of mutability are, at least in part, under the control of the SOS regulon in both replicating and resting/ stationary phase bacterial populations /306,656, 965/. Although not yet fully elucidated, the emerging pattern of the SOS-mediated control of repair/ mutagenesis balance indicates an intricate network of promiscuous transduction pathways and regulators which engage an array of molecular chameleon effectors. These elicit context-specifically a dichotomous adaptive response resulting in either maintenance or change of the genetic information /306,656,967/. In brief, the activation of highly promiscuous RecA is followed by a variety of limited proteolytic steps to yield effector molecules with activities in either the repair or mutagenesis response /656,937/. Thus, the LexA regulon exerts both positive and negative control of the mutagenesis response /656/. The mismatch repair system antagonizes the mutagenesis system /355,618/, but is downregulated during stationary phase /618/. Other antagonistic repair/mutagenesis balances are also operative /301,804,1100/, suggesting that DNA repair or mutagenesis are context-specific alternative survival mechanisms. In stationary phase bacteria, LexA proteolysis can be induced by dilution, highlighting the relevance of bacterial density sensing for the balance of the repair/mutagenesis response /242/. Various aspects of this balance are dependent on oxidative stress whereby higher levels favor mutagenesis /283, 619,681,1100/. Importantly, the repair/mutagenesis balance is also modulated by interactions with HSPs /237,587,775/ which, dependent on fuel availability and subject to catabolite repression /619,620,681/, may provide the regulatory input of the metabolic/oxidative homeostasis derangement during stress /488,620, 898/.

Remarkably, homologues of the SOS system have also been detected in Archaea /260,532/, dating the roots of this system to the time before they and eubacteria diverged from a common ancestor. Thus, in the approx. 1.5 billion years of prokaryotic evolution, the response to environmental challenges was established as the driving force of unicellular adaptation /105,967/ and speciation /967,1045/.

3. DEPRIVATION SYNDROMES, THE MULTICELLULAR SOPHISTICATION OF UNICELLULAR STRESS RESPONSES

Stress-induced mutagenesis, although the putative vehicle of unicellular evolution, is not compatible with the cooperative sociability in a multicellular organism. Rather, its mechanisms leading to the egoistic survival of the fittest clones will be encountered as the asocial deprivation response of the carcinogenic process. Stress resistance, on the other hand, seems to lack the dynamic nature to be an active player in the evolutionary process. Thus, at the moment it is hardly conceivable how deprivation may have maintained its momentum as the driving force of multicellular development and phylogenesis. To address these issues in a first approach, surrogate markers of stress responses in cell cycle events indicating phylogenetically conserved mechanisms are explored. It is assessed how intercellular communication in multicellular organisms may affect stress responses, cell cycle

decisions and signaling pathways, whereby social bacteria and Protista have a unique role in bridging uni- and multicellular behavior. Furthermore, the notion is elaborated that evolutionary conservation links signal transduction pathways, effector mechanisms and metabolic adaptations in unicellular stress responses and multicellular cell cycle events.

3.1 The deprivation syndrome and intercellular communication

Bacteria and Protista have already evolved complex social interactions. They have succeeded in forming multicellular communities, e.g. biofilms or slimes, with sophisticated signal transduction networks mediating coordinated multicellular behavior /738,904/. These communities provide a protective environment and therefore during phases of environmental challenge microorganisms can increase adhesive forces and search for this shelter /846, 904/. The cellular aggregates evolved as prerequisites for developmental stages in the life cycle of microbes /70/; cumulative evidence suggests that this link has been conserved throughout phylogeny /142/ and that social behavior shapes the metazoan cell cycle /801/. Intercellular communication of bacteria and Protista integrates information about cell density and nutrient availability /427,959/. Thus, quorum sensing and intercellular communication are involved in the induction of stress responses such as the stationary growth phase /544, 989/, stress tolerance /989/, sporulation /418,544/, genetic competence, a primitive mating behavior /78/, and antimicrobial agent production /418,503/. Remarkably, quorum sensing molecules, e.g. N-acyl homoserone lactones, mediate starvation survival /62,989/. With increasing sociability, microorganisms achieved the elaboration of multicellular stress resistance responses, with differentiated structures such as cysts or fruiting bodies dependent on highly coordinated social behavior, integrating information about cell density and nutrient availability into a dynamic tuning of the survival/death balance /335,352,474/.

Intercellular communication became even more important in social units such as a metazoan organism. In the early evolution of animals before the parazoan-eumetazoan split, intercellular communication appears to have increased dramatically, as evidenced by extensive duplications of genes involved in cell-cell communication /611,956/. In fact, gene duplication may be an adaptive mutagenic mechanism in genes under selective pressure /107,174,1111/. With the evolution of Metazoa, the external milieu was increasingly replaced by a more protective and better controllable internal milieu. On the other hand, the environmental conditions which had evolved as triggers of developmental events had to be mimicked by internal agents. A myriad of messengers evolved which convey their signals by a host of receptors in a highly spatially and temporally coordinated way to effect a variety of life- and cell-cycle events such as differentiation /408/ and apoptosis /239,1000/. Conversely, differentiation, apoptosis and conjugation are inhibited by the lack of social interaction at low cell densities /78,689,1094/. Since cell adhesion is protective and anti-apoptotic /74,209,768/, cell-cell and cell-matrix contacts have to be loosened at a certain stage of morphogenesis to drive cells into the apoptotic response /28,63/. On the other hand, the social community had to harness the alternative, yet asocial, deprivation response leading to clonally proliferating hypermutable survivors. Therefore, phylogenetic regression and mutagenic oncogenesis are repressed by intercellular communication but can be released following disruption of cell-to-cell and extracellular matrix communication /610, 1002/. Bacteria and protozoa already have options for social and asocial deprivation responses dependent on the inverse relationship of resource availability and intercellular communication. Bacteria which are shear-stressed by constant shaking /281/ are deprived of humoral or cellular contacts with their siblings. In such an asocial environment and exposed to abundant nutrient resources, bacteria exhibit substantially attenuated capacities to differentiate following starvation /1030/. Mutagenic responses may be enhanced in bacteria following dilution of stationary phase cultures /242/, putatively due to the lack of multicellular oxidant defense /616/ and the ensuing shift of the repair/-mutagenesis balance (see above). Thus, mutagenesis is enhanced by stressors and at low cell densities across the entire phylogenesis /94,95,989/.

3.2 Conserved stress transduction pathways and effector mechanisms

Cell stress signaling pathways are remarkably conserved throughout phylogeny /171,327/. Furthermore, the notion that these transduction pathways are shared by a variety of cell cycle events /327/ adds plausibility to the concept of a common evolutionary origin.

Cyclic AMP (cAMP) transduction pathways are virtually ubiquitous in all phyla /772/ and play a role in a wide range of cellular processes. cAMP is a symbol for carbon-source starvation and regulates stress signaling /45,98/, as well as developmental decisions such as differentiation/apoptosis /21,161, 443/, sex development, mating behavior, gametogenesis /794,973/ and stationary phase- and aging-related mutagenesis /620,965,967/. In bacteria and yeast, the coordination of these effects may be achieved by a universal integrator function of nutrient availability /620,992/. Fundamental similarities between catabolite modulation of cAMP in prokaryotes and hormonal effects in Metazoa /387, 772,992/ emphasize the role of hormones as carriers of environmental messages conveying energetic/metabolic information in the metazoan internal milieu. cAMP is also a putative regulator of intercellular communication through gap junctions /1002/ thus exerting control over social and asocial deprivation response decisions. Throughout phylogenesis, protein kinases of the mitogen-activated protein kinase (MAPK) cascade and their homologues, the extracellular-related kinases (ERKs) and stress-activated protein kinases (SAPKs), are regulators of stress /475,761,1072/, differentiation /11/, apoptosis /671,1105/, and sexual development /477,1072/. The sphingomyelin-ceramide pathway is another evolutionary conserved response which is activated upon stress and regulates tolerance, differentiation and apoptosis /325,369,583/. The yeast SNF1 and mammalian AMP-activated protein kinase (AMPK) are homologous mediators of cellular stress responses /373/. The SNF1/AMPK pathway is activated under conditions of an elevated AMP-ATP ratio and constitutes a cellular protection system which switches off ATP-consuming processes and coordinates adaptations of the glucose-fatty acid cycle /374/. The retinoic acid (RA) signaling pathway is among the most primordial deprivation syndrome transduction pathways and controls apoptosis, differentiation, and carcinogenesis /132,605,848/. RA-induced growth arrest /630,971/ may be mediated by a downregulation of energy metabolism /903/, decrease of mitochondrial membrane potential /834/, generation of oxidative stress and a drain to antioxidant reserves /630,981/. Thus as the putative basis of its developmental actions, RA elicits distinct stress responses /153, 536/ and synergizes with stress /811/.

A signaling network integrates multiple cross-talk between different types of stress in the same signaling pathway and coordinates different pathways in response to the same stressor /23,992, 1059/. Both agonistic and antagonistic interactions exists /803,876/. Pleiotropic agents interpret these signals in a cell type and context dependent manner to orchestrate a comprehensive process leading to distinct outcomes. The expression of HSPs as a universal response to stressors has evolved in Cyanobacteria, Archaea, and Bacteria /271,617/, and constitutes a molecular representative of the GAS. Expression and phosphorylation of Bcl-2 family members are prominent targets of cell stress phosphorylation cascades /61,220/. Other mediators and effectors which will also be addressed later include p53, NF-κB, NAD^+, and DNA repair enzymes. The p53 protein which functions in a SOS-like capacity /264/ is an integration point for stress signals /21,944,1059/, is activated by DNA damage, and has a role as cell cycle check point in the transcriptional/translational control of growth arrest /529,983/, apoptosis /458,944/, differentiation /14/, and tumourigenesis /944/.

The perturbation of the energy-Ca^{2+}-redox balance is of utmost importance for the induction of cellular stress responses. Energy homeostasis is under stress not only in conditions such as apoptosis and aging /387/ but also during cell cycle events perceived as less stressful, such as differentiation and conjugation (see below). Ca^{2+} ions adapt the supply of high-energy phosphates to cellular energy demands by regulating the activity of a variety of rate-limiting enzymes of the TCA and respiratory chain. Increased Ca^{2+} levels uncouple mitochondrial electron transfer and oxidative phosphorylation and increase the production of oxygen radicals /387/. Conversely, redox homeostasis

modulates Ca^{2+} signaling /1097/ and may perturb Ca^{2+} homeostasis /743/. A central target of signaling networks is the redox balance, e.g. the glutathione cycle /1069/, which is modulated via the generation of reactive radicals /796,822,995/. The Ca^{2+}-redox tandem as mediators and effectors of the energy crisis drive the tolerogenic and mutagenic responses. DNA repair is subject to Ca^{2+}-redox modulation /518/, and both DNA repair /805/ and mutagenesis /283,619,681,1100/ are induced by reactive oxygen and nitrogen species. Ca^{2+} modulates these processes on various levels /316,518,898/, possibly in a U-shaped concentration relationship /316/. The modulation of DNA repair systems may be regarded as a defining feature of deprivation syndromes.

Tolerance induction constitutes the first level of stress defense; a comparison of unicellular (see above) and multicellular processes may serve as a tentative proof of the concept of phylogenetic conservation of stress adaptation mechanisms. As in bacteria, in Metazoa many forms of stress, when experienced at mild-to-moderate preconditioning intensities, create tolerance, e.g. thermotolerance, radiation tolerance, ischemic tolerance. The common denominator of tolerance induction in eukaryotes appears to be oxidative stress /606,814, 999/, even with such seemingly inconspicuous stressors as salinity, water deficit, hydrostatic pressure, heat, freezing, and emotional stress /308, 395,442,457,585,606/. Ca^{2+} is involved /84,337/ and also stress transduction pathways, such as cAMP /631,782/, MAPK /311,522/ and ceramide /230,584/. The tolerogenic mechanisms include increase of antioxidant defenses /735,744/, upregulation of HSP expression /867,1031/, Bcl-2 expression /868,912/, and DNA repair /518,893/. The tolerance provides cross-protection to a variety of other stressors, including ischemia /407,1089/. Metazoan stress resistance is also associated with energy efficiency /758/, as evidenced by lowered metabolic rate /407/, resistance to hypometabolism /550/ and increased metabolic reserves /234/. These features verify the basic conservation of stress responses between bacteria and Metazoa. In addition, mitochondria appear to be involved in tolerance formation /336/, putatively via mitochondrially generated oxidative stress /796,995/. Remarkably, simple deprivation responses, such as radiation tolerance or dietary restriction, can provide cross-protection against complex cell- and life-cycle events such as differentiation /1006/ and aging /1046/.

3.3 The metabolic adaptations in deprivation syndromes

Too small to accumulate substantial energy depots during phases of nutrient surfeit, microbial populations enter stationary phases when facing nutrient shortage. The characteristic pattern of metabolic adaptations to deprivation was established as early as in stationary phase bacteria and protozoa: hypometabolism and downregulation of oxidative respiration /368,722,723/, upregulation of glycogen synthesis /710/, and oxidation of lipids from endogenous polyhydroxybutyrate/alkanoate reserves, membranes, and exogenous sources /449, 722,723/. The cell takes advantage of the higher energy yield from fatty acid β-oxidation while glucose is saved for anabolic purposes /389/. Thus, these adaptations subserve the dual purpose of reducing the mitochondrial generation of toxic oxygen species and of minimizing the utilization of endogenous reserves /722,723/.

Plausibly, these adaptive responses are repressed during glucose abundance. Catabolite repression is a common feature of prokaryote and protist metabolic regulation and is highly coordinated by regulons /459/. Catabolite repression is exerted on acetate utilization /27,354/, SOS mutagenesis /619,620/, motility and chemotaxis /745,772,1042/, bacteriocin and antibiotic production /288,787/, social behavior and intercellular communication /745,788/, differentiation including sporulation and encystation /772,787, 941/, apoptosis /319/, and conjugation /854,926/, and may also control at least some aspects of tolerance induction /373,771, 1066/ and aging /305,496/. Oxidative stress /397/ and antioxidant enzyme defense /194,378/ appear to be signal transducers and effectors of catabolite repression/derepression balances. Metazoan differentiation /88,781,952/ and apoptosis /524, 1094/ are also subject to glucose repression. Remarkably, mitochondria are active players in the cellular catabolite repression process /382,943/.

The storage of fuels during phases of food abundance represented a metazoan evolutionary breakthrough. Multicellular organisms evolved cells which are specialized to store energy-rich fuels, particularly triglycerides, during phases of nutrient excess which can be mobilized and catabolised during shortage. The so-called glucose-fatty acid cycle /809/ can be regarded as a metazoan sophistication of the unicellular catabolite repression/derepression regulation. The control of energy balance at the systemic level and the cellular adaptation to the changing fuel supply are primarily mediated by the reciprocal insulin/glucocorticosteroid (GC) systems /200,895/ and modulated by the thyroid system /436/. This hormonal regulation is complemented by the neurotransmitter system, particularly the dual acetylcholine/catecholamine system /49,389/. In principle, the eutrophic, pro-glucolytic insulin/acetylcholine system is opposed by the dystrophic, pro-lipolytic GC/catecholamine system. The evolution of the GC/catecholamine stress response system enabled multicellular organisms to activate their fuel depots as a first step in response to more severe and/or persistent stressors before the phylogenetically older apoptosis/differentiation pathway is pursued (see below). Thus, both animals and plants resort to fatty acid oxidation following glucose starvation /231,389/. In addition, as in microorganisms, the adaptive mechanism to a variety of environmental stressors is hypometabolism, as in hibernation, aestivation and anaerobiosis of amphibians, insects, reptiles and mammals /389,951/. The mediators of this metabolic switch are GC and amyloid β-protein, a metabolite of amyloid precursor protein, which in appreciation of its pleiotropic actions in this adaptation has been proposed to be called deprivin /389/. These agents orchestrate also the differentiation/apoptosis balance /389/, enabling a smooth and coordinated transition from mild (metabolic switch as in sleep and exercise) to severe deprivation responses (ontogenetic events and tissue damage). Neurotransmitters are the archetypal carriers of trophic signals which evolved in unicellular organisms long before they developed their secondary sophisticated roles in perception, affect and cognition in the nervous system /389/. In their dual capacity as trophic and affective/cognitive messengers, they provide the link between psychosocial stressors and somatic energetic responses giving rise to and representing the pathophysiological substrate of a whole array of psychosomatic diseases (Heininger, in preparation). Thus, in its last consequence and as its defining signature, each stressor elicits metabolic stress and triggers an adaptive metabolic response.

As outlined earlier, hormones are conveyors of energetic/metabolic information, thus replacing environmental messages in the metazoan organism /387,992/. In response to hormones and by integrating stress sensing, reporting and responding, the adaptive responses of the glucose-fatty acid cycle are regulated by a network of stress signal transduction pathways. cAMP can be regarded as a universal signal for carbon source deprivation and mediates the mobilization of fuel stores in response to a variety of hormones and neurotransmitters such as glucagon or adrenaline /992/. SNF1/AMPK may be the metabolic master switch /374,459/. cAMP and cAMP-activated protein kinase signal transduction are mediators of glucose transport inhibition /792/. Fatty acid oxidation is stimulated by a variety of stress signal transduction systems such as cAMP /91,653/, AMP /374,459/, and ceramide /92/. cAMP and its signal transduction pathways are also mediators of catabolite repression /269, 439/.

The regulatory interfaces of the glucose-fatty acid cycle also control cell cycle decisions. These transduction pathways are exemplified by the anti-apoptotic interaction of the insulin receptor substrate and Bcl-2 /1011/ and the key functions of glycogen synthase kinase /389,403/ and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) /389/ during cell cycle events (see below). A pivotal mechanism linking deprivation syndromes and fatty acid metabolism appears to be related to peroxisome proliferator activated receptors (PPARs). PPARs are members of the nuclear steroid hormone receptor superfamily of transcription factors and mediate peroxisome proliferation, activate mitochondrial and peroxisomal fatty acid metabolism and ketogenesis /274,389,543/ and modulate cellular redox status /790/. PPARs play a pivotal role in the cellular metabolic response to fasting by inducing mitochondrial fatty acid oxidation and ketogenesis /561/. As a protagonist in the depriva-

tion syndrome metabolic response, PPARs mediate inhibition of glucose transport /333,597/ and inactivation of pyruvate dehydrogenase complex /1086/. PPARs are regulated by GC /555,1035/ and stressors /556/ and activated by oxidative stress /226,852/. HSP which bind to PPAR may mediate this uniform stress response /423/. Control of lipid metabolism and redox status are intimately linked such that abundance of lipid fuel may mitigate while lack of lipids may enhance oxidative stress /425/. Cross-talk between various members of the steroid receptor family integrates the signaling pathways /484,509/. In particular, the synergistic interaction with the retinoid signaling pathway and the retinoid X receptor through heterodimer formation /154,483,504/ argues for a role of lipid metabolism in differentiation and apoptosis /1023/. As a counterregulatory response during apoptosis, mitochondrial fatty acid β-oxidation is enhanced by expression of carnitine palmitoyltransferase I (CPT I), while the inhibition of CPT I shunts fatty acids into sphingolipid/ceramide metabolism and drives the cell into apoptosis /762/. Importantly, retinoid signaling appears to be the ancient system from which GC and gonadal hormone transduction pathways have evolved (after the level of *Caenorhabditis elegans*) and these findings are evidence of the evolutionary continuity of fatty acid metabolism regulation and its importance for cell cycle decisions /50/. PPAR agonists also inhibit inflammatory cytokine generation and negatively regulate macrophage activation /455,832/. The 'silencing' of inflammatory responses during stress and GC treatment /797/ appears to be regulated by this pathway.

4. APOPTOSIS AND DIFFERENTIATION: THE JANUS FACES OF A SOCIAL DEPRIVATION RESPONSE

It should be stressed that the following is not intended to oversimplify the huge diversity of processes leading to differentiation and apoptosis. Particularly in metazoan organisms, each tissue appears to follow its own differentiation/apoptosis program. However, a wealth of common features exists which can be traced back to the early bacterial and metazoan ancestors and which allows the deduction of shared roots and evolutionary rationales.

In general, cell death develops along two pathways: apoptosis and necrosis. Apoptosis (Greek 'falling off') describes the silent demise of cells which occurs during development, cell maturation, and in response to various noxious stimuli /591/. Apoptosis is often regarded as altruistic suicide since it does not elicit an inflammatory response and thus cells die without affecting their neighbors. Frequently, programmed cell death during tissue maturation and apoptosis during tissue damage (sometimes referred to as accidental death) are regarded as different phenomena, and, in fact, cell death pathways of immature cells may differ from apoptosis in differentiated cells due to different starting points in the cell cycle /422/. However, multiple shared processes suggest their common origin /591/.

In contrast to asocial bacteria, such as *E. coli*, social bacteria, such as *Streptomyces* or *Myxococcus* have evolved multicellular development programs under nutrient deprivation. These microbes differentiate into fruiting bodies or aerial mycelia which give birth to highly resistant, metabolically dormant spores which are well endowed to survive even during extremely adverse conditions /143, 415,544/. 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 /143,247/. It will be outlined below that to ensure the sufficient flow of resources this cellular death had to be linked to differentiation and was programmed in an intercellularly coordinated process. An extreme version of this differentiation/apoptosis link is encountered in the asymmetric cell division of *Bacillus subtilis,* in which a dying mother cell nurses the development of a daughter spore /273,602/. Evolutionarily conserved, the apoptotic cell contents ensure also the survival of fellow vertebrate embryo cells /268/. Thus phylogenetically, differentiation and apoptosis became closely interrelated and in fact are both 'flip-flop' phenomena of a deprivation syndrome. Established at a unicellular evolutionary stage /17,143,1092/, the link between differentiation and apoptosis is maintained throughout the entire evolution and has been demonstrated in a variety of mammalian cell lines /823,988,1062/. In some metazoan tissues,

e.g. during erythropoiesis and terminal differentiation of keratinocytes and lens fiber cells, differentiation and apoptosis are tied together by hybrid processes /199,320,684/. The occurrence of apoptosis in both animals /591/ and plants /591/ is further evidence that apoptosis is not an accomplishment of multicellular organisms but has evolved at least as early as at the level of their common eukaryotic ancestors. Microbial processes such as sporulation, stationary-phase cell death, and fruiting body formation carry features of apoptotic cell death /143,186,402,1092/. Accordingly, the evolution of many anti-apoptotic and pro-apoptotic protein domains, including caspase domains, can be traced back to unicellular eukaryotes and even bacteria /30,1019/.

The mechanisms of differentiation/apoptosis regulation have been investigated in the social amoeba *Dictyostelium discoideum*. This protozoon undergoes a multicellular development following nutrient deprivation to form a fruiting body consisting of dead stalk cells supporting a mass of spores /109,677,704/. Differentiation and apoptosis are closely linked in a social stress response /171, 186/ in which cAMP acts as an inter- and intracellular stress messenger /992/. Cell-autonomous developmental features exist which determine the prespore/prestalk commitment dependent on the cell cycle phase at the beginning of the deprivation response /109,677/. Randomly distributed cell types are then differentially sorted to create a spatial patterning of prestalk and prespore cells along an anterior-posterior axis /704/. On the other hand, the relative proportion of differentiating spore and apoptotic stalk cells is determined by nutrient availability, quorum sensing and secreted factors, so-called morphogens, such as differentiation-inducing factors (DIFs) /109,481,677/. DIF production is controlled by food sensing /319/. The morphogens elicit evolutionarily highly conserved, dose-dependent and context-specific ambiguous effects causing growth arrest, differentiation and apoptosis in various mammalian cell lines /527, 528/. The DIFs appear to be synthesized in prespore cells and are inactivated in prestalk cells /481/. At low doses DIFs may induce prespore differentiation /741/ but at higher doses are requisite for prestalk cell development /481/. The cell types remain totipotent until late in development, leading to a high plasticity of differentiation /677/. In accordance with the ambiguity of the signal, regulation of transduction pathways is highly promiscuous and coordinated /1033,1077/. Effector mechanisms of DIFs include the elevation of intracellular Ca^{2+} /878,1076/ and uncoupling of mitochondrial respiratory activity /907,1076/, both pathways to oxidative stress. Mitochondrial uncouplers, on the other hand, can induce stalk cell differentiation /1076/. As in mammalian differentiation, mitochondrial biogenesis is necessary for prespore differentiation /907/. Further circumstantial evidence, such as the requirement of an oxygen atmosphere and of mitochondrial functional changes /648,870/, emphasize the developmental involvement of mitochondria and metabolic/oxidative stress. Remarkably, prespore cells determine the fate of apoptosing prestalk cells and ensure the provision of nutrient-supplying and spore dispersion-mediating apoptotic stalk cells. Thus, prespore cells inhibit the conversion of prestalk to prespore cells /438,906/, while prespore cells become apoptotic stalk cells when prestalk cells are removed from the equilibrium /697/. The evolutionary rationale of these mechanisms was further highlighted by a system involving successive cell killing by ricin A. Killing of prestalk cells had no impact on cell-type proportions (nutrients for the prespore cells are thus abundantly provided by the dead cells) while prespore cell killing led to the eventual conversion of all prestalk cells to prespore cells (to provide gene survival-ensuring spores) /906/. It can be inferred that survival and death of cells depend on environmental cues, the proportion of dying cells being determined by and hence regulated according to the needs of the surviving cells. *Dictyostelium* is also an illustrative example of how differentiation as the primary stress resistance process (providing spores) cooperates with apoptosis in morphogenesis to create a fruiting body which ensures the aerial distribution of spores /109,677,704/. At the onset of metazoan phylogenesis, clones of protozoa forming permanent or long-term clusters may have lost their ability to adequately supply the cells in the core of the aggregates, thus exposing them to deprivation stress. A potential mechanism for such a defect was

recently demonstrated in biofilms of mutant bacteria. These microbes failed to maintain the elaborate architecture of pillars and columns with water channels between them which function like a primitive circulatory system /206/. The ensuing differentiation/apoptosis response may have created a cavern which could have developed into a sphere or simple stomach as seen in primitive Metazoa such as *Volvox*, the sponges and hydras /330,498/, and as mimicked during the development of mammalian blastocysts /188,1061/. Later, the formation of the metazoan internal milieu allowed the regulation of the tropism of individual cells by an intricately tuned array of neurotransmitters, hormones and growth factors which constitutively engender deprivation responses independent of environmental conditions. Mediated by these agents, multicellular organisms "learned" to create circumscriptive deprivation domains to employ the evolutionary fixed differentiation/apoptosis response for the molding of specialized structures and diversification of organ functions.

In the following, the conservation of the outlined features of *Dictyostelium* development will be traced through the entire phylogenesis to highlight the followings notions: 1) The differentiation/apoptosis coupling is an evolutionarily fixed deprivation syndrome. 2) The process is plastic until late stages and hence is regulated by a multitude of promiscuous pathways. 3) Controlled by the cellular environment and context-specific mediators, apoptosis is not suicide but cytocide.

4.1 The differentiation/apoptosis coupling is an evolutionarily fixed deprivation syndrome

While the classification of apoptosis as a deprivation syndrome is more or less trivial as it corresponds to routine experimental experience, the appreciation of differentiation as a deprivation syndrome is not as readily plausible. A first clue comes from the findings that metazoan differentiation may be regulated by SOS-like systems /396/, hence conserving regulatory pathways established in differentiating bacteria /1093/. Induction of stress responses, stationary phase and differentiation are all controlled by the same regulons /43, 1010/. In Metazoa, as in unicellular organisms, cell cycle arrest is a prerequisite of differentiation /178/. Growth arrest is associated with loss of clonogenicity /54,667/, a phenomenon which is routinely ascribed to apoptotic processes which may result in a variety of misinterpretations /113,328,391/. Differentiation is a common response of metazoan cells which are exposed to stressors, such as ionizing radiation, anaerobiosis, and mechanical, acid, osmotic or thermal stress /137,141,1041/, and is routinely associated with nutrient deprivation in prokaryotes and eukaryotes /298,602,979/. Like their unicellular progeny, differentiated metazoan cells from a variety of tissues are more resistant to stressors and apoptosis /40,857,1053,1112/, characterizing differentiation as a phylogenetically conserved stress resistance survival response. Particular emphasis should be given to the fact that differentiation is associated with increased oxidative stress in a multitude of cell lines /297,932, 961/. Indicating their causal role, differentiation can be induced by reactive oxygen species (ROS) /367, 700/ including nitric oxide (NO) /367,1003/ and lipid peroxidation products /228/, and suppressed by antioxidants /152,470/. Oxidative stress is also the common denominator and mediator of differentiation-inducing stressors /141/. Further evidence is a decreased generation of reducing equivalents, increased oxidant production, increased compensatory antioxidant enzyme activity and shift of redox balance /152,297,774,932/. The increased mitochondrial generation of ROS by differentiated cells /102/ may be related to their persistent state of stress tolerance /1034/ (see above). Another feature characterizing differentiating cells includes both decreased /85,570,910/ and increased /140,463,664/ DNA repair capacity. Poly(ADP-ribose) polymerase (PARP) is activated by DNA strand breaks and participates in DNA repair /777,902/. Decreased PARP activity is associated with delayed DNA repair /232,887/, elevated genetic rearrangements and genomic instability /454/. Inhibition of PARP and of topoisomerases, other DNA repair enzymes, induces differentiation /249,541/ and, conversely, differentiation may be associated with downregulation of these enzymes /82,478/. For instance, 4-hydroxynonenal, a lipid peroxidation product and inducer of oxidative stress, which activates stress signaling pathways /1008/, can induce differentiation /228/.

This process is mediated by PARP inhibition, which links oxidative stress and mutagenesis to differentiation /1015/. Remarkably, DNA fragmentation is a frequent mode of action of differentiation-inducing agents /182,349,357/. Quantitative and qualitative changes of a multitude of DNA repair enzymes may depend on the stage of differentiation with regard to the induction or fixation of mutagenic and recombinant changes /82,795/. The activity of differentiation-associated genetic rearrangement may be increased and thus PARP is particularly modulated during differentiation in lympho- and hematopoietic cell populations /82/.

Compliant with a deprivation syndrome, differentiating cells exhibit, depending on the cell type, a variety of metabolic features which suggest that, induced by hormones and mediated by stress transduction pathways /21,54,161,443/, the cells experience hypometabolic or energetic stress-like states. Cellular metabolic stress markers are expressed. HSPs are upregulated /153,244/, indicating ATP depletion /625/. The glucose-regulated proteins (GRPs), a phylogenetically conserved family of chaperones structurally related to HSP, are localized in the endoplasmic reticulum and activated following glucose/oxygen depletion, Ca^{2+} influx and a variety of stressors /547/. They have a role in the normalization of dysregulated Ca^{2+} and redox balance /1102/. GRPs are expressed during differentiation of various cell lines /979,1038/. Autophagy, the degradation and digestion of cellular contents, is another feature indicating cellular nutrient shortage. Autophagy is crucial for cellular survival during starvation and also plays a key role in differentiation and apoptosis /675,733/. Remarkably, autophagy is determined by the mitochondrial supply of carbon fuel /44,158/ and includes the clearance of mitochondria /554,733/. Together with mitochondrial biogenesis /1041/, mitochondrial autophagy may be a means to speed up mitochondrial turnover, thereby enforcing the adaptation of metabolism from proliferation to stasis. In fact, cellular stress /189,314/, differentiation /472/ and apoptosis /227,864/ are all associated with functionally heterogeneous, dynamically changing mitochondrial populations.

Differentiation is accompanied by stress response-like adaptations of the glucose-fatty acid cycle. Reminiscent of catabolite repression, glucose-containing media may deter differentiation /88, 952/. As further circumstantial evidence, proglycolytic nicotinic acetylcholine receptors /389/ are downregulated during differentiation /365/ and the cholinergic system only develops after maturation of the CNS /770/. Conversely, fatty acids may induce differentiation /968/, and differentiating cells exhibit fatty acid and ketone bodies utilization in preference to glucose /254,347/. The essential role of lipid metabolism is highlighted by the differentiation-associated upregulation of members of the low-density lipoprotein (LDL) receptor gene family in a variety of cell lines /277,1060/ and defective maturation following knockout of a LDL receptor gene family member /1078/. AMP-activated protein kinase, a key activator of fatty acid oxidation, is involved in animal and plant differentiation programs /100,399/ and inhibits apoptosis /946/. PPARs are activated not only in adipocyte differentiation but also in a multitude of cellular differentiation programs /274/ and are under control of Notch-1 /322/. Indicating its Janus-faced role, PPAR activation may augment differentiation /148/ and, following serum deprivation, apoptosis /148/, both mechanistically linked to the generation of oxidative stress /1096/. Finally, the regulation of PPARs by dietary fatty acids /223/ is evidence for regulatory interfaces of cellular stress-related redox homeostasis and lipid metabolism with substantial impact on cell fate decisions.

4.2 The process is plastic until late stages and therefore is regulated by a multitude of promiscuous pathways

The very existence of "programmed cell death" is hardly compatible with the biological bases of evolution. Should cells which have survived the harshest selection pressures for billions of years invest energy in their demise and submit to their fates at relatively moderate adverse conditions which did not consume their energy reserves? It was the contra-intuitive nature of this notion which, for 20 years, prevented the general acceptance of the apoptosis concept. Moreover, simple Metazoa such as nematodes develop grossly normal in the absence of apoptosis, indicating that programmed cell death, at least during early metazoan phylo-

geny, is not a developmental necessity /265/. On the other hand, the evolutionary rationale for this programming must be quite strong since it sufficed to overrule the more simple (and egoistic) reaction type of metabolic dormancy as it is followed in bacteria by sporulation and as would also have been feasible in Metazoa following ced-9/Bcl-2 expression /323,640/. That this rationale in its last consequence is anti-oncogenic can be inferred from the pro-oncogenic effects of Bcl-2 /20,276/. It has been argued that the apoptotic death of some ensures the survival of the species or as a silent demise causes their neighbors no trouble /22/ and thus has an altruistic rationale. Evolutionary biologists have learned to distrust altruistic theories that rely on advantages to whole populations /207, 833/. When individual and group advantage conflict, individual egoism usually prevails. In particular, at the level of genes altruism should be an unfavorable feature and evolutionarily doomed /207/. Since the differentiation/apoptosis pairing evolved at the unicellular stage, an evolutionary rationale which is able to elaborate the potential advantage(s) for the individual cell appears mandatory. Apoptosis cannot have evolved in unicellular, germ-like cells as a stand-alone process since such a process which would result in the reliable removal of the genotype from the population could not have persisted during natural selection /17/. Evolution selected for organisms which succeeded to reconcile the competing interests between the short-term, egoistic survival of the individual organism and the long-term goal of survival of the genes. These organisms obtained a fitness advantage (more resistant spores) by linking individual death and survival in a hybrid process. Far from being altruistic suicide, apoptotic death was programmed as a mutagenic survival response which, however, was socially thwarted (see below). In contrast to a programming of death, the programming of survival conserved the very basis and continuity of the evolutionary master-plan. In fact, pro-apoptotic protein domains, including caspase domains, can be traced back to unicellular eukaryotes and prokaryotes /30/. These domains are associated with cell stress functions and pathogen resistance in plants /165,844/ and antibiotic production and differentiation in the social bacteria *Streptomyces* /645,1016/, indicating that apoptosis is phylogenetically linked to and thus evolved from survival responses. But how may these organisms, which were selected for their hardiness and resilience, have been lured into actively pursuing a genetic program which ultimately leads to their demise? The clue to this enigma takes shape when comparing the elementary processes during both differentiation and apoptosis. A comprehensive literature search confirms that both processes share a multitude of stress-related signaling pathways and effectors which often exhibit Janus-faced mechanisms. Differences with regard to the usage of these signaling pathways may be more quantitative than qualitative. The differentiation/apoptosis balance appears to be determined, e.g., by the energy and redox status of the cell /34,132,152/, HSP expression /34/, the cyclic AMP level /161,210/ and its responsive element modulator CREM /872/, growth factor activity /673,717,851/, balance of pro- and anti-apoptotic factors of the Bcl-2 family /851,962, 1057,1112/, p53 activation /21,813,857/, Notch expression /37,670/, intracellular p21 expression and distribution /40,1057/, extracellular matrix constituents /5,1057/, caspase activation /729,1062/, DNA repair /840/, and finally the amount of DNA fragmentation /520,1068/. In fact, lymphoblastoid cells undergoing apoptosis exhibit a variety of differentiation-associated features including internucleosomal DNA fragmentation and convolution of nuclei, and only differ with respect to chromatin condensation and externalization of phosphatidylserine /807/. Thus, from *Dictyostelium* /677,730/ throughout phylogenesis /874,934/ deprivation induces a program in which the cell cycle stage at the onset of deprivation appears to determine the outcome which, however, is reached via a cascade of ambiguous events.

Although determined at an early stage, an as late as possible delay of survival/death commitment would have given cells the option to escape from demise should environmental conditions have improved in the meantime. Energy availability, therefore, ultimately controls death commitment /258,413,831/. The interpretation of apoptosis as an evolutionary trap would gain plausibility, the longer the pathways which are shared with differentiation would remain plastic and the further downstream

death commitment is irreversible. This decision point may vary depending on the cell type and, at least in part, due to the necessity of genome rearrangement and hence DNA breaks during differentiation. In a variety of cell lines, reduced mitochondrial membrane potential and release of cytochrome *c* from mitochondria is not the commitment step of apoptosis /245,445,639/. Cytochrome *c* release may be an early event and may serve to inhibit mitochondrial respiration /1026/ and stabilize the mitochondrial membrane potential by oxidation of extramitochondrial NADH /93,641/. These actions are compatible with a primary cytoprotective capacity during cellular stress. Moreover, cytochrome *c* appears to act as an antioxidant to protect cells exposed to oxidative stress /517,927/ and, in a Janus-faced manner, may exhibit pro-apoptotic, pro-oxidant activity only at higher concentrations /383,705/. Exemplifying this ambiguity of the signal, cytochrome *c* is also released from mitochondria during monocytic differentiation /749/. Nor does activation of downstream caspases mark the execution phase /267,445,468,1073/. In fact, caspase activation is also a feature of differentiation /729,749,1062/ and appears to be essential for T-cell activation and proliferation /485,1056,1073,1107/. The finding that PARP, the DNA repair protein, is cleaved by caspases during apoptosis has been taken as evidence for the detrimental actions of caspases. However, cleavage of PARP may also be cytoprotective, preventing NAD^+ exhaustion (see below). Experiments with mutant, uncleavable PARP reveal that PARP cleavage by caspases may function to delay or prevent the onset of apoptosis /99,393/. Intriguingly, findings suggesting the opposite function have been reported as well /361,739/ and the discrepancy may be due to different basal NAD^+ levels /185/. Activation of caspase-1 may be anti-apoptotic /1063/ and IL-1β, the proteolytic product of caspase-1, has both pro- and anti-apoptotic effects /307,531/. Converging lines of evidence suggest that DNAses which are activated by caspases are still subject to counterregulatory inhibition /749,861,865/. Single-strand breaks (the initial lesion in apoptosis /767/) and DNA fragmentation are reversible stress responses and prerequisites for DNA rearrangements /506/ but not death markers /936,1009/ which is also evidenced by the findings that cells with DNA damage can be rescued by Bcl-2 /219,819/. Furthermore, p53, the guardian of genome integrity and inducer of DNA repair (see below), is involved in several steps of differentiation pathways /14,51/, which strongly argues for the role of DNA breaks as a prerequisite for rearrangement. In fact, cell populations such as neurons, thymocytes, myocytes, bone marrow stem cells, intestinal crypt cells, germ cells and lens fiber cells require double strand breaks and even internucleosomal DNA fragmentation to create cellular diversity during differentiation /199,321,331,520,647,749,807,1068, 1080/. It should be emphasized that there are also apoptosis pathways, as in differentiation, in which DNA fragmentation is not required /179,280,890/. Intriguingly, undifferentiated myoblasts, when they undergo apoptosis, do not undergo DNA fragmentation but their differentiated counterparts do /292/. It is tempting to speculate that apoptotic DNA fragmentation is intimately related to the state of differentiation, particularly as endonuclease activities change during differentiation /26,658/. p53-mediated DNA repair is a constituent of p53 effector mechanisms in apoptosis /321,328,608, 976/ which further highlights the yin-yang nature of the differentiation-apoptosis balance. An impression of the 'perfidiousness' (from the viewpoint of the affected cell) of the regulatory networks turning a survival response into cell death may be gained from the redox-regulated "NAD^+ waste" pathway. Protagonists of this pathway are radical species (NO or ROS), GAPDH, the NAD^+/NADH couple, and PARP. GAPDH catalyses one of the most important steps of glycolysis, generating an energy-rich phosphate bond (which further yields ATP) and reducing NAD^+ to NADH whose electron fuels the mitochondrial electron transport chain after being shuttled across mitochondrial membranes. Moreover, GAPDH exerts pleiotropic effects depending on its oligomeric state. These functions may serve to adapt glycolytic flux to demand and simultaneously link metabolism with nuclear events related to ADP ribosylation in DNA repair, transcription activation, mutagenesis and DNA fragmentation. Thus, oxidative stress inhibits GAPDH activity and impairs carbohydrate metabolism /679, 884/. Furthermore, NO and ROS elicit the ADP-

ribosylation of GAPDH via covalent NAD^+ binding /679,922/. A further both NO-dependent and -independent GAPDH capacity includes an (auto)-ADP-ribosyl transferase activity /519,679,748/ which may involve the enzyme in the cellular ADP-ribosylation emergency response /612,1079/. In a variety of deprivation syndromes, GAPDH is upregulated by p53 /160/, translocated from the cytosol to the nucleus /875/, and is causally involved in apoptotic pathways /80/. In the nucleus, GAPDH, in a DNA-binding capacity /683,850/ and with its uracil DNA glycosylase activity /65,668/, may participate with PARP in the histone shuttling DNA repair mechanism /15,873/. NAD^+, however, is consumed by the poly(ADP-ribosyl)ation reactions /720,1110/. This functions as a primarily cytoprotective feedback loop in response to deprivation resulting in attenuation of oxygen radical toxicity /435/, induction of hypometabolism, depletion of cellular ATP and inhibition of proliferation /83, 985,1079/. On the other hand, the NAD^+ (and NADH) depletion may finally lead to loss of mitochondrial membrane potential /166/ and apoptosis /720,777,887/. NAD^+ precursors protect cells against apoptosis and the cytoprotective mechanisms are associated with increased nuclear and cytosolic levels of GAPDH /196,501,985/. As evidence of its Janus-faced capacity, ADP-ribosylation is requisite for differentiation in all phyla /284, 724/ and inhibition of ADP-ribosylation blocks differentiation pathways /463,489/. Likewise, GAPDH upregulation also plays an essential role in differentiation /58,124/ and cancerogenesis /338, 493/. Thus, in a (patho)physiological continuum the oxidative stress-dependent ribosylation response turns the cytoprotective DNA repair activity either into a survival/differentiation pathway or an NAD^+ waste syndrome and apoptosis vehicle. Thereby, cells literally rescue themselves to death. Another molecular 'Dr. Jekyll/Mr. Hyde' switch, turning a rescue program into a detrimental process, has been reported recently: an enzyme synthesized as a serpin with anti-protease activity is post-translationally modified during apoptosis to yield a protein with endonuclease activity /993/. A variety of other Janus-faced effectors such as ROS, deprivin/amyloid β-protein (Aβ) /389/, and tumor necrosis factor (TNF), to name just a few, appear to engage in dose-dependent and context-specific actions with ambiguous effects on the differentiation/apoptosis balance. For instance, ROS regulate caspases /279/ and either activate or downregulate DNA repair activity /149,805/, leading to tolerance, differentiation or apoptosis. Thus, in spite of the early cell fate decision, the process remains plastic and the final commitment point for cell death or differentiation appears to be quite late, possibly at the level of DNA repair fidelity.

4.3 Apoptosis is not suicide but cytocide

The contra-intuitive concept of cell suicide which was proposed for the first time in 1972 /487/ was only generally accepted 20 years later when genes (*ced-3* and *ced-4*) were identified in the worm *Caenorhabditis elegans* which code for proteases which are homologues of caspases /265/. The plausibility of this notion was determined decisively by the belief that the caspases are exclusively dedicated to the control of apoptosis /802/. However, the emerging realization that caspases regulate a variety of cell cycle processes /10, 485,749/ should instigate a thorough re-evaluation of this concept. Thus, I fundamentally question that a cell may be programmed to commit suicide. In fact, many features increasingly bring into question the distinction between altruistic suicide in programmed cell death and active killing during accidental or stressful apoptosis /810/. The definition of the differentiation/apoptosis balance as a socially coordinated hybrid process implies that the level of regulation of this process must be outside the individual cell. In fact, in all cases studied to date, apoptosis is regulated by signals provided by other cells /17/. Therefore, the concept is advanced that exogenous factor-mediated cytocide is the underlying mechanism of apoptosis.

Fratricide is already a routine finding in bacterial colony dynamics. During bacterial stationary phase, mutated cells take over the colony /294, 1103/ and the population dynamics suggest that this occurs by the killing of non-mutated cells /59, 1104/. Importantly, there are repeated cycles of takeovers of incrementally resistant cell populations /294,1103,1114/. The takeovers may be mediated by bacteriocins /446,975/. These agents, which may have evolved as vehicles of plasmid and

bacteriophage propagation, are employed by bacteria as cytotoxic weapons in intra- and interspecies combat /446,1092/. Bacteriocins are expressed under stationary phase conditions and following other environmental stressors and are under the control of the SOS regulon /270,446,863/. Bacteriocins exhibit a high diversity /270,446,746,835/. On the other hand, cells protect themselves against the toxicity of their own and foreign products by production of immunity proteins /446,746,835/. These immunity proteins may have broad specificities conferring a defense to related agents and hence a competitive advantage in the 'arms race' /746,975/. Intriguingly, bacteriocin production may also be dependent on quorum-sensing pheromones /380,503/ and bacteriocins themselves may have pheromone-like activities /380/. Antibiotics are paradigmatic weapons of microbial intra- and interspecies warfare. Strains of *Streptomyces* are particularly proficient in producing a variety of agents, such as streptomycin, chloramphenicol, neomycin or kanamycin /415,419/. Upon entry into stationary phase and after depletion of intracellular carbon reserves (glycogen and polyhydroxybutyrate) antibiotic production is upregulated /136,808, 826/. Regulated by the same genes as the antibiosynthetic circuit, a variety of mechanisms are employed by producing strains to induce resistance against their products and related agents /136,409, 415,419/. Antibiotic production is controlled by diffusible hormone-like factors (e.g. A-factor), which also regulate differentiation, leading to aerial mycelia and sporulation /151,418,482/. Remarkably, differentiation is accompanied by hyphal cell death which is reminiscent of eukaryotic apoptosis /672,712/. Death domains are widely distributed in *Streptomyces*, e.g. in proteins which regulate antibiotic production /30/, a finding which phylogenetically links the antibiotic effector and apoptotic response. The effector pathways are conserved, as evidenced by apoptogenic actions in mammalian cells of a variety of *Streptomyces*-produced agents /416,1017,1090/. An intriguing shared catabolite repression and regulation links starvation-induced expression of α-amylase /1037/, agarase /757/, chitinase /711/, and galactose and glycerol metabolism /400/ with antibiotic production /787,788/ and morphogenesis /787,788/. These links may define antibiotic production as yet another means to tap alternative carbon sources. A-factor biosynthesis is associated with an energetic cost /1027/ and hence is genetically unstable /417/. Thus, frequent loss of antibiotic production and resistance occurs /192, 497/, particularly under stress conditions /497/. Moreover, acquisition of resistance in a bacterial colony is dependent on the amount of cell material /136,310/. These mechanisms may serve to ensure the availability of 'prey' in conditions of demand. Another example of starvation-related cytocide is the cell density-dependent release of branched-chain fatty acids by myxobacterial cells during fruiting body formation which cause the death and autolysis of a portion of the population /241,913/. The defense may consist in the secretion of fatty acid modifying enzyme which detoxifies the fatty acids by esterification to cholesterol /144/. Yeasts also engage killer toxins in inter- and intraspecies aggression /119/. Again, an immunity system protects the toxin-producing cell.

At the evolutionary advent of metazoan cells, cytocide was firmly established in prokaryotic and protist colonies. These processes have been exploited in metazoan organisms for the enforcement of tissue homeostasis. Target cell lysis by professional killer cells, e.g. cytotoxic T lymphocytes and natural killer cells, is a well-known phenomenon of immune surveillance and a means to remove infected or transformed cells. In a race of arms, tumor cells fight back and kill killer cells /133/. Target cell death is induced via both the Fas ligand (FasL) (see below) and the perforin/granzymes pathways /607,784/. Evolutionarily conserved, perforin /947/, like bacteriocins /760/ and yeast killer toxins /119/, use transmembrane channels as the mechanism to induce cell death. Bystander killing, the killing of naive cells adjacent to damaged cells or activated immunocompetent cells /156,235, 866/, also carries features of cytocide and may, at least in part, be mediated by p53-dependent secretion of growth inhibitors /508/ or by FasL /110,638/. Without any doubt, cytocide is the mechanism in immunocompetent killing. Intriguingly, however, the targeted cells respond to the cytotoxic aggression with apoptotic events /110,133,156, 235,784,866/.

To further elucidate the nature of apoptosis, the question is addressed as to whether developmental and accidental cell death/apoptosis are also due to cytotoxic aggression. Intriguing evidence for the occurrence of stress-related cytocide in Metazoa comes from a variety of experiments: 1). In irradiated cell populations, cell death or genomic instability result from both direct damage and a so-called 'bystander effect' in non-hit cells /600,691, 1113/. Findings argue for the generation of a humoral apoptogenic/mutagenic signal underlying the bystander effect /600,691/. As such, growth arrest and/or killing of naive cells is elicited by medium conditioned by cells exposed to irradiation, heat or oxidative stress /508,689,949,1012/. This effect was even enhanced after disruption of intercellular communication /690/. In addition, distant progeny of bystanders and conditioned medium-exposed cells persistently exhibit genomic instability /600,690,691/. On the other hand, conditioned medium from cells collected 22 h after irradiation, a time interval necessary to induce tolerance, is able to protect naive cells against irradiation and oxidative stress /329/. Oxidative stress appears to play a role in the bystander effect /177,266/. Energy metabolism and redox balance modulate both the induction of the humoral signal and the death response /691/, indicating the requirement of metabolic competence and vital endangerment for the cytotoxic signal generation. Intriguingly, a GPDH mutant cell line with impaired glycolytic competence is unable to produce the killing signal but is able to express the bystander response /691/, corroborating the different roles of GPDH in metabolic activity and apoptosis (see above). In plant cells, exposure to medium conditioned by senescent cells may lead context-dependently to apoptosis /601/, which is further evidence for the relevance of these mechanisms to the general deprivation syndrome. 2). Single cells exposed to radiation have a substantially better initial survival but increased delayed cell death and lethal mutations in the progeny than when irradiated in microcolonies /581,689/. These findings may support the notion that social stress responses are associated with socially-induced cell death while asocial survival programs lead to genetic instability and mutated phenotypes. In another experimental setting, crowded cultures had a survival disadvantage following oxygen and glucose deprivation /1094/. A clue to the mechanism mediating the stress survival handicap of cells in high density communities is provided by the finding that high cell density (which itself can be a stress factor) is associated with the release of soluble peptide factor(s) which induce apoptosis /129,551,858/. 3). Membrane- and soluble factor-associated cytocide appears to be associated with cell-cycle events during ontogenesis in the blastocyst /778/, during blastocyst endometrial adherence /317/, organogenesis /810/ and cyclic apoptotic changes in the endometrium /614/. 4). Killing of adjacent cells may also be achieved via intercellular gap junctions /577/. These phenomena are compatible with a concept that non-immunological cytocide (like tolerance, see above) is a soluble factor- and intercellular communication-mediated metazoan behavior which is expressed following stress and during developmental events.

A multitude of agents qualify as cytocidal mediators. Importantly, these agents are ambiguous signals which can mediate either survival or death depending on the energy and redox status of the target cells and the dose of the agent: 1). Members of the transforming growth factor (TGF) and fibroblast growth factor (FGF) families lead in target cells to the suppression of survival factors and/or production of factor(s) which can induce oxidative stress-mediated apoptosis of normal and transformed cells /239,379/. Reminiscent of ambivalent DIFs in *Dictyostelium* development, TGFs are also expressed during differentiation /494,714/ and support the differentiation and morphogenesis of a variety of tissues /473,494,546,714/. The differentiation-apoptosis switch appears to be dependent for instance on functional markers in monocytes /473/ or the maintenance of supportive synaptic connectivity in neurons /216/. 2). Deprivin (Aβ), the product of APP metabolism under deprivation conditions, is at the crossroads of cellular stress responses and, as a paracrine and autocrine agent, mediates metabolic adaptations and cell fate decisions /389/. 3). The Fas/FasL system represents membrane-associated and soluble agents which mediate an intricate network of pro- and anti-apoptotic aggressors and defenses in immune-

competent and -incompetent cells /66,698,699,780, 810/. FasL (the killer) is expressed and released by professional and nonprofessional phagocytes and may induce apoptosis in a variety of organ systems /66,780/. For instance, FasL may be responsible for soluble factor-associated cytocide in chronic renal failure and multiple sclerosis /12,881/. Intriguingly, oxidative stress appears to induce upregulation of Fas /215,958/ and FasL /64,1039/ expression, while Fas signaling involves mitochondrially-generated oxidative stress /55,1064/ and inhibition of HSP upregulation /882/, thus increasing the apoptotic vulnerability of cells. 4). SARPs, a family of proteins secreted by growth arrested but not exponentially growing cells, may render other cells either more or less susceptible to apoptotic stimuli /662/, thus mediating both apoptosis and tolerance. 5). Exogenous factors also control the defensive capacities of cells, e.g. by regulating the expression of Fas and FasL /46,168/, HSPs /888,1099/ or Bcl-2 family members /180,851,977/. Deprivin/Aβ may at least in part exert its pro-apoptotic effects by downregulating Bcl-2 and upregulating bax expression /753/. 6). TNF can serve as an example of the context-specificity and oxidative stress-related nature of the signal. TNF may induce survival /57,535/ or silence survival signals /1032/ and trigger cell death /812/. Importantly, these varied actions are associated with either upregulation of antioxidant defenses /57,111,918/ or oxidative stress /344,917/. The cellular redox system thus plays an essential role in the signaling of TNF /341/ and also regulates its expression /582/ establishing a complex feedforward and feedback cycle. 7.) This list could be extended by a multitude of Janus-faced agents, such as interleukins, growth factors (e.g. neurotrophins /131/), and hormones. 8). Finally, cellular Ca^{2+}-redox homeostasis is the common pathway mediating the agents' effects context-specifically and thus is the final arbiter of life or death. Increase of Ca^{2+} in the target cells is the integrator of cytocide mechanisms which involve the target cell's endogenous machinery to achieve DNA fragmentation /622,652/. NO and H_2O_2 and their interaction products exert both inter- and intracellular, pro-apoptotic and anti-apoptotic effects depending on the redox status of the target cell /112,275,1003/. Redox balance is the integrative level which is targeted by the morphogens (such as TNF and TGF). As amplifiers which entertain radical chain reactions, cytotoxic lipid peroxidation products such as oxidized low-density lipoproteins, malondialdehyde or 4-hydroxynonenal /669,1008/ may also mediate fratricide.

Taken at face value, a variety of metazoan cell death programs are induced following plain cytotoxic aggressions. If these events would lead to necrosis the interpretation as cell killing would be unanimous. What confounds even the unbiased observer is the fact that during apoptosis a program is actively pursued which suggests the collaboration of the victim with the aggressor in the causation of cell death. Hence, target cell apoptosis was interpreted as "involuntary suicide" /784/. However, linking the deprivation context, the unicellular egoistic programming, the association with differentiation and the social demands in a coherent, plausible evolutionary rationale yields an apoptosis scenario in which social compulsions collide with selfish resilience, a conflict which is resolved by a socially thwarted egoistic survival response. These conflicting interests manifest in a confounding push-pull phenotype (see below). The concept of apoptosis as cytocide not only has to define cytocidal mechanisms but is also supported by the identification of, at least transient, defensive behaviors which argue against a tacit consent on the part of the victim. In fact, apoptotic death does not come voluntarily and needs some violent "persuasion" /31/ as evidenced by the finding of cellular antidotes against cytocidal agents. Saturation of fatty acids in membrane phospholipids increases during apoptosis /921/ as a means against lipoperoxidation, a protective behavior which is also employed by stressed bacterial /828/, yeast /945/ and mammalian cells /388,1043/. p53 is not the unconditional relentless "terminator" but upregulates antioxidant defense /974/ and activates DNA repair /321,328,608,976/. A family of apoptosis inhibitory proteins (IAP) is phylogenetically conserved from yeast to insects and mammals /1019/. IAPs are expressed during apoptosis and mediate the anti-apoptotic effects of Rel/NF-κB transcription factors /1085,1101/. IAPs act to prevent cell death by inhibiting caspases /224/, Fas receptors /245/ and the tumor necrosis signaling pathway /1018/.

Importantly, IAPs also play a role in differentiation /3,1020/. Anti-apoptotic agents, such as HSPs /6, 385,783/ and Bcl-2 /868,953/, are expressed in apoptosing cells. In a push-pull mechanism these defenses, however, are weakened and overwhelmed, determining the fate of the cell.

Finally, fratricide-associated cannibalism is not only a necessity in deprived bacteria but is also employed by metazoan professional and non-professional phagocytic cells. Intriguingly, engulfment of apoptotic bodies by neighboring cells has been demonstrated to sustain their proliferation and differentiation /69,1022/. This again exemplifies the phylogenetically conserved rationale of the differentiation/apoptosis tandem, although 'anachronistic' in a multicellular organism with its systemically available resources. As a phylogenetic link, the whole range of differentiation/apoptosis features can be detected in mammalian blastocysts, and evidence suggests its dependence on metabolic deprivation /213,398/ and oxidative stress in association with fratricide /754/ and cannibalism /533/.

The mechanisms acting in establishing the differentiation/apoptosis deprivation response are not unidirectional. It should be borne in mind that differentiation initially served to generate dormant, resistant life forms which, under favorable environmental conditions, could dedifferentiate and, e.g. in the case of *Dictyostelium*, yield fully vital, vegetative amoebae. This process is, at least in part, conserved in metazoans. During tissue injury and repair, a program recapitulates developmental processes in reverse order and allows populations of differentiated cells to re-enter the cell cycle /377, 389/. Importantly, retrodifferentiation is associated with the loss of specific function of differentiated tissues /389,824/ and, together with apoptosis, aggravates the damage-related initial dysfunction. Hence the retrodifferentiation/apoptosis pathway is a universal response to injury and plays a salient role in virtually every disease.

5. CARCINOGENESIS, THE ASOCIAL DEPRIVATION SYNDROME

Carcinogenesis can be defined as an asocial deprivation response. According to this concept, chronic stressors, including proinflammatory agents, exert an adaptive stimulus which context-specifically leads to the selection of autonomous cell survival. Importantly, malignant transformation carries features of both deprivation /313,440/ and regression to unicellular life forms /313,460/. Disintegration of intercellular communication appears to be a requirement for the asocial deprivation response /610,1001,1002/. Stress and asociality may determine cellular events which recapitulate the mechanisms of bacterial SOS mutagenesis /362,441,799/. Carcinogenesis is characterized by hypermutability, and mutator phenotypes that have higher mutation rates than wild-type cells are causally related to hereditary and sporadic forms of cancer /592,593,676/. Moreover, this genetic instability may be elicited by culture medium supernatants conditioned by stressed cells /94,901/. In a pathogenic continuum, oxidative stress due to endogenous and exogenous sources effects carcinogenic mutagenesis /594,634,860/, and elicits the disruption of intercellular communication /1001/, maintenance of transformed phenotype /464/, and tumor promotion /139/. Importantly, generation of ROS is implicated in the mutagenic activity of a variety of carcinogens /634,860/ and ionizing radiation /1001/. Via intercellular communication, mutagenicity may also be transmitted to naive neighboring cells /1113/, while irradiated stroma promotes the expression of tumorigenic potential /56/, suggesting that intercellular communication and the tissue milieu may not only inhibit but may also enhance neoplastic transformation. Since mutagenesis is subject to catabolite repression, early events during malignant transformation appear to be enhanced under nutrient deprivation /353,1091/. However, along the way to tumor progression some phenomena of catabolite repression may be lost /955/. Thus, propagation of tumor cells unwinds preferentially under fuel abundance conditions and is impaired by dietary restriction /346,450,1046/. The notion that malignant transformation carries features of disturbed differentiation and apoptosis /60,821/, but is inhibited by differentiation /897/, corroborates its interpretation as an atavistic survival program under conditions of cellular social deprivation /78, 689,1094/. Malignant transformation may also

occur in chronically stressed non-dividing cells /169/ in a process mimicking bacterial stationary phase SOS mutagenesis /362/. Loss of DNA mismatch repair contributes to genetic instability in carcinogenesis /592,593,676,991/ and, additionally, may play a role in the failure to employ apoptosis /991/. Importantly, mismatch repair deficiency may manifest conditionally in stressful environments /830/. Substantial genomic destabilization is an early step of tumor development and can already be detected in precancerous cells, suggesting it is a cause rather than an effect of malignancy /592,950/. Conversely, competence of mismatch repair prevents clonal expansion of cancer cells by growth arrest or cell death /128/. The genetic instability of tumor cells which encompasses sequential and chromosomal instability /246,557/ confers on transformed cells a growth advantage in a stressful environment /122,592/. Intriguingly, the mutator phenotype may arise in descendants many generations after the triggering event /94,901/. Aging and neoplastic transformation have common mechanisms /170/. A multitude of factors which favor carcinogenesis are increased during aging, e.g. loss of intercellular communication /538/, cellular energetic stress /387/ and downregulation of DNA repair /389/. A scenario can be drafted in which these factors, with or without genetic disposition and exogenous stressors, create a milieu in which the social, anti-mutagenic surveillance is lost, particularly in rapidly renewable but also in terminally differentiated tissues, leading to the manifestation of cancer.

The role of the p53 tumor suppressor gene in neoplastic development epitomizes the deprivation survival response-type of carcinogenesis. p53 encodes a protein which has a key role as integrator of genotoxic and non-genotoxic stress signals by which it is post-translationally modified /29,944, 1059/. The p53 signaling and effector system is a member of a superfamily of evolutionarily conserved stress-responsive checkpoint proteins which regulate cell cycle progression in response to stresses /529,718,983/. The product of the p53 tumor suppressor gene acts as a transcriptional regulatory protein with sequence-specific DNA-binding capacity /282,486/. Wild-type p53 is required for social deprivation responses, e.g. differentiation and tolerance induction, by affecting both redox balance and DNA repair /321,328,608, 976/. In these capacities, p53 appears to fulfill functions in a metazoan SOS-like response /264/. The redox modulation of p53 conformation and DNA binding /360,756/ and the control of redox balance mediated by p53 /458,572/ may have a role in its differential regulation of differentiation and apoptosis /96,857/. Inactivation of the growth arrest- and apoptosis-related functions of p53 appears to be a requisite step in tumorigenesis. The p53 gene is frequently mutated in tumors of diverse origins /411,563/. p53 inactivation may also be achieved by viral proteins /90,184/. p53 mutagenesis at hotspots in response to cellular stressors of both environmental and endogenous origin /688, 776/ is not a random response but selective and regulated /564,688/. ROS, including NO, possibly by a joint action, are the mutagenic agents /431, 695/, again suggesting a (patho)physiological continuum of oxidative stress which modulates p53 activation /603/, DNA binding and transcriptional regulation /360,756/ and mutagenesis. Mutational hotspots fall in the highly evolutionary conserved DNA-binding domain of p53, leading to a phenotypic inactivation of p53 /282,486,1050/, a feature which emphasizes the importance of the phylogenetically conserved function in the cell cycle control of a multicellular organism and the detrimental (carcinogenic) sequelae of mutations. Intriguingly, the anti-apoptotic activity of p53 located at the C-terminal domain is resistant against mutational modulation /542/. The mutations involve a dominant-negative regulation of wild-type p53 and oncogenic gain of function of mutant p53 /529,564,688,847/ and confer increased cellular resistance to stressors and chemotherapeutic agents /130,1029/, enhanced mutagenesis /412,1087/ and recombination /81/, and growth advantage even under growth factor deprivation /562,763/ and following genotoxic damage /351/. The interactions of p53 with HSPs are of telltale relevance with regard to the deprivation response properties of p53. p53 tetramer binding to DNA may assume either wild-type or mutant phenotypes with its unbound dimer, an equilibrium which is subject to modulation by regulators /657/. HSPs are such regulators, and the binding of HSPs to both wild-type /370,646/ and

mutant p53 /302,957/ has been reported. Evidently, HSPs are involved in the wild-type/mutant conformational switch of p53 /359,540/ with hsc70 favoring the wild-type /1095/ and HSP90 the mutant conformation /87/. Through this mechanism, stressors may energy-dependently /359/ trigger alternative social or asocial deprivation responses. HSP-associated modulation of p53 thus remakes in a multicellular context what has evolved as the regulation of the repair/mutagenesis balance in the prokaryote SOS response (see above). A feature of the regulatory p53-mdm2 feedback loop emphasizes the asocial stress rationale of p53 inactivation. mdm2 inhibits p53 by binding to it, blocking its ability to transactivate gene expression and stimulating its degradation /381/. In cultured, dispersed cells, mdm2 expression is constitutively activated by p53, while in intact tissues p53 induces mdm2 expression only following conditions of stress /663/. The expression of gap junctional proteins may also be subject to p53 regulation /900/, and p53 activation after irradiation is mitigated by gap junction disruption and low cell densities /47/, consistent with an interdependence of p53 tumor suppressor function and intercellular communication.

Cells from a variety of cancers display features of tolerance (see above), such as constitutive HSP expression /36,444/, overexpression of proto-oncogenes of the Bcl-2 family /48,820/, and upregulation of antioxidants /214,512/ and DNA repair /75,893/. These features occur as naive and drug resistance traits and are markers of malignancy and prognosis. The integrated Bcl-2/HSP families of stress resistance agents may be the ultimate mediators of an asocial/egoistic response. They are upregulated during a tolerogenic process following chronic stressors (see above) including inflammation /312/. HSP overexpression may be due to the loss of wild-type p53 HSP repressor function /4/ and is causally involved in the proliferation and apoptosis resistance of tumor cells /36, 444/. Bcl-2 inhibits stress-dependent p53 nuclear translocation and transcriptional activity /68,1109/, inhibits differentiation /372/, protects transformed cells against cytocide induced by surrounding normal cells /465/, and may facilitate cell proliferation /1013/. To the latter end may contribute the upregulation of telomerase activity /433,627/. Intriguingly, the extent to which Bcl-2 may contribute to neoplastic transformation is dependent on the cell's intercellular communication /221/. Thus, in an asocial tolerance-like mechanism, members of the Bcl-2 family confer survival, a mutator phenotype /163,1075/, and proliferation.

6. SOCIAL AND ASOCIAL STRESS RESISTANCE AND MUTAGENESIS: THE EVOLUTIONARY FRAMEWORK OF DIFFERENTIATION, APOPTOSIS AND CARCINOGENESIS

Modulated by quorum sensing, nutrient availability, and stressor intensity, asocial prokaryotes respond to deprivation by oppositely regulating DNA repair, leading to either stress resistance or mutagenesis. In the social prokaryotes, such as *Streptomyces* and *Myxococcus,* these adaptations evolved into the multicellular phenomena of differentiation and apoptosis. The increasing cooperation of cells allowed the development of sophisticated structures (e.g. fruiting bodies or aerial mycelia), which served to form highly resistant organisms (e.g. spores), and their efficient dissemination. To fuel these complex adaptations in the face of the environmental depletion of resources, the carbon sources had to be provided by dead siblings. As outlined earlier, subpopulations in a given colony follow alternative survival strategies. Given the much higher chance (in bacteria approx. 10,000-fold) of detrimental than beneficial effects of mutagenesis /491,966/, the mutagenic road to survival is by far the more hazardous one, and hence mutable subpopulations were likely suppliers of building blocks and fuel. However, hypermutability is only an option for a minority of cells in a population (about 0.05-2% /121,715/). Plausibly, those colonies of cooperatively differentiating microorganisms had an evolutionary advantage which succeeded in ensuring a constant nutrient supply by converting tolerators into mutators. However, since mutators, if present in comparable number at the outset, always win in competitions with wild-type microorganisms and take over the whole culture /800/, the wild-type, differentiating bacteria have to prevent the success of the mutagenic survival pathway. The road to

accomplish these goals is marked by the phenomenon that too much mutation is certainly lethal /291/. Thus, stress resistance, mutagenesis and cytotoxicity are distinct outcomes of cellular responses to a severity continuum of metabolic/oxidative stressors /212,526,869/. Intriguingly, in bacteria the regulation of the whole range of these differential outcomes - DNA repair, mutagenesis, and cell lysis - is mediated by the SOS system /306, 635/. Thus, creating an increasingly stressful environment by means of morphogens became the apoptogenic pathway. *Dictyostelium* is an excellent example of how the differentiating prespore cells, by means of ambivalent DIFs, drive the prestalk cells into the mutagenesis/cytotoxicity trap. The environmental modulators of these balances were increasingly replaced by the matrix constituents, growth factors and hormones of the internal milieu of the metazoan organism. Intercellular communication became the driving force of the failed mutagenesis/apoptosis pathway, e.g. via death receptor signaling /41/ and by modulating the endogenous level of survival factors /239,1000/.

The interpretation of apoptosis as programmed mutagenic error catastrophe is supported by a multitude of circumstantial findings. Mutagenesis is a transitional stage of apoptosis, as evidenced by the finding that oxidative DNA damage precedes DNA fragmentation /197,384,708/. Furthermore, initial apoptotic DNA fragmentation is targeted at or adjacent to transposable elements /489a/ which are interchangeable genetic modules facilitating genome rearrangements and combinatorial exploration /126,287/. Expression of a mammalian death effector domain in *E. coli* induces mutagenesis, chromosomal DNA breaks and cell death in an oxidative stress-dependent manner (also arguing for the determination of these effector mechanisms in non-altruistic bacteria) /552/. Downregulation of DNA repair is a mutagenic and apoptogenic mechanism (see above). Both mutagenesis and apoptosis are enhanced by inhibition of DNA repair *in vitro* /978/ and are associated with downregulation of DNA repair *in vivo* /321,480,865/. In this context, caspase-mediated PARP cleavage during apoptosis /248,785/ can be interpreted as another means to promote genomic instability and mutagenesis /978, 1004/. Of note, antioxidants prevent PARP cleavage and apoptosis, confirming the mutagenesis/apoptosis balance as redox-dependent /654/. Mutagenesis is repressed by intercellular communication /610,1002/ and, as further evidence of the mutagenic state, cell-cell contacts are disrupted at a late stage of the apoptosis pathway /28,63/. If apoptosis is failed mutagenesis, the converse should also be true. In fact, mutagenesis is a result of failed apoptosis /163,1075/ and, thus, carcinogenesis carries features of dysregulated apoptosis /821/. Likewise, viral anti-apoptosis leads to neoplastic transformation /184/. In general, virtually all anti-apoptotic effectors are (proto)oncogenes /184/. Successful (carcinogenesis) and failed (apoptosis) mutagenesis are interrelated with regard to intensity and acuity of noxious stimuli /889/. Intriguingly, and in accordance with this concept, carcinogenic agents can also act as anticarcinogens /1040/. Cancer therapy with mutagenic agents /290,467,925/ mimics the strategy of nature in orchestrating developmental apoptosis as mutagenic error catastrophe. The flip side of this therapeutic approach, and in further support of the severity continuum of metabolic/oxidative stressors' effects /212,526,869/, is the induction of tolerogenic mechanisms leading to malignant progression and drug resistance /441/.

Thus, evolutionary pressure, by exploiting the *intracellular* repair/mutagenesis dichotomy, created a highly coordinated *intercellular* dichotomous survival/cell death process. By these mechanisms, somatic mutagenesis as asocial survival response was driven by social forces into a mutagenic spiral, ending in apoptogenic collapse. In this push-pull hybrid, the cell-autonomous, actively pursued mutagenic survival response gives the whole death process a voluntary element which for the outside observer may create a suicide-like appearance. Within this conceptual framework, the context-specific tolerogenic/mutagenic/cytotoxic effect of stressed cells' conditioned medium on naive cells becomes comprehensible /94,329,508,689,690,949, 1012/. Evolutionarily conserved from bacterial spores to mammalian tissues, the original rationale for differentiation is tolerance generation. During the development of increasingly complex differentiation pathways in the generation of a variety of specialized tissues, highly targeted recombination processes /568/ evolved in variable proportions,

putatively for the creation of cellular diversity during tissue maturation /321,331,647,1080/. The downregulation of DNA repair requisite during these phases is an intricately regulated process whose failure is detrimental for the cell /285,489/. Conversely, apoptosis exhibits some aspects of stress resistance during the early stages of its course (as evidenced by p53-mediated DNA repair). Thus, it can be assumed that tolerogenic and mutagenic processes became integrated into a hybrid deprivation response in which the variable expression of the components is designed in view of the specialized functions of the differentiated tissue.

In bacterial and yeast stationary phase, increasingly fitter, hypermutable clones repetitively take over the colony /107,289,294,560,752,931/. In Metazoa as well, fitter mutable cells may eventually prevail in the 'arms race' /133,725/. Thus, to ensure their own survival, differentiating cells have to repress the asocial mutagenic/carcinogenic response which, with its regression to autonomous cell survival, represents a permanent vital threat for a complex organism. Under chronic selection pressure exerted by a multitude of exogenous and endogenous stressors, this control, however, may fail /214,429/. The disruption of intercellular communication, as occurs in aging /538/, appears to play a decisive role in the loss of this control /702,839/. Once unleashed of their social control, the cells regress to unicellular stationary phase behavior with increasing mutability, fitness and apoptosis-resistance as characteristics of tumor progression /894/. These deprivation-like features, however, contrast with the abundant availability of glucose in the metazoan organism which allows a yeast-like fermenting metabolism /459/ and proliferation of cancer cells. This discrepancy may point at microenvironments of insufficient supply /970/ for tumor progression. The cancerogenic realization of the unrestricted vitality of the 'selfish' gene /207/ is further evidence for the persistent unicellular heritage which is only poorly harnessed in a metazoan organism.

Although we are far from understanding the complex differentiation/apoptosis/carcinogenesis regulation, its emerging principles can be paradigmatically outlined with p53 and the transcription factor NF-κB/Rel family /410,856/. Like the SOS system in bacteria, p53 orchestrates the full range of social and asocial deprivation responses. Importantly, social responses are linked to the wild-type function, while the switch to the mutant/asocial functions, in a pathophysiological continuum, is brought about by the oxidative stressors which also control social responses (see above). As a primary stress response regulator /666/ and putative sensor of oxidative stress /571/, NF-κB plays a pivotal role in the apoptosis/carcinogenesis balance /217/ dependent on the cellular redox homeostasis /35,451,471/. Integrating these signals with the nutrient status of the cell /403/, NF-κB exerts both pro-apoptotic and anti-apoptotic effects /451,576,939/ and thus appears to be a context-specific target of stress-dependent signaling /666/. NF-κB is essential for cellular differentiation /358, 1057/ and has anti-apoptotic capacities /451,1024/. This is accomplished by activation of anti-apoptotic genes, e.g. of the Bcl-2 protein family /549/, antioxidant enzymes /623/ and IAPs /172,1055/. Conversely, IAPs activate NF-κB in a signal amplification loop /172/. On the other hand, NF-κB also plays a key role in apoptosis /856,939/. The pro-apoptotic activity of NF-κB is associated with its regulation of FasL (killer) /699/ and Fas (victim status) /698/ expression /145,644/. In this capacity, NF-κB appears to mediate the oxidative stress-modulated Fas /215,958/ and FasL /64,1039/ expression which is anti-carcinogenic in its consequence /806/. The redox dependence of both the killer and victim status confirms the notion that apoptosis is deprivation/oxidative stress-triggered cytocide in which opposite outcomes are shaped by the Janus faces of the same pathophysiological principle. It should be borne in mind, however, that the activation of the Fas system is not a death omen but also has a role in differentiation /678,972,1052/. In fact, the Fas system and NF-κB entertain mutual feedback loops establishing an intricate regulatory balance /476,815/. Opposite to the upregulation of the anti-apoptotic Bcl-2 family members during cell rescue /549/, NF-κB promotes apoptosis by repressing these anti-apoptotic agents /933/. Intriguingly, the apoptogenic activities of p53 and NF-κB depend on each other /856/. Evidence suggests that the survival/differentiation and apoptosis balance is dependent on the duration of NF-κB activation

/176/, on the cell type /451/, and its maturation state /576/ and stressor type /469,576/: cellular stressors activate a survival response which, dependent on the time course and cellular redox status, strains the cellular defenses (e.g. Bcl-2 and IAPs) and eventually overwhelms them in a constant cross-talk with exogenous signals mediated by the Fas/FasL system. In a cooperative network with p53 /410/, NF-κB also has a key role in carcinogenesis and drug resistance /217,650/. NF-κB activation (i.e. translocation to the nucleus) appears to be an early and causally involved event during malignant transformation /386,456,492/. The upregulation of anti-apoptotic agents /172,549,623,1055/ which mediate NF-κB's differentiation/survival capacity are also relevant for its proto-oncogenic actions /537,827/. In particular, aberrant constitutive NF-κB activation, which may be mediated by IκB (the NF-κB repressor) mutations /940/ or hyperphosphorylation /514/, confers resistance to apoptosis /332,492/. Intriguingly, NF-κB activation in cancer cells correlates with markers of oxidative stress and inversely with degree of differentiation /589/. The NF-κB-mediated balance between apoptosis and carcinogenesis appears to be modulated by both cooperative and antagonistic complex interactions with TGF /862,940/ and TNF signaling pathways /332,386,410/.

7. DEPRIVATION SYNDROME AND EVOLUTION OF SEX

The evolutionary cost of sex is 50%. Since males do not reproduce, sexual females would need a double amount of offspring (given a 1:1 sex ratio) to keep up with reproduction of asexual females. Additional costs of sex include cellular-mechanical costs, costs of genome dilution and of sexual selection /461,569/. However, the majority of species do reproduce sexually /942/. In contrast, asexual reproduction is mainly confined to small 'twigs' in the phylogenetic tree, suggesting that asexual lineages have a higher extinction rate than sexual lineages, possibly due to mutational meltdown /613,1044/. This conundrum has been described as "the outstanding puzzle in evolutionary biology" /1074/. Here, the concept is outlined that cellular stress is a trigger for mating behavior and the evolution and maintenance of sex established phylogenetically very early and conserved throughout evolution.

A plausible hypothesis, the Fisher-Muller model, puts forward that sexual reproduction offers the opportunity to produce recombinant types which can better adapt to changing environments and cope with environmental challenges /195,628, 766/. Computer simulations indicate that the advantage of sexual reproduction can be substantial in conditions in which the mutation rates are higher /293/ as is realized in adaptive responses to the selection pressure of a changing environment /117,1067/. In accordance, mating behavior is favored by unfavorable and fluctuating environmental conditions /303,841/. Suggesting an adaptive benefit, sexually reproducing populations are more likely to develop genetic resistance to pathogens, biocides or thermal stress than asexual populations /447,838/, presumably by creating and maintaining genetic variability /117,841,916/.

The clue for this striking feature of sexual reproduction can be traced back to primitive forms of life, the prokaryotic microorganisms. Under deprivation, a minority of bacteria from a colony become competent to bind and take up high-molecular-weight exogenous DNA. The heritable incorporation of this genetic information is a powerful mechanism of horizontal gene transfer. This genetic transformation is a widespread natural feature of bacteria /599,994/. Competence for genetic transformation is regulated by a Ca^{2+}-dependent stress response /998/ and is under control of the SOS regulon /162,1093/. Again, recA plays an essential role in this process both for uptake and repair of DNA and cell lysis /635/. The competence-regulatory apparatus senses and interprets environmental information and, via an elaborate signal transduction system, passes this information to the competence-specific transcriptional machinery. Remarkably, these regulatory pathways also play a role in the expression of other post-exponential phenomena, such as motility, sporulation, autolysis /935,994/, stress resistance /1093/, recombination /1093/, secondary metabolism /701/ and adaptive mutagenesis /798/. The external factors may include pheromones which act as quorum-sensing signals and induce competence

under a wide variety of conditions /687,994/. These pheromones and their transduction pathways may also function as a sexual isolation mechanism /994/. These findings link microbial mating behavior with population density as representing the cost of finding a mating partner /78/. As shown in computer simulations, bacterial transformation, which has been dubbed 'sex with dead cells' /816/, can increase the fitness of the recombinant progeny at equilibrium, although the DNA taken up may be from cells killed by selection against mutations and may be of inferior genetic quality /404,816/. Recombination as a fitness-fostering and genetic variability creating mechanism /117/, but not DNA repair /680,818/, appears to be the evolutionary rationale of bacterial transformation and hence the evolution of sex. Experimental evidence indicates that recombination of mutations may be both antagonistic and synergistic /262/ and thus argues against the mutational deterministic hypothesis which postulates that sex evolved to purge deleterious mutations from the genome /511/. The pheromone-induced conjugational transfer of plasmids has immense importance for the acquisition of antibiotic resistance and virulence /1106/. The finding that plasmids or chromosomal DNA from other bacterial species are also routinely taken up and integrated supports the adaptive concept, but is not compatible with the concept that the ingested DNA may serve as a template for recombinational repair /339,599,713/.

Fungi and yeast, facultatively sexual/asexual eukaryotes, exhibit sexual reproduction under various deprivations, such as nutritional and nitrogen starvation and following oxidative stress /77, 709/. Again, this mating behavior may be induced by pheromones /513,534/ which also require stress factors to induce their synthesis /453,682/. Reminiscent of bacterial induction of genetic competence, pheromone-induced Ca^{2+} uptake is required for sexual conjugation /734,747/. Remarkably, pheromones induce growth arrest in G1 /434,534/, the starting point of another deprivation response, differentiation. Chemically-induced G1 arrest alone is sufficient for mating /67/. Pheromone actions are also subject to catabolite repression/derepression regulation /854/. Entry into stationary phase, differentiation /414,553/, killer toxin production and secretion /236,553/, and stress and conjugation responses /18,477,621/ are regulated in yeast by the same signaling pathways and transcription factors. These pathways implicate the expression of HSPs /202/. HSPs are also involved in the entire cascade of mating-related events, ranging from pheromone production /659/ and signaling /604,707/ to nuclear fusion /716/. That this phylogenetically primordial mechanism is highly conserved throughout eukaryotes is indicated by a striking conservation from yeasts to humans of a signaling pathway /1072/ and gene /736/ controlling deprivation-induced sexual development in yeast.

Another feature of conjugational behavior is the formation of polyploid giant cells which can be formed by algae, yeasts and other Protozoa under various deprivation conditions, again facultatively mediated by pheromones /632,836,1021/. As an alternative to fruiting-body formation, *Dictyostelium* may exhibit this type of mating behavior. Intriguingly, sexual development is favored by darkness (which may signal to the amoebae that the soil surface is outside the reach of the fruiting bodies) and wet conditions /147,859/, conditions which may be disadvantageous for the aerial dissemination of spores. Importantly, mating behavior is repressed by glucose /565/. Various strains produce diffusible pheromones and cell fusion-inducing factors which trigger sexual development /726,1021/. In this process, regulated by Ca^{2+}, opposite mating-type cells fuse to form zygote giant cells /727/ which, in a Ca^{2+}-independent second step, chemoattract and cannibalize hundreds of local amoebae of the same species as a targeted food source /566/. These mechanisms result in the shuffling of genetic material through crosses, recombinations and mutations /309,1021/.

During metazoan phylogeny, many aspects of reproductive physiology, including the biosynthesis, structure and function of steroid hormones, show a remarkable degree of conservation, arguing for the maintenance of shared origins and rationales /208/. In simple metazoans, the impact of environmental challenges on the preference of sexual reproduction can still be observed /883/. Plants often exhibit labile sex expression but turn to sexual reproduction under environmental challenges /516/. The multicellular green alga, *Volvox carteri*, possesses

only two cell types, 16 reproductive cells in the interior of a sphere whose surface is formed by about 2000 biflagellate somatic cells /498/. This organism integrates differentiation, apoptosis and reproduction in a unique manner. A locus, regA, controls germ-soma differentiation and acts in somatic cells to suppress all germ cell functions. By preventing chloroplast biogenesis, regA determines the apoptotic fate of somatic cells /500,661/ whose debris fuels the maturation of the hatching gonidia. The regA locus is highly mutagenic at a particular embryonic stage, which confers on somatic cells the ability to redifferentiate as reproductive cells /499/, putatively thereby increasing reproductive success under environmental stress. Both asexual and sexual reproduction is possible. Sexual development is triggered by a glycoprotein pheromone which induces expression of the same set of genes as does wounding /19/. Either by stress factors or the pheromone, the extracellular matrix is modified to provide a signal amplification mechanism which allows the pheromone to act at a concentration below 10^{-16} M /364/, again epitomizing the preferential switch to sexual reproduction under environmental challenge.

In multicellular organisms with their increasing independence of environmental changes, a special variation of the stress/deprivation leitmotif is the maintenance of sexual reproduction in hosts to counter the pressure of parasitic coevolution /366, 420,637/, while climatic change may be a comodulating factor /42/. The same appears to be true for parasite reproduction to keep up with the host in the 'arms race'. A parasitic nematode reproduces sexually in immune-competent hosts but may propagate clonally in the less challenging environment of immune-deficient hosts /326/. In fact, random mating is by far the favored reproduction method of a pathogenic fungus in a natural immune-competent environment /159/. As further support of the coevolution concept, the genetic diversity of viruses is substantially higher in sexual than in asexual hosts /742/. The modulation of sexual reproduction appears even to be exploited as a strategy in the parasite/host arms race. Bacteria induce parthenogenesis in infected female wasps /426/, thus putatively reducing the hosts' evolutionary adaptability and immune competence. Both circumstantial evidence /175/ and theoretical calculations /198/ suggest that aging may contribute to the maintenance of sexual reproduction. Conversely, asymmetric reproduction, depending on the segregation of germ cells and soma by differentiation (see below), is the very basis of senescence and death /390/. With the interdependence of these cell and life history events, the evolutionary rationale of the deprivation syndrome comes to a full circle.

Established as a unicellular deprivation response and as a means to increase diversity and fitness /117,447,838,841,916/, sexual reproduction retained its deprivation phenotype and was further sophisticated as a mutagenic vehicle along the phylogenetic axis. Oxidative stress, the hallmark of deprivation responses, is involved during the entire course of sexual reproduction-related events (for gestation see below). Oxidative stress as the trigger of DNA breaks, recombinations and mutations is a constitutive feature of male /7,295/ and female /505,530,774/ gametogenesis. In particular, during meiosis, oxidative stress /969/ may serve to engender double-strand breaks /502,665/ and recombination /579,665/. Increased mitochondrial DNA (mtDNA) rearrangements and deletions in human gametes /104,825/ bear witness to this oxidative stress exposure. On the other hand, mild oxidative stress as a trigger of reparative events may be the mechanism (similar to tolerance induction) which ensures DNA repair /518,893/ and thus rejuvenation and the essential immortality of germ cell lines. p53 is the link between oxidative stress-generated DNA repair and recombination /892, 924/, and apoptotic quality control /892,1098/ during spermatogenesis. In fact, p53 and PARP have been detected in a protein complex at meiotic recombination hotspots /343/. A shared origin of tumor susceptibility genes, such as p53, and mating factor genes, which halt cell division in response to stress to generate genetic diversity by sexual mechanisms, has been suggested /342/. As early as during the evolution of bacterial transformation, the principle may have been established that the ingested high molecular weight exogenous DNA carried more mutations than the ingesting 'mother' cell /404,816/. In mammals and birds, mutations arise preferentially in the male gametes, and the

excess has been estimated to be tenfold in humans, sixfold in primates, twofold in rodents and up to fivefold in birds compared to female mutations /263,817,914/. These figures suggest that the evolutionary rate may have accelerated along the mammalian lineage. Data derived from studies in X-linked diseases, although variable, strongly support the notion of male-driven mutagenesis /986, 987,1005/. These differences have been compared to the male-to-female ratio of the number of germ cell divisions per generation, and suggest that errors in DNA replication are the primary source of mutations /243,466/. However, recent data indicate a significant contribution of replication-independent mutagenic events in male germline cells /430,432/. Circumstantial evidence indicates that at least part of the excess male germ cell mutation rate is due to a high level of developmental oxidative stress; during spermatogenesis, germ cells massively undergo apoptosis /89,793/ induced by oxidative stress /272/. HSPs, markers of oxidative stress, are constitutively expressed during both female and male germ cell maturation /233,732/. However, a variety of HSPs are uniquely expressed in male spermatogenesis, and particularly during meiotic synaptonemal complex formation when recombination occurs /257,595/ HSPs play an essential role /79,233,938/. HSP70-2 knockout leads to failed meiosis, germ cell apoptosis and infertility in male but not female mice /253/, arguing for a specific spermatocyte vulnerability. The increased oxidative stress exposure of spermatozoa in comparison to oocytes is also exemplified by their defective maintenance of mtDNA /825/ which may underlie the almost exclusive maternal inheritance of mtDNA /731/. This high level of germ cell maturational stress may also explain the conspicuous susceptibility of mammalian male germ cells to additional stressors /467,925/, for instance, their lower temperature threshold for HSP activation /871/ and susceptibility to abdominal temperature in cryptorchidism /911/. These features of spermatogenesis could also plausibly explain the contra-intuitive notion why mammalian evolution moved the testicles, the most important male organ from an evolutionary point of view, but not the ovaries, outside the body, although they are then more exposed to environmental hazards.

The evolution of sex had to resolve the dilemma that mutagenesis not only creates potential beneficial effects but carries the much higher hazard of effects detrimental to the viability of germline cells /491,966/. No evidence, however, so far suggests that cells may have evolved the capacity to direct or choose which genetic variants will arise /558/ or may have developed a censor other than function and thus eventual survival to differentiate between beneficial and detrimental mutations. Notably, such a mechanism would require the reverse flow of coded information from phenotype to genotype or from protein to RNA or DNA, a transfer which has been excluded according to the central dogma of molecular biology /193/. (Such an exclusion, however, does not preclude the flow of uncoded, stochastic information; see below.) In unicellular colonies with their billion-fold individuals (of which each can be viewed as a germ cell), chances are good that by the stochastic mutagenic process single organisms may have acquired adaptive mutations that increase their fitness and ensure their survival in the selective environment of their deprived habitat. With the advent of multicellular organisms, the specialization of sexual reproduction in a germline, and lower number of progeny, this selection process had to take place before fertilization. In contrast to asexual reproduction with its direct reproductive lineage, sex evolution introduced an additional selection process which subjects germ cells, particularly the sperm, to a rigid 'quality control' (a feature which has received little attention in all sex evolution theories). To compensate for the stochastic nature of the mutation and recombination process, sexual reproduction relies on apoptosis-mediated quality control by p53 /892,1098/. Moreover, the quorum of the large numbers of oocytes and sperm and the vitality censors of sperm motility /909,948/ and competition, e.g. tightened by the purgatory of a life-hostile vaginal milieu, create a state of 'quality-checked' mutagenesis.

The existence of this intermediate selection process is able to reconcile the contradictions of the two most popular theories of the evolution of sex, the Fisher-Muller model and Muller's ratchet model /628/. The former model (also dubbed 'Red Queen' hypothesis) emphasizes the adaptive role of

sex, leading to genetic diversity and mutagenesis. The latter advocates a role for sex in the maintenance of genetic fitness based on the notion that sexual reproduction can preserve beneficial mutations /765/ and reduce the number of deleterious mutations /25,511,628,1108/. Recombination appears to be the tool to serve this purpose, as is exemplified by the non-recombining, degenerating Y chromosome /150/. Stand-alone unrestrained stochastic mutagenesis would particularly increase deleterious mutations, while faithful DNA repair would reduce genetic diversity. Subjecting the mutated genes to the test of vitality before fertilization allows the simultaneous generation of both genetic diversity and selection against detrimental mutations. Theoretical considerations also argue for the simultaneous operation of both processes /420, 421/. Taken together, mutation and recombination as genetic diversity- and fitness-enhancing mechanisms are the evolutionary rationale of bacterial transformation, eukaryotic and metazoan mating behavior, and hence the evolution of sex. This ensures the superiority of sexual reproduction in a changing environment.

8. SOMA AND GERM CELLS: MORTAL BREEDING DEVICE AND IMMORTAL EVOLUTIONARY VEHICLE

Differentiation, apoptosis and sexual reproduction - how are these deprivation syndromes related to each other? Common features, such as oxidative stress, HSP expression /255/, p53 involvement /342/ and DNA repair modulation, suggest their shared phylogenetic roots. The early differentiation events served to segregate immortal germ cells (e.g. spores) from a mortal body (e.g. fruiting body in *Dictyostelium* /109,677,704/ or sphere in *Volvox* /500,661/). The apoptosing body supports the morphogenesis and dissemination of the germ cells. Intriguingly, throughout phylogenesis this remains the basic function of the soma. With increasing and persistent nutrient resources supplied by the metazoan fuel stores, the reproductive phase could be prolonged. To assist these reproductive activities, the mortal body evolved into an ever-diversified and sophisticated breeding device. This was achieved by the growing plasticity and versatility of the differentiation/apoptosis hybrid, creating a multitude of specialized organ functions. Apoptosis, the final fate of the fruiting body, could be delayed by many cell generations and evolved into a protracted aging process /390,928/. In the soma, mutagenesis was greatly repressed by means of the differentiation/apoptosis balance. In animals, the segregated germ cells evolved into a highly mutable evolutionary vehicle by means of an environmental stressor-independent, constitutive expression of the deprivation response during germ cell maturation. Given the higher chance for deleterious than beneficial mutations, evolution favored a variety of strategies to evade the mutational meltdown which asexual populations undergo /25/. Ploidy cycles are employed by both asexually and sexually reproducing organisms /510/. Asexually reproducing Metazoa may achieve some genetic diversity by differentiation/dedifferentiation cycles /52,479/ which appear to be fuelled by apoptotic events /52/. Sexual reproduction greatly increases genetic diversity and fitness /86,118/ thereby overcompensating its at least 50% greater cost. As variability within populations and not between populations determines evolutionary rates /920/, sexual reproduction largely accounts for the accelerated evolutionary tempo since the Cambrian explosion /886/. Evolution introduced a variety of tools, such as transposons /287/, retrotransposons /315/, integrons /363/, and palindromes /567/, which helped to develop mutagenesis into a highly regulated, almost "predictable" event /126, 837/. Finally, the conjugation of two previously independent sets of chromosomes during sexual reproduction introduces a phenomenon which may only be another variation of the 'selfish gene' theorem /207/. Conflict of interest of the combining haploids may lead to a genomic war in which each haploid tries to dominate by silencing genes of the other, in insects even to the disposal of entire sets of chromosomes /759,769/. Consequently, eliminating potential counterselection in one sex decreases its fitness and increases the fitness of the other /829/. Yet, sexual conflict due to coevolution between the sexes may also work to elicit a rapid evolution of reproductive barriers and increased speciation rates /324/. With these processes, sexual reproduction succeeded in accelerating evolution substantially, creating in the last 600 million years a

wealth of taxa and species /942/.

9. DEPRIVATION SYNDROME AND GESTATION

Embryonal development of higher Metazoa appears to recapitulate phylogenesis /345,719/, indicating that evolution largely proceeded by terminal addition /833/. This feature is now exploited in evo-devo biology for the study of the evolution of body plans and designation of phylogenetic maps /340/. A corollary of the notion that differentiation of tissues proceeds under deprivation conditions implies that the fetal milieu is characterized by an intricately tuned and hence vulnerable metabolic balance allowing both proliferation and differentiation of cells. Mammal ontogeny occurs in a low oxygen environment during the initial stages of development, similar to the environment in which primitive unicellular organisms lived /448/. Evolution of primitive Metazoa is mimicked by the development of mammalian blastocysts and gastrulation /1061/. Energy metabolism in the blastocyst is characterized by anaerobic glycolysis /398/, while both high glucose and insulin concentrations are inhibitory to blastocyst development /213/; the whole range of differentiation/apoptosis features in blastocysts appears to be dependent on metabolic deprivation /213,398/ and oxidative stress in association with fratricide /754/ and cannibalism /533/. A variety of HSPs are expressed throughout embryogenesis /24, 609/. The prominent role of cellular stress in ontogeny is reflected in the hormonal regulation and maternal/fetal interactions during gestation. The maternal organism exhibits the full picture of a stress response, as evidenced by oxidative stress /114/, hypercortisolism /896,1048/ and metabolic syndrome /191,437/. Tolerance phenomena to oxidative stress are also observed /954/.

Importantly, the placenta appears to be a driving force in hypercortisolism, while amniotic fluid and the fetal organism may accumulate GC /624,1047, 1048/. In line with the metabolic requirements of the developing organs, maternal GC play an important role for fetal organogenesis and maturation /636,1047/ and are particularly necessary for brain development /996/. The increased lipolysis contributes to the loss of insulin sensitivity /923/. A variety of markers of oxidative stress are elevated in pregnant females /256,686/ and umbilical blood /885/, possibly with feto-placental mitochondria and agents as the triggering factors /424,1054/. Both the hormonal and metabolic alterations and oxidative stress are causally related to the increased susceptibility to pregnancy-associated diabetes mellitus, hypertension, metabolic syndrome, eclampsia and teratogenic vulnerability /437,686,1054/. The teratogenic vulnerability during prenatal development /255/, like the vulnerability of rapidly renewing organs to a variety of toxic agents, e.g. anticancer drugs, highlights the decreased adaptive ability and functional reserve during maturational cell stress.

10. DEPRIVATION SYNDROME AND AGING

After the evolution of asymmetric reproduction, the disposal of the ancestors after the end of their reproductive phase was an evolutionary necessity /982/ to preserve the limited resources for the reproduction-competent progeny. To this end, a reproductive phase-modulated aging process evolved. The post-reproductive somatic cells are subjected to starvation in the internal milieu, accomplished by the more or less gradual deprivation of nutrient-procuring hormones /387/ which elicits a cellular and systemic deprivation response. In this response, oxidative stress and accumulation of mutations are not the causes but the secondary adaptive responses of the deprived cells. In analogy to apoptosis, aging is a survival pathway in response to the death sentence imposed by evolutionary pressures /390/. Thus aging and death were established as a universal, inescapable fate of somal life while, on the other hand, the immortality of germline cells is maintained /660/.

11. MITOCHONDRIA, METABOLISM AND DEPRIVATION SYNDROMES

Mitochondria are the centers of eukaryotic cellular energy metabolism /879,1007/. Knowledge about mitochondrial functions exceeding this traditional capacity has expanded tremendously during recent years /523,1041/. With the appreciation of the key role of energy deprivation in the triggering

of the deprivation response, the center stage of mitochondria in these processes becomes plausible. The pivotal role of mitochondria in apoptosis /348, 525/, differentiation /1041/, carcinogenesis /134, 240/ and aging /390/ has been recognized. Mitochondrial biogenesis is a prerequisite of differentiation /692, 1041/, possibly induced by a mitochondrial oxidative stress signal to the nucleus /548,674/. A concomitant shift from glycolytic to oxidative metabolism can be observed /545,1070/. In addition, mitochondrial Ca^{2+} loading /1081/, which ensues differentiation- and apoptosis-related cytosolic Ca^{2+} increases (see above), uncouples electron transfer and oxidative phosphorylation /387/. During differentiation, these processes, together with the mitochondrial release of cytochrome *c* /749/, may mechanistically underlie the increased generation of oxidative stress /102/ and increased susceptibility to oxidative stress /181/ and, as in apoptosis, may account for a diminution of the mitochondrial membrane potential /626,842/. NO may be causally involved in the loss of the mitochondrial membrane potential /108,300/. Together with the finding that differentiation is repressed by glucose catabolites /88,781,952/, these events are reminiscent of the phenomena in yeast catabolite repression when de-repression elicits mitochondrial biogenesis accompanied by a switch from glycolysis to oxidative metabolism /880,1014/. While mitochondrial biogenesis appears to be a common mechanism in differentiation, mitochondria can exhibit a wide spectrum of behaviors in apoptosis, dependent on the type of tissue and phase of death. Loss of mitochondrial membrane potential and cytochrome *c* are routine findings in apoptosis, while both mitochondrial proliferation /125/ and degeneration /187,1028/ can occur. These changes happen at different time points relative to DNA fragmentation /187/ in a functionally heterogeneous, dynamically changing mitochondrial population /227,864/.

Mediated by Ca^{2+} /1081/, proliferating cells, including bacterial strains /696/, entertain high glycolytic activity (the Crabtree effect) /350/. This appears as a means both to provide substrates for nucleic base synthesis /164/ and protein synthesis /334/ and to curb oxidative stress /101,102/ in a cytosolic-mitochondrial interplay which may be controlled by mitochondria /103/. Metabolic features of cancer cells also include an increased dependency on glycolysis /201/, which was recognized by Warburg 70 years ago. Thus, cancer cells share many features with fermenting yeast cells /459/. Intriguingly, hexokinase type II, which is a key element of yeast glucose repression signaling pathways /459/, plays a critical role in the conversion and maintenance of tumor cell glycolysis involving the action of mutant p53 /642,703/. In particular, its binding to mitochondrial porin, a feature which is not encountered in yeast /521/, gives hexokinase access to mitochondrial ATP /33, 915/ and may serve to render oxidative phosphorylation of cancer cells independent of catabolite repression/derepression circuits /334/. Furthermore, in contrast to normal cells, cancer cells are more sensitive to the Ca^{2+}-dependent inhibition of ADP translocase and F_1F_0-ATPase resulting in the inhibition of oxidative phosphorylation /1081/. Together with changes in the expression of respiratory chain constituents /97,127/ and reduced expression of manganese superoxide dismutase /173,1088/, this may be causally involved in the carcinogenesis-related generation of ROS /53,97, 278/. Since mtDNA is very susceptible to oxidative stress and mutagenesis /1,490/, tumor cells carry a very high amount of mtDNA mutations /299,786/. In a vicious cycle, these mutagenic changes may further increase oxidative stress /53/. Of note, the mutant mtDNA may become dominant in tumor cells /299/ and is associated with a higher copy number localized in nuclear DNA /573,908/, suggesting its replicative advantage and a role in malignant transformation, stabilization of tumor phenotype and drug resistance /134,240/. Thus, the mutagenic activity of α-particles was found to be mediated, at least in part, by oxidative stress elicited by some cytoplasmic constituents, presumably mitochondria /1084/.

Throughout eukaryotic phylogeny, the nucleus and mitochondria entertain a bidirectional communication cycle which aims at maintaining mitochondrial efficiency in a variety of stress and nutrient conditions and resorts to mitochondrial ROS generation as the mediator of cell cycle decisions. In yeast, nuclear genes have been identified which sense the functional state of mitochon-

dria, operate in the adaptation of metabolic conditions /755,929/, and are also required for expression of peroxisomal proteins /155/. Thus, the two main generators of ROS, mitochondria and peroxisomes, are linked with the nucleus in a feedback cycle. Likewise in mammals and plants, the nuclear genome controls respiratory chain expression /655, 877/. Environmental oxygen sensors that regulate the adaptation of energy balance have been detected in cyanobacteria /428/, appear to be located in the photosynthetic apparatus in plants /428/ and cytochrome *c* oxidase in animals /146/, and mediate the adaptation of energy flow. Mitochondrial cytochrome *c* oxidase capacity has a low functional reserve and, hence, exerts a tight control on *in vivo* respiration /1036/. Cytochrome oxidase is also the target of NO in its control of mitochondrial respiration /108,300/. Cytochrome oxidase subunit expression decreases following both decreased and increased energy demands /586/. Intriguingly, cytochrome oxidase and its substrate, cytochrome *c*, are regulatory targets of catabolite repression/derepression in yeast /694,919/. In both yeast and humans, cytochromes and oxygen radicals appear to be members of the oxygen sensing pathway and are, in yeast, targets of aerobic adaptation /259,304/. Cytochrome *c*, when released from mitochondria in deprivation syndromes, sets in motion a cascade of mitochondrial/nuclear signaling /789/ and oxidative stress /120/. Another mitochondrial/nuclear redox messenger may be AIF /205,960/. To target their message during stress responses, mitochondria accumulate perikaryally /9,225,229/. This mitochondria/nucleus directed stress signal appears to be mediated by H_2O_2 in plants and animals /655,791,877, 963/. ROS fulfill key functions in the activation of kinase cascades and nuclear transcription factors /318,471,571/. The ambiguity of these transduction pathways for cell fate decisions depends crucially on the availability of ATP /462/. Hence, the mitochondrial electron transport chain as ROS generator /588/ sets in motion an energy-dependent cascade of nuclear signaling, is a trigger for nuclear expression of mitochondrial biogenesis genes /674/, and is required for differentiation /548/, apoptosis /120,796/, and carcinogenesis /134,240/.

12. ENERGY AND MATTER

According to the central dogma of molecular biology /193,984/, the transfer of coded information from gene to protein, from genotype to phenotype, is unidirectional. This dogma, however, does not take into account the flow of information from the environment to the genome, resulting in genomic plasticity. Thus, organisms have evolved the capacity to respond to environmental challenges with heritable changes of their genetic information /651/ which has persistent consequences for phenotypes of clonal progeny /891/. The body of evidence presented in this paper suggests that environmental conditions affecting energy availability have a profound impact on evolutionary mutagenesis. For instance, the evolution of locomotion was triggered by the necessity of foraging: the catabolite repression of unicellular chemotaxis and motility and its derepression under energetic stress /745,772,1042/ indicate that procurement of nutrient was the driving force of this evolutionary accomplishment. Photoautotrophic organisms equipped with chloroblasts and capable of photosynthesis just have to take root and wait for the sunlight of the next day, while chemoheterotrophs evolved a wealth of mobility-providing tools ranging from flagella to fins, wings and limbs to ensure the life-sustaining nutrient supply.

Increasingly, the mechanisms which organisms have evolved to employ mutagenesis as a fitness-fostering, regulated process are being elucidated /126,837/. The agent(s), however, which link environmental stress with genetic change are less well defined. To fulfill their varied functions, these agents have to be ubiquitous and codeless (to account for the basic randomness of mutagenesis), should be either regulated or produced by metabolic processes, be linked to an energy-sensing system, and either elicit reactive molecules or be reactive themselves (to act as mutagenic agents). Ideally, these agents should also have a role in the whole range of deprivation responses to ensure the coordinated transition between DNA repair fidelity and flexibility. Recently, the phylogenetically highly conserved PAS domain superfamily has been described which monitors overall energy level through sensing of oxygen and the redox potential of the electron transport system in bacteria and

animals and light in bacteria and plants /980/ and has a role in the sensing and integration of environmental signals and developmental processes /356, 980/. These close functional links cast light on the metabolism-driven regulatory role of redox homeostasis. Metabolic stress leads to dysregulation of the prokaryotic energy-redox and eukaryotic Ca^{2+}-energy-redox homeostasis /387/. Thus, both reactive oxygen and nitrogen species (in all phyla) and Ca^{2+} (in eukaryotes) qualify as agents to mediate the adaptive pressure exerted by energetic stress. ROS and RNS are mediators of metabolic stress adaptations. In particular, superoxide anion, H_2O_2 and NO, as relatively inert ROS, have long-range signaling properties /367/ and qualify as signal transducers and primary mitochondrial/nuclear messengers for gene transcription /13,539/. Through Fenton-type reactions, transition metals, e.g. iron and copper /764, 779/, located at the DNA target sites, may convert these ROS into more aggressive radicals, e.g. hydroxyl radical or peroxynitrite, which induce DNA breaks, recombination, amplification and oxidative mutagenesis /429,579, 634,665/. In addition, oxidative DNA injury affects DNA methylation, leading to altered gene activation/silencing balances /138/. Through this range of actions, ROS/RNS and Fenton-type reactions control gene expression of stress response systems /728/ and mediate a variety of cell cycle events (see above) including proliferation /115,855/. In eukaryotes, Ca^{2+} was introduced as a messenger system regulating and being regulated by the energy and redox homeostasis, thus forming a homeostatic triangle /387/. Mitochondrial Ca^{2+} signals are relayed to the nucleus /286/ to evoke specific changes in gene expression /375,843/. Ca^{2+} is an ambiguous messenger conveying a multitude of regulatory signals and cell fate decisions /649,1071/, including differentiation /32/ and apoptosis /452/. Via regulation of DNA methylation /222/ and DNA repair /316,518/, Ca^{2+} also controls mutagenesis /898/.

The phenotypic-genotypic feedback is not coded and specific, as from gene to protein, but random. The randomness of the process relies on the simple, codeless messenger agents Ca^{2+} and free radicals, both regulated by and regulating energy metabolism. These agents effect stress tolerance, differentiation, apoptosis and carcinogenesis on a (patho)physiological continuum. Mutations, although random events, may be adaptive not only due to selection pressure but also due to intrinsic variations of regulatory and transcriptional activity /126/. Various mechanisms may cooperate in creating "regulated randomness" /126,837/. DNA sequence is a primary determinant of DNA base damage probability /8/. Mobile genetic elements /287,315,363,567/ which can be released under stress /590,1049/ introduce mutational hotspots and conditional breaks for recombinational rearrangements /706/. Fenton-type reactions may be targeted by an intricate process involving both transition metals and oxidants. Iron metabolism, for instance, is regulated in response to oxidative stress coordinated with oxidative stress defenses /371,750/. Cellular iron accumulates dependent on metabolic and oxidative stress /849,1058/ and may sensitize cells to oxidative stress /580/ in a positive feedback loop. Liberated into the nucleus from its cytoplasmic sequestration /8,123/, iron and other trace metals may replace zinc in zinc finger domains of transcription factors, generate free radicals and induce transcription-dependent mutations /183, 740/. In fact, high levels of transcription /204,394/, derepression of an operon and activation during the stringent response, target the operon for hypermutation /515,1083/. By this type of "directed" mutagenesis, the mutation in the MnSOD promoter in cancer cells /1088/, the catalase gene amplification following chronic exposure to oxidative stress /429/, or the gene duplication of yeast hexose transport genes in response to selection in a glucose-limited environment /107/, may be effected. Genes encoding for stress-related proteins are also preferentially targeted /116/. Further regulatory influences may stem from the type of metal ion catalyzing the Fenton reaction, or protection of DNA by histones and chromatin structure /167, 737/. Although regulated to a certain extent, the stochastic nature of the effectors leads to chance events and allows multiple adaptive solutions for a given stressor /294,559,853/, and therefore has given rise to the huge diversity of evolution with an ever-increasing complexity /2/.

Thus, the central dogma of molecular biology can be modified (Fig. 1). Organisms developed a

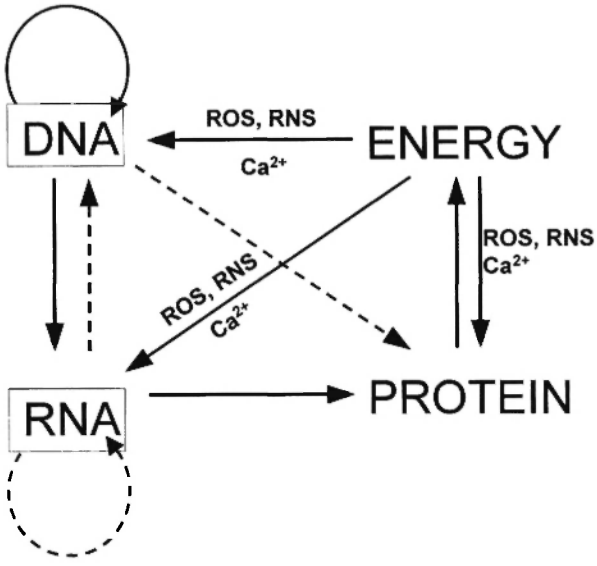

Fig. 1: Schematic representation of the phenotype-genotype feedback cycle. According to the central dogma of molecular biology, coded information flows unidirectionally from DNA or RNA to proteins /193/. Proteins catalyze the production of energy. Energy and redox balance (in all phyla) and, in addition, Ca^{2+} (in eukaryotes) are linked in a feed-forward and feed-backward cycle, efficiently being regulated by and regulating each other /387/. By modulating a multitude of transduction pathways, the Ca^{2+}-redox agents signal the energetic status to the genome (DNA and RNA) and elicit transcriptional or mutagenic activity. Moreover, these agents regulate the enzymatic activity of proteins, thereby tuning energy production. In anaerobic conditions, other electron acceptors (e.g. elemental sulfur /615/, sulfate, thiosulfate, or Fe_{III} /1025/) may step in to complete the cycle. ROS = reactive oxygen species, RNS = reactive nitrogen species (modified from /193/).

dynamic stimulus/response feedback loop in which the genotype determines the fitness of the phenotype and is itself shaped by the phenotype-dependent cellular energy flow. While in unicellular, germ cell-like organisms, this feedback leads to heritable traits in the progeny, the segregation of germ cells from the soma in higher metazoan organisms renders the body the breeding device whose fitness ensures reproductive success and thus directs the selection-driven phenotypic adaptation at the population level. At any rate, phenotypic fitness is the Darwinian selection principle and molding force which mediates the interaction between the selfish genes /207/ and their biotic and abiotic environment /261a/. Along the phylogenetic axis, organisms have evolved their evolvability /800/ and their capacity to exploit the evolutionary phenotype-genotype feedback cycle. Extreme examples are bradytelic (slowly evolving) living fossils /920/ such as cyanobacteria and tachytelic organisms such as mammals. The former, which already thrived in the CO_2-rich, O_2-poor primordial environment (and created the O_2-rich atmosphere), are strictly asexual and have an effective DNA repair /886/ and antioxidant defense system /252, 990/, while the latter reproduce sexually and employ constitutive oxidative stress during gametogenesis.

According to Morowitz /685/, flow of energy through any open system is sufficient to organize that system. The organizing principle may be represented by the energy-dependent phenotype-genotype feedback cycle in which the DNA sequence may be regarded as the stochastic materialization of the cellular energy flow. Thus, animate nature, like inanimate nature, may be subject to a duality of energy and matter which are interlocked in an adaptive cycle whose relationship can be described by nonequilibrium thermodynamics.

REFERENCES

1. Abramova NE, Davies KJA, Crawford DR. Polynucleotide degradation during early stage response to oxidative stress is specific to mitochondria. Free Radical Biol Med 2000; 28: 281-288.
2. Adami C, Ofria C, Collier TC. Evolution of biological complexity. Proc Natl Acad Sci USA 2000; 97: 4463-4468.
3. Adida C, Crotty PL, McGrath J, Berrebi D, Diebold J, Altieri DC. Developmentally regulated expression of the novel cancer anti-apoptosis gene survivin in human and mouse differentiation. Am J Pathol 1998; 152: 43-49.
4. Agoff SN, Hou J, Linzer DI, Wu B. Regulation of the human hsp70 promoter by p53. Science 1993; 259: 84-87.
5. Aharoni D, Meiri I, Atzmon R, Vlodavsky I, Amsterdam A. Differential effect of components of the extracellular matrix on differentiation and apoptosis. Curr Biol 1997; 7: 43-51.

6. Ahn SG, Jeong SY, Rhim H, Kim IK. The role of c-Myc and heat shock protein 70 in human hepatocarcinoma Hep3B cells during apoptosis induced by prostaglandin A_2/δ_{12}-prostaglandin J_2. Biochim Biophys Acta 1998; 1448: 115-125.
7. Aitken RJ. Free radicals, lipid peroxidation and sperm function. Reprod Fertil Dev 1995; 7: 659-668.
8. Akman SA, O'Connor TR, Rodriguez H. Mapping oxidative DNA damage and mechanisms of repair. Ann NY Acad Sci 2000; 899: 88-102.
9. Al-Abdulla NA, Martin LJ. Apoptosis of retrogradely degenerating neurons occurs in association with the accumulation of perikaryal mitochondria and oxidative damage to the nucleus. Am J Pathol 1998; 153: 447-456.
10. Alam A, Cohen LY, Aouad S, Sekaly RP. Early activation of caspases during T lymphocyte stimulation results in selective substrate cleavage in nonapoptotic cells. J Exp Med 1999; 190: 1879-1890.
11. Alberola-Ila J, Forbush KA, Seger R, Krebs EG, Perlmutter RM. Selective requirement for MAP kinase activation in thymocyte differentiation. Nature 1995; 373: 620-623.
12. Alcazar A, Regidor I, Masjuan J, Salinas M, Alvarez-Cermeno JC. Induction of apoptosis by cerebrospinal fluid from patients with primary-progressive multiple sclerosis in cultured neurons. Neurosci Lett 1998; 255: 75-78.
13. Allen RG, Tresini M. Oxidative stress and gene regulation. Free Radical Biol Med 2000; 28: 463-499.
14. Almog N, Rotter V. Involvement of p53 in cell differentiation and development. Biochim Biophys Acta 1997; 1333: F1-F27.
15. Althaus FR, Hofferer L, Kleczkowska HE, Malanga M, Naegeli H, Panzeter PL, Realini CA. Histone shuttling by poly ADP-ribosylation. Mol Cell Biochem 1994; 138: 53-59.
16. Alvarez LW, Alvarez W, Asaro F, Michel H. Extraterrestrial cause for the Cretaceous-Tertiary extinction. Science 1980; 208: 1095-1108.
17. Ameisen JC. The evolutionary origin and role of programmed cell death in single-celled organisms: a new view at executioners, mitochondria, host-pathogen interactions, and the role of death in the process of natural selection. In: Lockshin RA, Zakeri Z, Tilly JL, eds. When Cells Die. New York: Wiley-Liss, 1998; 3-56.
18. Ammerer G. Sex, stress and integrity: the importance of MAP kinases in yeast. Curr Opin Genet Dev 1994; 4: 90-95.
19. Amon P, Haas E, Sumper M. The sex-inducing pheromone and wounding trigger the same set of genes in the multicellular green alga *Volvox*. Plant Cell 1998; 10: 781-789.
20. Amstad PA, Liu H, Ichimiya M, Chang S, Berezesky IK, Trump BF. Bcl-2 enhancement of malignant transformation in mouse epidermal JB6 cells. Mol Carcinogen 1997; 20: 231-239.
21. Amsterdam A, Keren-Tal I, Aharoni D. Cross-talk between cAMP and p53-generated signals in induction of differentiation and apoptosis in steroidogenic granulosa cells. Steroids 1996; 61: 252-256.
22. Anderson GP. Resolution of chronic inflammation by therapeutic induction of apoptosis. Trends Pharmacol Sci 1996; 17: 438-442.
23. Anderson P. Kinase cascades regulating entry into apoptosis. Microbiol Mol Biol Rev 1997; 61: 33-46.
24. Anderson RL. Stress proteins and apoptosis in prenatal development, cancer and medicine. Cell Stress Chaperones 1998; 3: 209-212.
25. Andersson DI, Hughes D. Muller's ratchet decreases fitness of a DNA-based microbe. Proc Natl Acad Sci USA 1996; 93: 906-907.
26. Anzai N, Kawabata H, Hirama T, Masutani H, Ueda Y, Yoshida Y, Okuma M. Types of nuclear endonuclease activity capable of inducing internucleosomal DNA fragmentation are completely different between human $CD34^+$ cells and their granulocytic descendants. Blood 1995; 86: 917-923.
27. Aon JC, Aon MA, Spencer JF, Cortassa S. Modulation of sporulation and metabolic fluxes in *Saccharomyces cerevisiae* by 2-deoxy glucose. Antonie Van Leeuwenhoek 1997; 72: 283-290.
28. Aoshiba K, Rennard SI, Spurzem JR. Cell-matrix and cell-cell interactions modulate apoptosis of bronchial epithelial cells. Am J Physiol 1997; 272: L28-L37.
29. Appella E, Anderson CW. Signaling to p53: breaking the posttranslational modification code. Pathol Biol 2000; 48: 227-245.
30. Aravind L, Dixit VM, Koonin EV. The domains of death: evolution of the apoptosis machinery. Trends Biochem Sci 1999; 24: 47-53.
31. Arch RH, Thompson CB. Lymphocyte survival. The struggle against death. Annu Rev Cell Dev Biol 1999; 15: 113-140.
32. Archer F, Ashworth R, Bolsover S. Calcium and neuronal development and growth. In: Verkhratsky A, Toescu EC, eds. Integrative Aspects of Calcium Signalling. New York: Plenum Press, 1998; 239-265.
33. Arora KK, Pedersen PL. Functional significance of mitochondrial bound hexokinase in tumor cell metabolism. Evidence for preferential phosphorylation of glucose by intramitochondrially generated ATP. J Biol Chem 1988; 263: 17422-17428.
34. Arrigo AP. Small stress proteins: chaperones that act as regulators of intracellular redox state and programmed cell death. Biol Chem 1998; 379: 19-26.
35. Arrigo AP. Gene expression and the thiol redox state. Free Radical Biol Med 1999; 27: 936-944.
36. Arrigo AP. sHsp as novel regulators of programmed cell death and tumorigenicity. Pathol Biol (Paris) 2000; 48: 280-288.

37. Artavanis-Tsakonas S, Rand MD, Lake RJ. Notch signaling: cell fate control and signal integration in development. Science 1999; 284: 770-776.
38. Asad LM, de Carvalho AA, Felzenszwalb I, Leitao AC, Asad NR. H_2O_2-induced cross-protection against UV-C killing in *Escherichia coli* is blocked in a lexA(Def) background. J Photochem Photobiol B 2000; 54, 67-71.
39. Asad NR, Asad LM, Silva AB, Felzenszwalb I, Leitao AC. Hydrogen peroxide effects in *Escherichia coli* cells. Acta Biochim Pol 1998; 45: 677-690.
40. Asada M, Yamada T, Ichijo H, Delia D, Miyazono K, Fukumuro K, Mizutani S. Apoptosis inhibitory activity of cytoplasmic p21(Cip1/WAF1) in monocytic differentiation. EMBO J 1999; 18: 1223-1234.
41. Ashkenazi A, Dixit VM. Death receptors: signaling and modulation. Science 1998; 281: 1305-1308.
42. Atkinson D. Sexual showiness and parasite load: correlations without parasite coevolutionary cycles. J Theor Biol 1991; 150: 251-260.
43. Aubert M, Weber E, Gintz B, Chater KF, Decaris B. Inactivation or amplification of the spa2 gene, encoding a potential stationary phase regulator, affects differentiation in *Streptomyces ambofaciens*. Can J Microbiol 1997; 43: 1118-1125.
44. Aubert S, Gout E, Bligny R, Marty-Mazars D, Barrieu F, Alabouvette J, Marty F, Douce R. Ultrastructural and biochemical characterization of autophagy in higher plant cells subjected to carbon deprivation: control by the supply of mitochondria with respiratory substrates. J Cell Biol 1996; 133: 1251-1263.
45. Axelrod J, Reisine TD. Stress hormones: their interaction and regulation. Science 1984; 224: 452-459.
46. Ayroldi E, Zollo O, Cannarile L, D'Adamio FD, Grohmann U, Delfino DV, Riccardi C. Interleukin-6 (IL-6) prevents activation-induced cell death: IL-2-independent inhibition of Fas/fasL expression and cell death. Blood 1998; 92: 4212-4219.
47. Azzam EI, de Toledo SM, Gooding T, Little JB. Intercellular communication is involved in the bystander regulation of gene expression in human cells exposed to very low fluences of α particles. Radiat Res 1998; 150: 497-504.
48. Bagg A, Cossman J. Bcl-2: physiology and role in neoplasia. Cancer Treat Res 1992; 63: 141-166.
49. Bahnsen M, Burrin JM, Johnston DG, Pernet A, Walker M, Alberti KG. Mechanisms of catecholamine effects on ketogenesis. Am J Physiol 1984; 247: E173-E180.
50. Baker ME. Evolution of mammalian 11β- and 17β-dihydroxysteroid dehydrogenases-type 2 and retinol dehydrogenases from ancestors in *Caenorhabditis elegans* and evidence for horizontal transfer of a eukaryote dehydrogenase to *E. coli*. J Steroid Biochem Mol Biol 1998; 66: 355-363.
51. Banerjee D, Lenz HJ, Schnieders B, Manno DJ, Ju JF, Spears CP, Hochhauser D, Danenberg K, Denenberg P, Bertino JR. Transfection of wild-type but not mutant p53 induces early monocytic differentiation in HL60 cells and increases their sensitivity to stress. Cell Growth Differ 1995; 6: 1405-1413.
52. Balser EJ. Cloning by ophiuroid echinoderm larvae. Biol Bull 1998; 194: 187-193.
53. Bandy B, Davison AJ. Mitochondrial mutations may increase oxidative stress: implications for carcinogenesis and aging? Free Radical Biol Med 1990; 8: 523-539.
54. Bang YJ, Pirnia F, Fang WG, Kang WK, Sartor O, Whitesell L, Ha MJ, Tsokos M, Sheahan MD, Nguyen P, Niklinski WT, Myers CE, Trepel JB. Terminal neuroendocrine differentiation of human prostate carcinoma cells in response to increased intracellular cyclic AMP. Proc Natl Acad Sci USA 1994; 91: 5330-5334.
55. Banki K, Hutter E, Gonchoroff NJ, Perl A. Elevation of mitochondrial transmembrane potential and reactive oxygen intermediate levels are early events and occur independently from activation of caspases in Fas signaling. J Immunol 1999; 162: 1466-1479.
56. Barcellos-Hoff MH, Ravani SA. Irradiated mammary gland stroma promotes the expression of tumorigenic potential by unirradiated epithelial cells. Cancer Res 2000; 60: 1254-1260.
57. Barger SW, Horster D, Furukawa K, Goodman Y, Krieglstein J, Mattson MP. Tumor necrosis factor α and β protect neurons against amyloid β-peptide toxicity: evidence for involvement of a κB-binding factor and attenuation of peroxide and Ca^{2+} accumulation. Proc Natl Acad Sci USA 1995; 92: 9328-9332.
58. Barroso I, Benito B, Garcia-Jimenez C, Hernandez A, Obregon MJ, Santisteban P. Norepinephrine, triiodothyronine and insulin upregulate glyceraldehyde-3-phosphate dehydrogenase mRNA during brown adipocyte differentiation. Eur J Endocrinol 1999; 141: 169-179.
59. Barrow PA, Lovell MA, Barber LZ. Growth suppression in early-stationary-phase nutrient broth cultures of *Salmonella typhimurium* and *Escherichia coli* is genus specific and not regulated by sigma S. J Bacteriol 1996; 178: 3072-3076.
60. Baserga R, Morrione A. Differentiation and malignant transformation: two roads diverged in a wood. J Cell Biochem 1999; Suppl 32-33: 68-75.
61. Basu A, You SA, Haldar S. Regulation of Bcl2 phosphorylation by stress response kinase pathway. Int J Oncol 2000; 16: 497-500.
62. Batchelor SE, Cooper M, Chhabra SR, Glover LA, Stewart GS, Williams P, Prosser JI. Cell density-regulated recovery of starved biofilm populations of ammonia-oxidizing bacteria. Appl Environ Microbiol 1997; 63: 2281-2286.
63. Bates RC, Lincz LF, Burns GF. Involvement of integrins in cell survival. Cancer Metastasis Rev 1995; 14: 191-203.
64. Bauer MKA, Vogt M, Los M, Siegel J, Wesselborg S, Schulze-Osthoff K. Role of reactive oxygen inter-

mediates in activation-induced CD95 (APO-1/Fas) ligand expression. J Biol Chem 1998; 273: 8048-8055.
65. Baxi MD, Vishwanatha JK. Uracil DNA-glycosylase/glyceraldehyde-3-phosphate dehydrogenase is an Ap4A binding protein. Biochemistry 1995; 34: 9700-9707.
66. Becher B, Barker PA, Owens T, Antel JP. CD95-CD95L: can the brain learn from the immune system? Trends Neurosci 1998; 21: 114-117.
67. Bedard DP, Li AW, Singer RA, Johnston GC. Mating ability during chemically induced G1 arrest of cells of the yeast *Saccharomyces cerevisiae*. J Bacteriol 1984; 160: 1196-1198.
68. Beham A, Marin MC, Fernandez A, Herrmann J, Brisbay S, Tari AM, Lopez-Berestein G, Lozano G, Sarkiss M, McDonnell TJ. Bcl-2 inhibits p53 nuclear import following DNA damage. Oncogene 1997; 15: 2767-2772.
69. Bell DA, Morrison B. The spontaneous apoptotic cell death of normal human lymphocytes in vitro: the release of, and immunoproliferative response to, nucleosomes in vitro. Clin Immunol Immunopathol 1991; 60: 13-26.
70. Belozerskaya TA. Cell-to-cell communication in differentiation of mycelial fungi. Membr Cell Biol 1998; 11: 831-840.
71. Benito A, Ventoura G, Casadei M, Robinson T, Mackey B. Variation in resistance of natural isolates of *Escherichia coli* O157 to high hydrostatic pressure, mild heat and other stresses. Appl Environ Microbiol 1999; 65: 1564-1569.
72. Bennett AF, Dao KM, Lenski RE. Rapid evolution in response to high-temperature selection. Nature 1990; 346: 79-81.
73. Bennett AF, Lenski RE. Experimental evolution and its role in evolutionary physiology. Am Zool 1999; 39: 346-362.
74. Bergin E, Levine JS, Koh JS, Lieberthal W. Mouse proximal tubular cell-cell adhesion inhibits apoptosis by a cadherin-dependent mechanism. Am J Physiol 2000; 278: F758-F768.
75. Bergqvist M, Brattström D, Stalberg M, Vaghef H, Brodin O, Hellman B. Evaluation of radiation-induced DNA damage and DNA repair in human lung cancer cell lines with different radiosensitivity using alkaline and neutral single cell gel electrophoresis. Cancer Lett 1998; 133: 9-18.
76. Bernhardt J, Volker U, Volker A, Antelmann H, Schmid R, Mach H, Hecker M. Specific and general stress proteins in *Bacillus subtilis* - a two-dimensional protein electrophoresis study. Microbiology 1997; 143: 999-1017.
77. Bernstein C, Johns V. Sexual reproduction as a response to H_2O_2 damage in *Schizosaccharomyces pombe*. J Bacteriol 1989; 171: 1893-1897.
78. Bernstein H, Byerly HC, Hopf FA, Michod RE. The evolutionary role of recombinational repair and sex. Int Rev Cytol 1985; 96: 1-28.
79. Berruti G, Perego L, Borgonovo B, Martegani E. MSJ-1, a new member of the DnaJ family of proteins, is a male germ cell-specific gene product. Exp Cell Res 1998; 239: 430-441.
80. Berry MD, Boulton AA. Glyceraldehyde-3-phosphate dehydrogenase and apoptosis. J Neurosci Res 2000; 60: 150-154.
81. Bertrand P, Rouillard D, Boulet A, Levalois C, Soussi T, Lopez BS. Increase of spontaneous intrachromosomal homologous recombination in mammalian cells expressing a mutant p53 protein. Oncogene 1997; 14: 1117-1122.
82. Bhatia M, Kirkland JB, Meckling-Gill KA. Modulation of poly(ADP-ribose) polymerase during neutrophilic and monocytic differentiation of promyelocytic (NB4) and myelocytic (HL-60) leukaemia cells. Biochem J 1995; 308: 131-137.
83. Bhatnagar A. Contribution of ATP to oxidative stress-induced changes in action potential of isolated cardiac myocytes. Am J Physiol 1997; 272: H1598-H1608.
84. Bickler PE. Cerebral anoxia tolerance in turtles: regulation of intracellular calcium and pH. Am J Physiol 1992; 263: R1298-R1302.
85. Bill CA, Grochan BM, Vrdoljak E, Mendoza EA, Tofilon PJ. Decreased repair of radiation-induced DNA double-strand breaks with cellular differentiation. Radiat Res 1992; 132: 254-258.
86. Birdsell J, Wills C. Significant competitive advantage conferred by meiosis and syngamy in the yeast *Saccharomyces cerevisiae*. Proc Natl Acad Sci USA 1996; 93: 908-912.
87. Blagosklonny MV, Toretsky J, Bohen S, Neckers L. Mutant conformation of p53 translated in vitro or in vivo requires functional HSP90. Proc Natl Acad Sci USA 1996; 93: 8379-8383.
88. Blais A, Jalal F, Crine P, Paiement J, Berteloot A. Increased functional differentiation of rabbit proximal tubule cells cultured in glucose-free media. Am J Physiol 1992; 263: F152-F162.
89. Blanco-Rodriguez J. A matter of death and life: the significance of germ cell death during spermatogenesis. Int J Androl 1998; 21: 236-248.
90. Blattner WA. Human retroviruses: their role in cancer. Proc Assoc Am Physicians 1999; 111: 563-572.
91. Blazquez C, Sanchez C, Velasco G, Guzman M. Role of carnitine palmitoyltransferase I in the control of ketogenesis in primary cultures of rat astrocytes. J Neurochem 1998; 71: 1597-1606.
92. Blazquez C, Sanchez C, Daza A, Galve-Roperh I, Guzman M. The stimulation of ketogenesis by cannabinoids in cultured astrocytes defines carnitine palmitoyltransferase I as a new ceramide-activated enzyme. J Neurochem 1999; 72: 1759-1768.
93. Bodrova ME, Dedukhova VI, Mokhova EN, Skulachev VP. Membrane potential generation coupled to oxidation of external NADH in liver mitochondria. FEBS Lett 1998; 435: 269-274.

94. Boesen JJB, Dieteren N, Bal E, Lohman PHM, Simons JWIM. A possible factor in genetic instability of cancer cells: stress-induced secreted proteins lead to decrease in replication fidelity. Carcinogenesis 1992; 13: 2407-2413.
95. Boesen, JJB, Niericker MJ, Dieteren N, Simons JWIM. How variable is a spontaneous mutation rate in cultured mammalian cells? Mutat Res 1994; 307: 121-129.
96. Bogue MA, Zhu CM, Aguilar-Cordova E, Donehower LA, Roth DB. p53 is required for both radiation-induced differentiation and rescue of V(D)J rearrangement in scid mouse thymocytes. Genes Dev 1996; 10: 553-565.
97. Boitier E, Merad-Boudia M, Guguen-Guillouzo C, Defer N, Ceballos-Picot I, Leroux JP, Marsac C. Impairment of the mitochondrial respiratory chain activity in diethylnitrosamine-induced rat hepatomas: possible involvement of oxygen free radicals. Cancer Res 1995; 55: 3028-3035.
98. Bolwell GP. Cyclic AMP, the reluctant messenger in plants. Trends Biochem Sci 1995; 20: 492-495.
99. Boulares AH, Yakovlev AG, Ivanova V, Stoica BA, Wang G, Iyer S, Smulson M. Role of poly(ADP-ribose) polymerase (PARP) cleavage in apoptosis. Caspase 3-resistant PARP mutant increases rates of apoptosis in transfected cells. J Biol Chem 1999; 274: 22932-22940.
100. Bouly JP, Gissot L, Lessard P, Kreis M, Thomas M. *Arabidopsis thaliana* proteins related to the yeast SIP and SNF4 interact with AKINα1, an SNF1-like protein kinase. Plant J 1999; 18: 541-550.
101. Brand K. Aerobic glycolysis by proliferating cells: protection against oxidative stress at the expense of energy yield. J Bioenerg Biomembrane 1997; 29: 355-364.
102. Brand KA, Hermfisse U. Aerobic glycolysis by proliferating cells: a protective strategy against reactive oxygen species. FASEB J 1997; 11: 388-395.
103. Brandt RB, Laux JE, Spainhour SE, Bear HD, Kline ES. Cytosolic-mitochondrial interactions (mitochondrial control of glycolysis). Prog Clin Biol Res 1989; 292: 497-506.
104. Brenner CA, Wolny YM, Barritt JA, Matt DW, Munne S, Cohen J. Mitochondrial DNA deletion in human oocytes and embryos. Mol Hum Reprod 1998; 4: 887-892.
105. Bridges BA. Microbial genetics - hypermutation under stress. Nature 1997; 387: 557-558.
106. Bridges BA, Timms A. Effects of endogenous carotenoids and defective RpoS sigma factor on spontaneous mutation under starvation conditions in *Escherichia coli*: evidence for the possible involvement of singlet oxygen. Mutat Res 1998; 403: 21-28.
107. Brown CJ, Todd KM, Rosenzweig RF. Multiple duplications of yeast hexose transport genes in response to selection in a glucose-limited environment. Mol Biol Evol 1998; 15: 931-942.
108. Brown GC. Nitric oxide and mitochondrial oxidation. Biochim Biophys Acta 1999; 1411: 351-369.
109. Brown JM, Firtel RA. Just the right size. Cell counting in *Dictyostelium*. Trends Genet 2000; 16: 191-193.
110. Brown SB, Savill J. Phagocytosis triggers macrophage release of Fas ligand and induces apoptosis of bystander leukocytes. J Immunol 1999; 162: 480-485.
111. Bruce-Keller AJ, Geddes JW, Knapp PE, McFall RW, Keller JN, Holtsberg FW, Parthasarathy S, Steiner SM, Mattson MP. Anti-death properties of TNF against metabolic poisoning: mitochondrial stabilization by MnSOD. J Neuroimmunol 1999; 93: 53-71.
112. Brune B, Sandau K, von Knethen A. Apoptotic cell death and nitric oxide: activating and antagonistic transducing pathways. Biochemistry 1998; 63: 817-825.
113. Brunet CL, Gunby RH, Benson RSP, Hickman JA, Watson AJM, Brady G. Commitment to cell death measured by loss of clonogenicity is separable from the appearance of apoptotic markers. Cell Death Differ 1998; 5: 107-115.
114. Buemi M, Allegra A, Corica F, D'Anna R, Ruello A, Jasonni VM. B cell leukaemia/lymphoma-2 protein concentrations during normal pregnancy. Br J Obstet Gynaecol 2000; 107: 133-134.
115. Burdon RH. Control of cell proliferation by reactive oxygen species. Biochem Soc Trans 1996; 24: 1028-1032.
116. Burdon RH, Gill V, Boyd PA, Rahim RA. Hydrogen peroxide and sequence-specific DNA damage in human cells. FEBS Lett 1996; 383: 150-154.
117. Burger R. Evolution of genetic variability and the advantage of sex and recombination in changing environments. Genetics 1999; 153: 1055-1069.
118. Burt A. Perspective: sex, recombination, and the efficacy of selection. Was Weismann right? Evolution 2000; 54: 337-351.
119. Bussey H. K1 killer toxin, a pore-forming protein from yeast. Mol Microbiol 1991; 5: 2339-2343.
120. Cai J, Jones DP. Mitochondrial redox signaling during apoptosis. J Bioenerg Biomembrane 1999; 31: 327-334.
121. Cairns J. Mutation and cancer: the antecedents to our studies of adaptive mutation. Genetics 1998; 148: 1433-1440.
122. Cahill DP, Kinzler KW, Vogelstein B, Lengauer C. Genetic instability and Darwinian selection in tumours. Trends Cell Biochem 1999; 9: M57-M60.
123. Calderaro M, Martins EA, Meneghini R. Oxidative stress by menadione affects cellular copper and iron homeostasis. Mol Cell Biochem 1993; 126: 17-23.
124. Calvo EL, Boucher C, Coulombe Z, Morisset J. Pancreatic GAPDH gene expression during ontogeny and acute pancreatitis induced by caerulein. Biochem Biophys Res Commun 1997; 235: 636-640.
125. Camilleri-Broet S, Vanderwerff H, Caldwell E, Hockenbery D. Distinct alterations in mitochondrial mass and function characterize different models of apoptosis. Exp Cell Res 1998; 239: 277-292.

126. Caporale LH. Mutation is modulated: implications for evolution. Bioessays 2000; 22, 388-395.
127. Capuano F, Varone D, Deri N, Russo E, Tommasi S, Montemurro S, Prete F, Papa S. Oxidative phosphorylation and F_0F_1 ATP synthase activity of human hepatocellular carcinoma. Biochem Mol Biol Int 1996; 38: 1013-1022.
128. Carethers JM, Hawn MT, Chauhan DP, Luce MC, Marra G, Koi M, Boland CR. Competence in mismatch repair prohibits clonal expansion of cancer cells treated with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine. J Clin Invest 1996; 98: 199-206.
129. Carpentier Y, Mayer P, Bobichon H, Desoize B. Co-factors in in vitro induction of apoptosis in HL60 cells by all-trans retinoic acid (ATRA). Biochem Pharmacol 1998; 55: 177-184.
130. Carson DA, Lois A. Cancer progression and p53. Lancet 1995; 346: 1009-1011.
131. Casaccia-Bonnefil P, Gu C, Chao MV. Neurotrophins in cell survival/death decisions. Adv Exp Med Biol 1999; 468: 275-282.
132. Castro-Obregon S, Covarrubias L. Role of retinoic acid and oxidative stress in embryonic stem cell death and neuronal differentiation. FEBS Lett 1996; 381: 93-97.
133. Cavalcanti M, Jewett A, Bonavida B. Irreversible cancer cell-induced functional anergy and apoptosis in resting and activated NK cells. Int J Oncol 1999; 14: 361-366.
134. Cavalli LR, Liang BC. Mutagenesis, tumorigenicity, and apoptosis: are the mitochondria involved? Mutat Res 1998; 398: 19-26.
135. Cayrol C, Petit C, Raynaud B, Capdevielle J, Guillemot JC, Defais M. Recovery of respiration following the SOS response of *Escherichia coli* requires RecA-mediated induction of 2-keto-4-hydroxyglutarate aldolase. Proc Natl Acad Sci USA 1995; 92: 11806-11809.
136. Cella R, Vining LC.. Resistance to streptomycin in a producing strain of *Streptomyces griseus*. Can J Microbiol 1975; 21: 463-472.
137. Cellier MF, Taimi M, Chateau MT, Cannat A, Marti J. Thermal stress as an inducer of differentiation of U937 cells. Leuk Res 1993; 17: 649-656.
138. Cerda S, Weitzman SA. Influence of oxygen radical injury on DNA methylation. Mutat Res 1997; 386: 141-152.
139. Cerutti PA. Prooxidant states and tumor promotion. Science 1985; 227: 375-381.
140. Chabert MG, Niedergang CP, Hog F, Partisani M, Mandel P. Poly(ADPR) polymerase expression and activity during proliferation and differentiation of rat astrocyte and neuronal cultures. Biochim Biophys Acta 1992; 1136: 196-202.
141. Chae HU, Chae SW, Kang JS, Bang BG, Han JI, Moon SR, Park RK, So HS, Jee KS, Kim HM, Kim HR. Effect of ionizing radiation on the differentiation of ROS 17/2.8 osteoblasts through free radicals. J Radiat Res 1999; 40: 323-335.
142. Chailakhyan LM. Intercellular interactions as a basis for the expedient behaviour of multicellular systems. Membr Cell Biol 1998; 11: 693-700.
143. Chaloupka J, Vinter V. Programmed cell death in bacteria. Folia Microbiol 1996; 41: 451-464.
144. Chamberlain NR, Imanoel B. Genetic regulation of fatty acid modifying enzyme from *Staphylococcus aureus*. J Med Microbiol 1996; 44: 125-129.
145. Chan H, Bartos DP, Owen-Schaub LB. Activation-dependent transcriptional regulation of the human Fas promoter requires NF-κB p50-p65 recruitment. Mol Cell Biol 1999; 19: 2098-2108.
146. Chandel NS, Budinger GR, Choe SH, Schumacker PT. Cellular respiration during hypoxia. Role of cytochrome oxidase as the oxygen sensor in hepatocytes. J Biol Chem 1997; 272: 18808-18816.
147. Chang MT, Raper KB. Mating types and macrocyst formation in *Dictyostelium*. J Bacteriol 1981; 147: 1049-1053.
148. Chang TH, Szabo E. Induction of differentiation and apoptosis by ligands of peroxisome proliferator-activated receptor gamma in non-small cell lung cancer. Cancer Res 2000; 60: 1129-1138.
149. Chang YY, Fujimura M, Morita-Fujimura Y, Kim GW, Huang CY, Wu HS, Kawase M, Copin JC, Chan PH. Neuroprotective effects of an antioxidant in cortical cerebral ischemia: prevention of early reduction of the apurinic/apyrimidinic endonuclease repair enzyme. Neurosci Lett 1999; 277: 61-64.
150. Charlesworth B. The evolution of chromosomal sex determination and dosage compensation. Curr Biol 1996; 6: 149-162.
151. Chater KF. Genetics of differentiation in *Streptomyces*. Annu Rev Microbiol 1993; 47: 685-713.
152. Chau YP, Shiah SG, Don MJ, Kuo ML. Involvement of hydrogen peroxide in topoisomerase inhibitor β-lapachone-induced apoptosis and differentiation in human leukemia cells. Free Radical Biol Med 1998; 24: 660-670.
153. Chaufour S, Mehlen P, Arrigo AP. Transient accumulation, phosphorylation and changes in the oligomerization of Hsp27 during retinoic acid-induced differentiation of HL-60 cells: possible role in the control of cellular growth and differentiation. Cell Stress Chaperones 1996; 1: 225-235.
154. Chawla A, Lazar MA. Peroxisome proliferator and retinoid signaling pathways co-regulate preadipocyte phenotype and survival. Proc Natl Acad Sci USA 1994; 91: 1786-1790.
155. Chelstowska A, Butow RA. RTG genes in yeast that function in communication between mitochondria and the nucleus are also required for expression of genes encoding peroxisomal proteins. J Biol Chem 1995; 270: 18141-18146.

156. Chen HC, Yip YK, George I, Tyorkin M, Salik E, Sperber K. Chronically HIV-1-infected monocytic cells induce apoptosis in cocultured T cells. J Immunol 1998; 161: 4257-4267.
157. Chen JY, Oliveri P, Li C-W, Zhou GQ, Gao F, Hagadorn JW, Peterson KJ. Precambrian animal diversity: putative phosphatized embryos from the Doushantuo Formation of China. Proc Natl Acad Sci USA 2000; 97: 4457-4462.
158. Chen MH, Liu LF, Chen YR, Wu HK, Yu SM. Expression of α-amylases, carbohydrate metabolism, and autophagy in cultured rice cells is coordinately regulated by sugar nutrient. Plant J 1994; 6: 625-636.
159. Chen RS, McDonald BA. Sexual reproduction plays a major role in the genetic structure of populations of the fungus *Mycosphaerella graminicola*. Genetics 1996; 142: 1119-1127.
160. Chen RW, Saunders PA, Wei HF, Li ZW, Seth P, Chuang DM. Involvement of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and p53 in neuronal apoptosis: evidence that GAPDH is upregulated by p53. J Neurosci 1999; 19. 9654-9662.
161. Chen TC, Hinton DR, Zidovetzki R, Hofman FM. Up-regulation of the cAMP/PKA pathway inhibits proliferation, induces differentiation, and leads to apoptosis in malignant gliomas. Lab Invest 1998; 78: 165-174.
162. Cheo DL, Bayles KW, Yasbin RE. Elucidation of regulatory elements that control damage induction and competence induction of the *Bacillus subtilis* SOS system. J Bacteriol 1993; 175: 5907-5915.
163. Cherbonnel-Lasserre C, Gauny S, Kronenberg A. Suppression of apoptosis by Bcl-2 or Bcl-xL promotes susceptibility to mutagenesis. Oncogene 1996; 13: 1489-1497.
164. Chesney J, Mitchell R, Benigni F, Bacher M, Spiegel M, Al-Abed Y, Han JH, Metz C, Bucala R. An inducible gene product for 6-phosphofructo-2-kinase with an AU-rich instability element: role in tumor cell glycolysis and the Warburg effect. Proc Natl Acad Sci USA 1999; 96: 3047-3052.
165. Chinnaiyan AM, Chaudhary D, O'Rourke K, Koonin EV, Dixit VM. Role of CED-4 in the activation of CED-3. Nature 1997; 388: 728-729.
166. Chinopoulos C, Tretter L, Adam-Vizi V. Reversible depolarization of in situ mitochondria by oxidative stress parallels a decrease in NAD(P)H level in nerve terminals. Neurochem Int 2000; 36: 483-488.
167. Chiu SM, Xue LY, Friedman LR, Oleinick NL. Copper ion-mediated sensitization of nuclear matrix attachment sites to ionizing radiation. Biochemistry 1993; 32: 6214-6219.
168. Choi C, Park JY, Lee J, Lim JH, Shin EC, Ahn YS, Kim CH, Kim SJ, Kim JD, Choi IS, Choi IH. Fas ligand and Fas are expressed constitutively in human astrocytes and the expression increases with IL-1, IL-6, TNF-α, or IFN-γ. J Immunol 1999; 162: 1889-1895.
169. Chow M, Yao A, Rubin H. Cellular epigenetics: topochronology of progressive "spontaneous" transformation of cells under growth constraint. Proc Natl Acad Sci USA 1994; 91: 599-603.
170. Chow M, Rubin H. Irreversibility of cellular aging and neoplastic transformation: a clonal analysis. Proc Natl Acad Sci USA 1996; 93: 9793-9798.
171. Christensen ST, Leick V, Rasmussen L, Wheatley DN. Signaling in unicellular eukaryotes. Int Rev Cytol 1998; 177: 181-253.
172. Chu ZL, McKinsey TA, Liu L, Gentry JJ, Malim MH, Ballard DW. Suppression of tumor necrosis factor-induced cell death by inhibitor of apoptosis c-IAP2 is under NF-κB control. Proc Natl Acad Sci USA 1997; 94: 10057-100062.
173. Church SL, Grant JW, Ridnour LA, Oberley LW, Swanson PE, Meltzer PS, Trent JM. Increased manganese superoxide dismutase expression suppresses the malignant phenotype of human melanoma cells. Proc Natl Acad Sci USA 1993; 90: 3113-3117.
174. Clark AG. Invasion and maintenance of a gene duplication. Proc Natl Acad Sci USA 1994; 91: 2950-2954.
175. Clark WR. Sex and the Origins of Death. New York: Oxford University Press, 1996.
176. Clemens JA, Stephenson DT, Yin TG, Smalstig EB, Panetta JA, Little SP. Drug-induced neuroprotection from global ischemia is associated with prevention of persistent but not transient activation of nuclear factor-κB in rats. Stroke 1998; 29: 677-682.
177. Clutton SM, Townsend KMS, Walker C, Ansell JD, Wright EG. Radiation induced genomic instability and persisting oxidative stress in primary bone marrow cultures. Carcinogenesis 1996; 17: 1633-1639.
178. Coffman FD, Studzinski GP. Differentiation-related mechanisms which suppress DNA replication. Exp Cell Res 1999; 248: 58-73.
179. Cohen GM, Sun XM, Snowden RT, Dinsdale D, Skilleter DN. Key morphological features of apoptosis may occur in the absence of internucleosomal DNA fragmentation. Biochem J 1992; 286: 331-334.
180. Cohen SB, Crawley JB, Kahan MC, Feldmann M, Foxwell BM. Interleukin-10 rescues T cells from apoptotic cell death: association with an upregulation of Bcl-2. Immunology 1997; 92: 1-5.
181. Comelli M, Lippe G, Mavelli I. Differentiation potentiates oxidant injury to mitochondria by hydrogen peroxide in Friend's erythroleukemia cells. FEBS Lett 1994; 352: 71-75.
182. Constantinou A, Huberman E. Genistein as an inducer of tumor cell differentiation: possible mechanisms of action. Proc Soc Exp Biol Med 1995; 208: 109-115.
183. Conte D, Narindrasorasak S, Sarkar B. In vivo and in vitro iron-replaced zinc finger generates free radicals and causes DNA damage. J Biol Chem 1996; 271: 5125-5130.

184. Cooper GM. Oncogenes, 2nd Ed. Sudbury, MA: Jones and Bartlett Publishers, 1995.
185. Coppola S, Nosseri C, Maresca V, Ghibelli L. Different basal NAD levels determine opposite effects of poly (ADP-ribosyl) polymerase inhibitors on H_2O_2-induced apoptosis. Exp Cell Res 1995; 221: 462-469.
186. Cornillon S, Foa C, Davoust J, Buonavista N, Gross JD, Golstein P. Programmed cell death in *Dictyostelium*. J Cell Sci 1994; 107: 2691-2704.
187. Cossarizza A, Kalashnikova G, Grassilli E, Chiappelli F, Salvioli S, Capri M, Barbieri D, Troiano L, Monti D, Franceschi C. Mitochondrial modifications during rat thymocyte apoptosis: a study at the single cell level. Exp Cell Res 1994; 214: 323-330.
188. Coucouvanis E, Martin GR. Signals for death and survival: a 2-step mechanism for cavitation in the vertebrate embryo. Cell 1995; 83: 279-287.
189. Couee I, Jan M, Carde JP, Brouquisse R, Raymond P, Pradet A. Effects of glucose starvation on mitochondrial subpopulations in the meristematic and submeristematic regions of maize root. Plant Physiol 1992; 100: 1891-1900.
190. Courtillot V. Evolutionary Catastrophes: The Science of Mass Extinction. Cambridge: Cambridge University Press, 1999.
191. Cousins L. Insulin sensitivity in pregnancy. Diabetes 1991; 40 (Suppl 2): 39-43.
192. Crameri R, Kieser T, Ono H, Sanchez J, Hutter R. Chromosomal instability in *Streptomyces glaucescens*: mapping of streptomycin-sensitive mutants. J Gen Microbiol 1983; 129: 519-527.
193. Crick F. Central dogma of molecular biology. Nature 1970; 227: 561-563.
194. Cross HS, Ruis H. Regulation of catalase synthesis in *Saccharomyces cerevisiae* by carbon catabolite repression. Mol Gen Genet 1978; 166: 37-43.
195. Crow JF. Advantages of sexual reproduction. Dev Genet 1994; 15: 205-213.
196. Crowley CL, Payne CM, Bernstein H, Bernstein C, Roe D. The NAD^+ precursors, nicotinic acid and nicotinamide protect cells against apoptosis induced by a multiple stress inducer, deoxycholate. Cell Death Differ 2000; 7: 314-326.
197. Cui JK, Holmes EH, Greene TG, Liu PK. Oxidative DNA damage precedes DNA fragmentation after experimental stroke in rat brain. FASEB J 2000; 14: 955-967.
198. Cui Y, Chen RS, Wong WH. The coevolution of cell senescence and diploid sexual reproduction in unicellular organisms. Proc Natl Acad Sci USA 2000; 97: 3330-3335.
199. Dahm R. Lens fibre cell differentiation. A link with apoptosis? Ophthalmic Res 1999; 31: 163-183.
200. Dallman MF, Akana SF, Strack AM, Hanson ES, Sebastian RJ. The neural network that regulates energy balance is responsive to glucocorticoids and insulin and also regulates HPA axis responsivity at a site proximal to CRF neurons. Ann NY Acad Sci 1995; 771: 730-742.
201. Dang CV, Semenza GL. Oncogenic alterations of metabolism. Trends Biochem Sci 1999; 24: 68-72.
202. Danjoh I, Fujiyama A. Ras-mediated signaling pathway regulates the expression of a low-molecular-weight heat-shock protein in fission yeast. Gene 1999; 236: 347-352.
203. Darwin CR. On the Origin of Species. London: John Murray, 1859.
204. Datta A, Jinks-Robertson S. Association of increased spontaneous mutation rates with high levels of transcription in yeast. Science 1995; 268: 1616-1619.
205. Daugas E, Susin SA, Zamzami N, Ferri KF, Irinopoulou T, Larochette N, Prevost MC, Leber B, Andrews D, Penninger J, Kroemer G. Mitochondrio-nuclear translocation of AIF in apoptosis and necrosis. FASEB J 2000; 14: 729-739.
206. Davies DG, Parsek MR, Pearson JP, Iglewski BH, Costerton JW, Greenberg EP. The involvement of cell-to-cell signals in the development of a bacterial biofilm. Science 1998; 280: 295-298.
207. Dawkins R. The Selfish Gene, 2nd Ed. Oxford: Oxford University Press, 1989.
208. Dawson A. Comparative reproductive physiology of nonmammalian species. Pure Appl Chem 1998; 70: 1657-1669.
209. Day ML, Zhao X, Vallorosi CJ, Putzi M, Powell CT, Lin C, Day KC. E-Cadherin mediates aggregation-dependent survival of prostate and mammary epithelial cells through the retinoblastoma cell cycle control pathway. J Biol Chem 1999; 274: 9656-9664.
210. De A, Boyadjieva NI, Pastorcic M, Reddy BV, Sarkar DK. Cyclic AMP and ethanol interact to control apoptosis and differentiation in hypothalamic β-endorphin neurons. J Biol Chem 1994; 269: 26697-26704.
211. Deamer DW. The first living systems: a bioenergetic perspective. Microbiol Mol Biol Rev 1997; 61: 239-261.
212. De Groote MA, Granger D, Xu Y, Campbell G, Prince R, Fang FC. Genetic and redox determinants of nitric oxide cytotoxicity in a *Salmonella typhimurium* model. Proc Natl Acad Sci USA 1995; 92: 6399-6403.
213. De Hertogh R, Vanderheyden I, Pampfer S, Robin D, Dufrasne E, Delcourt J. Stimulatory and inhibitory effects of glucose and insulin on rat blastocyst development in vitro. Diabetes 1991; 40: 641-647.
214. Deichman GI. Natural selection and early changes of phenotype of tumor cells in vivo: acquisition of new defense mechanisms. Biochemistry (Mosc) 2000; 65: 78-94.
215. Delneste Y, Jeannin P, Sebille E, Aubry JP, Bonnefoy JY. Thiols prevent Fas (CD95)-mediated T cell apoptosis by down-regulating membrane Fas expression. Eur J Immunol 1996; 26: 2981-2988.

216. de Luca A, Weller M, Fontana A. TGF-β-induced apoptosis of cerebellar granule neurons is prevented by depolarization. J Neurosci 1996; 16: 4174-4185.
217. de Martin R, Schmid JA, Hofer-Warbinek R. The NF-κB/Rel family of transcription factors in oncogenic transformation and apoptosis. Mutat Res 1999; 437: 231-243.
218. Demple B, Halbrook J. Inducible repair of oxidative DNA damage in *Escherichia coli*. Nature 1983; 304: 466-468.
219. Deng GM, Su JH, Ivins KJ, Van Houten B, Cotman CW. Bcl-2 facilitates recovery from DNA damage after oxidative stress. Exp Neurol 1999; 159: 309-318.
220. Deng X, Ruvolo P, Carr B, May WS Jr. Survival function of ERK1/2 as IL-3-activated, staurosporine-resistant Bcl2 kinases. Proc Natl Acad Sci USA 2000: 97: 1578-1583.
221. DeoCampo ND, Wilson MR, Trosko JE. Cooperation of bcl-2 and myc in the neoplastic transformation of normal rat liver epithelial cells is related to the down-regulation of gap. Carcinogenesis 2000; 21: 1501-1506.
222. DePaoli-Roach A, Roach PJ, Zucker KE, Smith SS. Selective phosphorylation of human DNA methyltransferase by protein kinase C. FEBS Lett 1986; 197: 149-153.
223. Desvergne B, Ijpenberg A, Devchand PR, Wahli W. The peroxisome proliferator-activated receptors at the cross-road of diet and hormonal signalling. J Steroid Biochem Mol Biol 1998; 65: 65-74.
224. Deveraux QL, Reed JC. IAP family proteins - suppressors of apoptosis. Genes Dev 1999; 13: 239-252.
225. De Vos K, Goossens V, Boone E, Vercammen D, Vancompernolle K, Vandenabeele P, Haegeman G, Fiers W, Grooten J. The 55-kDa tumor necrosis factor receptor induces clustering of mitochondria through its membrane-proximal region. J Biol Chem 1998; 273: 9673-9680.
226. Dhaunsi GS, Singh I, Hanevold CD. Peroxisomal participation in the cellular response to the oxidative stress of endotoxin. Mol Cell Biochem 1993; 126: 25-35.
227. D'Herde K, De Prest B, Mussche S, Schotte P, Beyaert R, Van Coster R, Roels F. Ultrastructural localization of cytochrome c in apoptosis demonstrates mitochondrial heterogeneity. Cell Death Differ 2000; 7: 331-337.
228. Dianzani MU, Barrera G, Parola M. 4-Hydroxy-2,3-nonenal as a signal for cell function and differentiation. Acta Biochim Pol 1999; 46: 61-75.
229. Diaz G, Setzu MD, Zucca A, Isola R, Diana A, Murru R, Sogos V, Gremo F. Subcellular heterogeneity of mitochondrial membrane potential: relationship with organelle distribution and intercellular contacts in normal, hypoxic and apoptotic cells. J Cell Sci 1999; 112: 1077-1084.
230. Dickson RC, Lester RL. Metabolism and selected functions of sphingolipids in the yeast *Saccharomyces cerevisiae*. Biochim Biophys Acta 1999; 1438: 305-321.
231. Dieuaide M, Couee I, Pradet A, Raymond P. Effects of glucose starvation on the oxidation of fatty acids by maize root tip mitochondria and peroxisomes: evidence for mitochondrial fatty acid β-oxidation and acyl-CoA dehydrogenase activity in a higher plant. Biochem J 1993; 296: 199-207.
232. Ding RC, Pommier Y, Kang VH, Smulson M. Depletion of poly(ADP-ribose) polymerase by antisense RNA expression results in a delay in DNA strand break rejoining. J Biol Chem 1992; 267: 12804-12812.
233. Dix DJ. Hsp70 expression and function during gametogenesis. Cell Stress Chaperones 1997; 2: 73-77.
234. Djawdan M, Chippindale AK, Rose MR, Bradley TJ. Metabolic reserves and evolved stress resistance in *Drosophila melanogaster*. Physiol Zool 1998; 71: 584-594.
235. Djordjevic B. Bystander effects: a concept in need of clarification. Bioessays 2000; 22: 286-290.
236. Dmochowska A, Dignard D, Henning D, Thomas DY, Bussey H. Yeast KEX1 gene encodes a putative protease with a carboxypeptidase B-like function involved in killer toxin and alpha-factor precursor processing. Cell 1987; 50: 573-584.
237. Donnelly CE, Walker GC. groE mutants of *Escherichia coli* are defective in umuDC-dependent UV mutagenesis. J Bacteriol 1989; 171: 6117-6125.
238. Donovan SK, ed. Mass Extinctions: Processes and Evidence. New York: Columbia University Press, 1989.
239. Dormann S, Schwieger A, Hanusch J, Haufel T, Engelmann I, Bauer G. Intercellular induction of apoptosis through modulation of endogenous survival factor concentration: a review. Anticancer Res 1999; 19: 87-103.
240. Dorward A, Sweet S, Moorehead R, Singh G. Mitochondrial contributions to cancer cell physiology: redox balance, cell cycle, and drug resistance. J Bioenerg Biomembrane 1997; 29: 385-392.
241. Downard J, Toal D. Branched-chain fatty acids: the case for a novel form of cell-cell signalling during *Myxococcus xanthus* development. Mol Microbiol 1995; 16: 171-175.
242. Dri AM, Moreau PL. Phosphate starvation and low temperature as well as ultraviolet irradiation transcriptionally induce the *Escherichia coli* LexA-controlled gene sfiA. *Mol Microbiol* 1993; 8: 697-706.
243. Drost JB, Lee WR. Biological basis of germline mutation: comparisons of spontaneous germline mutation rates among *Drosophila*, mouse and human. Environ Mol Mutagen 1995; 25 (Suppl 26): 48-64.
244. D'Souza SM, Brown IR. Constitutive expression of heat shock proteins Hsp90, Hsc70, Hsp70 and Hsp60 in neural and non-neural tissues of the rat during postnatal development. Cell Stress Chaperones 1998; 3: 188-199.
245. Duckett CS, Li F, Wang Y, Tomaselli KJ, Thompson CB, Armstrong RC. Human IAP-like protein regulates

programmed cell death downstream of Bcl-x_L and cytochrome c. Mol Cell Biol 1998; 18: 608-615.
246. Duesberg P, Rausch C, Rasnick D, Hehlmann R. Genetic instability of cancer cells is proportional to their degree of aneuploidy. Proc Natl Acad Sci USA 1998; 95: 13692-13697.
247. Dukan S, Levi Y, Touati D. Recovery of culturability on an HOCl-stressed population of *Escherichia coli* after incubation in phosphate buffer: resuscitation or regrowth? Appl Environ Microbiol 1997; 63: 4204-4209.
248. Duriez PJ, Shah GM. Cleavage of poly(ADP-ribose) polymerase: a sensitive parameter to study cell death. Biochem Cell Biol 1997; 75: 337-349.
249. Durkacz BW, Lunec J, Grindley H, Griffin S, Horner O, Simm A. Murine melanoma cell differentiation and melanogenesis induced by poly(ADP-ribose) polymerase inhibitors. Exp Cell Res 1992; 202: 287-291.
250. Duwat P, Sourice S, Ehrlich SD, Gruss A. recA gene involvement in oxidative and thermal stress in *Lactococcus lactis*. Dev Biol Stand 1995; 85: 455-467.
251. Duwat P, Ehrlich SD, Gruss A. Effects of metabolic flux on stress response pathways in *Lactococcus lactis*. Mol Microbiol 1999; 31: 845-858.
252. Dwivedi K, Sen A, Bullerjahn GS. Expression and mutagenesis of the dpsA gene of *Synechococcus sp. PCC7942*, encoding a DNA-binding protein involved in oxidative stress protection. FEMS Microbiol Lett 1997; 155: 85-91.
253. Eddy EM. Role of heat shock protein HSP70-2 in spermatogenesis. Rev Reprod 1999; 4: 23-30.
254. Edmond J, Robbins RA, Bergstrom JD, Cole RA, de Vellis J. Capacity of substrate utilization in oxidative metabolism by neurons, astrocytes, and oligodendrocytes from developing brain in primary culture. J Neurosci Res 1987; 18: 551-561.
255. Edwards MJ. Apoptosis, the heat shock response, hyperthermia, birth defects, disease and cancer. Where are the common links? Cell Stress Chaperones 1998; 3: 213-220.
256. Egberts J. Circulating markers of oxidative stress are raised in normal pregnancy and pre-eclampsia. Br J Obstet Gynaecol 1999; 106: 751.
257. Egel R. The synaptonemal complex and the distribution of meiotic recombination events. Trends Genet 1995; 11: 206-208.
258. Eguchi Y, Srinivasan A, Tomaselli KJ, Shimizu S, Tsujimoto Y. ATP-dependent steps in apoptotic signal transduction. Cancer Res 1999; 59: 2174-2181.
259. Ehleben W, Bolling B, Merten E, Porwol T, Strohmaier AR, Acker H. Cytochromes and oxygen radicals as putative members of the oxygen sensing pathway. Respir Physiol 1998; 114: 25-36.
260. Eisen JA, Hanawalt PC. A phylogenomic study of DNA repair genes, proteins, and processes. Mutat Res 1999; 435: 171-213.
261. Eisenstark A, Calcutt MJ, Becker-Hapak M, Ivanova A. Role of *Escherichia coli* rpoS and associated genes in defense against oxidative damage. Free Radical Biol Med 1996; 21: 975-993.
261a. Eldredge N. The Pattern of Evolution. New York: Freeman and Co., 1999.
262. Elena SF, Lenski RE. Test of synergistic interactions among deleterious mutations in bacteria. Nature 1997; 390: 395-398.
263. Ellegren H, Fridolfsson AK. Male-driven evolution of DNA sequences in birds. Nat Genet 1997; 17: 182-184.
264. Eller MS, Maeda T, Magnoni C, Atwal D, Gilchrest BA. Enhancement of DNA repair in human skin cells by thymidine dinucleotides: evidence for a p53-mediated mammalian SOS response. Proc Natl Acad Sci USA 1997; 94: 12627-12632.
265. Ellis RE, Yuan JY, Horvitz HR. Mechanisms and functions of cell death. Annu Rev Cell Biol 1991; 7: 663-698.
266. Emerit I, Filipe P, Meunier P, Auclair C, Freitas J, Deroussent A, Gouyette A, Fernandes A. Clastogenic activity in the plasma of scleroderma patients: a biomarker of oxidative stress. Dermatology 1997; 194: 140-146.
267. Enari M, Sakahira H, Yokoyama H, Okawa K, Iwamatsu A, Nagata S. A caspase-activated DNase that degrades DNA during apoptosis, and its inhibitor ICAD. Nature 1998; 391: 43-50.
268. Endrich MM, Grossenbacher D, Geistlich A, Gehring H. Apoptosis-induced concomitant release of cytosolic proteins and factors which prevent cell death. Biol Cell 1996; 88: 15-22.
269. Epstein W, Rothman-Denes LB, Hesse J. Adenosine 3′:5′-cyclic monophosphate as mediator of catabolite repression in *Escherichia coli*. Proc Natl Acad Sci USA 1975; 72: 2300-2304.
270. Eraso JM, Chidambaram M, Weinstock GM. Increased production of colicin E1 in stationary phase. J Bacteriol 1996; 178: 1928-1935.
271. Eriksson MJ, Clarke AK. The heat shock protein ClpB mediates the development of thermotolerance in the cyanobacterium *Synechococcus sp.* strain PCC 7942. J Bacteriol 1996; 178: 4839-4846.
272. Erkkila K, Hirvonen V, Wuokko E, Parvinen M, Dunkel L. *N*-Acetyl-L-cysteine inhibits apoptosis in human male germ cells in vitro. J Clin Endocrinol Metab 1998; 83: 2523-2531.
273. Errington J. Determination of cell fate in *Bacillus subtilis*. Trends Genet 1996; 12: 31-34.
274. Escher P, Wahli W. Peroxisome proliferator-activated receptors: insight into multiple cellular functions. Mutat Res 2000; 448: 121-138.
275. Espey MG, Miranda KM, Feelisch M, Fukuto J, Grisham MB, Vitek MP, Wink DA. Mechanisms of cell death governed by the balance between nitrosative and oxidative stress. Ann NY Acad Sci 2000; 899: 209-221.

276. Evan G, Littlewood T. A matter of life and cell death. Science 1998; 281: 1317-1322.
277. Fabrizi C, Businaro R, Persichini T, Fumagalli L, Lauro GM. The expression of LDL receptor-related protein (LRP) correlates with the differentiation of human neuroblastoma cells. Brain Res 1997; 776: 154-161.
278. Factor VM, Laskowska D, Jensen MR, Woitach JT, Popescu NC, Thorgeirsson SS. Vitamin E reduces chromosomal damage and inhibits hepatic tumor formation in a transgenic mouse model. Proc Natl Acad Sci USA 2000; 97: 2196-2201.
279. Fadeel B, Ahlin A, Henter JI, Orrenius S, Hampton MB. Involvement of caspases in neutrophil apoptosis: regulation by reactive oxygen species. Blood 1998; 92: 4808-4818.
280. Falcieri E, Martelli AM, Bareggi R, Cataldi A, Cocco L. The protein kinase inhibitor staurosporine induces morphological changes typical of apoptosis in MOLT-4 cells without concomitant DNA fragmentation. Biochem Biophys Res Commun 1993; 193: 19-25.
281. Fang A, Pierson DL, Koenig DW, Mishra SK, Demain AL. Effect of simulated microgravity and shear stress on microcin B17 production by *Escherichia coli* and on its excretion into the medium. Appl Environ Microbiol 1997; 63: 4090-4092.
282. Farmer G, Bargonetti J, Zhu H, Friedman P, Prywes R, Prives C. Wild-type p53 activates transcription in vitro. Nature 1992; 358: 83-86.
283. Farr SB, Koguma T. Oxidative stress responses in *Escherichia coli* and *Salmonella typhimurium*. Microbiol Rev 1991; 55: 561-585.
284. Farzaneh F, Zalin R, Brill D, Shall S. DNA strand breaks and ADP-ribosyl transferase activation during cell differentiation. Nature 1982; 300: 362-366.
285. Farzaneh F, Meldrum R, Shall S. Transient formation of DNA strand breaks during the induced differentiation of a human promyelocytic leukaemic cell line, HL-60. Nucl Acid Res 1987; 15: 3493-3502.
286. Faulk EA, McCully JD, Tsukube T, Hadlow NC, Krukenkamp IB, Levitsky S. Myocardial mitochondrial calcium accumulation modulates nuclear calcium accumulation and DNA fragmentation. Ann Thor Surg 1995; 60: 338-344.
287. Fedoroff NV. Transposable elements as a molecular evolutionary force. Ann NY Acad Sci 1999; 870: 251-264.
288. Feng B, Friedlin E, Marzluf GA. A reporter gene analysis of penicillin biosynthesis gene expression in *Penicillium chrysogenum* and its regulation by nitrogen and glucose catabolite repression. Appl Environ Microbiol 1994; 60: 4432-4439.
289. Ferea TL, Botstein D, Brown PO, Rosenzweig RF. Systematic changes in gene expression patterns following adaptive evolution in yeast. Proc Natl Acad Sci USA 1999; 96: 9721-9726.
290. Ferguson LR, Baguley BC. Mutagenicity of anticancer drugs that inhibit topoisomerase enzymes. Mutat Res 1996; 355: 91-101.
291. Fijalkowska IJ, Schaaper RM. Mutants in the Exo I motif of *Escherichia coli* dnaQ: defective proofreading and inviability due to error catastrophe. Proc Natl Acad Sci USA 1996; 93: 2856-2861.
292. Fimia GM, Gottifredi V, Passananti C, Maione R. Double-stranded internucleosomal cleavage of apoptotic DNA is dependent on the degree of differentiation in muscle cells. J Biol Chem 1996; 271: 15575-15579.
293. Findlay S, Rowe G. Computer experiments on the evolution of sex: the haploid case: J Theor Biol 1990; 146: 379-393.
294. Finkel SE, Kolter R. Evolution of microbial diversity during prolonged starvation. Proc Natl Acad Sci USA 1999; 96: 4023-4027.
295. Fisher HM, Aitken RJ. Comparative analysis of the ability of precursor germ cells and epididymal spermatozoa to generate reactive oxygen metabolites. J Exp Zool 1997; 277: 390-400.
296. Fitt PS, Sharma N. Starvation as an inducer of error-free DNA repair in *Escherichia coli*. Mutat Res 1991; 262: 145-150.
297. Fleming JE, Bensch KG. Oxidative stress as a causal factor in differentiation and aging: a unifying hypothesis. Exp Gerontol 1991; 26: 511-517.
298. Fleming JV, Hay SM, Harries DN, Rees WD. Effects of nutrient deprivation and differentiation on the expression of growth-arrest genes (gas and gadd) in F9 embryonal carcinoma cells. Biochem J 1998; 330: 573-579.
299. Fliss MS, Usadel H, Caballero OL, Wu L, Buta MR, Eleff SM, Jen J, Sidransky D. Facile detection of mitochondrial DNA mutations in tumors and bodily fluids. Science 2000; 287: 2017-2019.
300. Forfia PR, Hintze TH, Wolin MS, Kaley G. Role of nitric oxide in the control of mitochondrial function. Adv Exp Med Biol 1999; 471: 381-388.
301. Foster PL, Trimarchi JM, Maurer RA. Two enzymes, both of which process recombination intermediates, have opposite effects on adaptive mutation in *Escherichia coli*. Genetics 1996; 142: 25-37.
302. Fourie AM, Hupp TR, Lane DP, Sang BC, Barbosa MS, Sambrook JF, Gething MJ. HSP70 binding sites in the tumor suppressor protein p53. J Biol Chem 1997; 272: 19471-19479.
303. Frank SA, Swingland IR. Sex ratio under conditional sex expression. J Theor Biol 1988; 135: 415-418.
304. Freire-Picos MA, Hollenberg CP, Breunig KD, Cerdan ME. Regulation of cytochrome c expression in the aerobic respiratory yeast *Kluyveromyces lactis*. FEBS Lett 1995; 360: 39-42.
305. Frese D, Stahl U. Oxidative stress and ageing in the fungus *Podospora anserina*. Mech Ageing Dev 1992; 65: 277-288.

306. Friedberg EC, Walker GC, Siede W. DNA Repair and Mutagenesis. Washington, DC: ASM Press, 1995.
307. Friedlander RM, Gagliardini V, Rotello RJ, Yuan J. Functional role of interleukin 1β (IL-1β) and IL-1β-converting enzyme-mediated apoptosis. J Exp Med 1996; 184: 717-724.
308. Foyer CH, Lopez-Delgado H, Dat JF, Scott IM. Hydrogen peroxide- and glutathione-associated mechanisms of acclimatory stress tolerance and signalling. Physiol Plant 1997; 100: 241-254.
309. Francis D. High frequency recombination during the sexual cycle of *Dictyostelium discoideum*. Genetics 1998; 148: 1829-1832.
310. Francis MM, Cella R, Vining LC. Streptomycin resistance in chloramphenicol-producing strains of *Streptomyces species 3022a*. Can J Microbiol 1975; 21: 911-919.
311. Franklin CC, Srikanth S, Kraft AS. Conditional expression of mitogen-activated protein kinase phosphatase-1, MKP-1, is cytoprotective against UV-induced apoptosis. Proc Natl Acad Sci USA 1998; 95: 3014-3019.
312. Frommel TO, Zarling EJ. Chronic inflammation and cancer: potential role of Bcl-2 gene family members as regulators of cellular antioxidant status. Med Hypotheses 1999; 52: 27-30.
313. Frost P, Chernajovsky Y. Transformation injury and the unicellular phenotype of malignant cells. Cancer Metastasis Rev 1990; 9: 93-98.
314. Funk RHW, Nagel F, Wonka F, Krinke HE, Golfert F, Hofer A. Effects of heat shock on the functional morphology of cell organelles observed by video-enhanced microscopy. Anat Rec 1999; 255: 458-464.
315. Gabriel A, Mules EH. Fidelity of retrotransposon replication. Ann NY Acad Sci 1999; 870: 108-118.
316. Gafter U, Malachi T, Ori Y, Breitbart H. The role of calcium in human lymphocyte DNA repair ability. J Lab Clin Med 1997; 130: 33-41.
317. Galan A, O'Connor JE, Valbuena D, Herrer R, Remohi J, Pampfer S, Pellicer A, Simon C. The human blastocyst regulates endometrial epithelial apoptosis in embryonic adhesion. Biol Reprod 2000; 63: 430-439.
318. Gamaley IA, Klyubin IV. Roles of reactive oxygen species: signaling and regulation of cellular functions. Int Rev Cytol 1999; 188: 203-255.
319. Gambino M, Kay RR, Bozzaro S. Morphogenesis and differentiation of *Dictyostelium* cells interacting with immobilized glucosides: dependence on DIF production. Differentiation 1992; 49: 133-141.
320. Gandarillas A. Epidermal differentiation, apoptosis, and senescence: common pathways? Exp Gerontol 2000; 35: 53-62.
321. Gao YJ, Ferguson DO, Xie W, Manis JP, Sekiguchi J, Frank KM, Chaudhuri J, Horner J, DePinho RA, Alt FW. Interplay of p53 and DNA-repair protein XRCC4 in tumorigenesis, genomic stability and development. Nature 2000; 404: 897-900.
322. Garces C, Ruiz-Hidalgo MJ, de Mora JF, Park C, Miele L, Goldstein J, Bonvini E, Porras A, Laborda J. Notch-1 controls the expression of fatty acid-activated transcription factors and is required for adipogenesis. J Biol Chem 1997; 272: 29729-29734.
323. Garland JM, Halestrap A. Energy metabolism during apoptosis - bcl-2 promotes survival in hematopoietic cells induced to apoptose by growth factor withdrawal by stabilizing a form of metabolic arrest. J Biol Chem 1997; 272: 4680-4688.
324. Gavrilets S. Rapid evolution of reproductive barriers driven by sexual conflict. Nature 2000; 403: 886-889.
325. Geilen CC, Wieder T, Orfanos CE. Ceramide signalling: regulatory role in cell proliferation, differentiation and apoptosis in human epidermis. Arch Dematol Res 1997; 289: 559-566.
326. Gemmill AW, Viney ME, Read AF. Host immune status determines sexuality in a parasitic nematode. Evolution 1997; 51: 393-401.
327. Gerhart J. 1998 Warkany lecture: Signaling pathways in development. Teratology 1999; 60: 226-239.
328. Geske FJ, Nelson AC, Lieberman R, Strange R, Sun T, Gerschenson LE. DNA repair is activated in early stages of p53-induced apoptosis. Cell Death Differ 2000; 7: 393-401.
329. Ghosh R, Bhaumik G. Supernatant medium from UV-irradiated cells influences the cytotoxicity and mutagenicity of V79 cells. Mutat Res 1995; 335: 129-135.
330. Gierer A. Biological features and physical concepts of pattern formation exemplified by hydra. Curr Top Dev Biol 1977; 11: 17-59.
331. Gilmore EC, Nowakowski RS, Caviness VS Jr, Herrup K. Cell birth, cell death, cell diversity and DNA breaks: how do they all fit together? Trends Neurosci 2000; 23: 100-105.
332. Giri DK, Aggarwal BB. Constitutive activation of NF-κB causes resistance to apoptosis in human cutaneous T cell lymphoma HuT-78 cells. Autocrine role of tumor necrosis factor and reactive oxygen intermediates. J Biol Chem 1998; 273: 14008-14014.
333. Goecke-Flora CM, Wyman JF, Jarnot BM, Reo NV. Effect of the peroxisome proliferator perfluoro-n-decanoic acid on glucose transport in the isolated perfused rat liver. Chem Res Toxicol 1995; 8: 77-81.
334. Golshani-Hebroni SG, Bessman, SP. Hexokinase binding to mitochondria: a basis for proliferative energy metabolism. J Bioenerg Biomembrane 1997; 29: 331-338.
335. Gomer RH. Intercellular signalling. Knowing that you're among friends. Curr Biol 1994; 4: 734-735.
336. Gong BD, Chen Q, Almasan A. Ionizing radiation stimulates mitochondrial gene expression and activity. Radiat Res 1998; 150: 505-512.
337. Gong M, Li YJ, Chen SZ. Abscisic acid-induced thermotolerance im maize seedlings is mediated by calcium and associated with antioxidant systems. J Plant Physiol 1998; 153: 488-496.

338. Gong YW, Cui L, Minuk GY. Comparison of glyceraldehyde-3-phosphate dehydrogenase and 28S-ribosomal RNA gene expression in human hepatocellular carcinoma. Hepatology 1996; 23: 734-737.
339. Goodman AE, Hild E, Marshall KC, Hermansson M. Conjugative plasmid transfer between bacteria under simulated marine oligotrophic conditions. Appl Environ Microbiol 1993; 59: 1035-1040.
340. Goodman CS, Coughlin BC. The evolution of evo-devo biology. Proc Natl Acad Sci USA 2000; 97: 4424-4425.
341. Goossens V, De Vos K, Vercammen D, Steemans M, Vancompernolle K, Fiers W, Vandenabeele P, Grooten J. Redox regulation of TNF signaling. Biofactors 1999; 10: 145-156.
342. Gosden CM, Liloglou T, Nunn J, Gardener D, Nickson P, Crampton JM, Field JK. The Knights of the Round Table hypothesis of tumour suppressor gene function - noble sacrifice or sexual dalliance: genes, including p53, BRCA1/2 and RB have evolved by horizontal and vertical transmission of mating factor genes and are involved in gametogenesis, implantation, development and tumourigenesis. Int J Oncol 1998; 12: 5-35.
343. Gotoh H, Zhu D, Eddy EM. Protein binding to meiotic recombination hotspots in mouse testis. Ann NY Acad Sci 1999; 870: 351-353.
344. Gottlieb E, Vander Heiden MG, Thompson CB. Bcl-xL prevents the initial decrease in mitochondrial membrane potential and subsequent reactive oxygen species production during tumor necrosis factor α-induced apoptosis. Mol Cell Biol 2000; 20: 5680-5689.
345. Gould SJ. Ontogeny and phylogeny - revisited and reunited. Bioessays 1992; 14: 275-279.
346. Grasl-Kraupp B, Bursch W, Ruttkay-Nedecky B, Wagner A, Lauer B, Schulte-Hermann R. Food restriction eliminates preneoplastic cells through apoptosis and antagonizes carcinogenesis in rat liver. Proc Natl Acad Sci USA 1994; 91: 9995-9999.
347. Graz CJM, Cowley HM. Energy state in HT-29 cells is linked to differentiation. In Vitro Cell Dev Biol-Animal 1997; 33: 277-281.
348. Green DR, Reed JC. Mitochondria and apoptosis. Science 1998; 281: 1309-1312.
349. Greenblatt MS, Elias L. The type-B receptor for tumor necrosis factor α mediates DNA fragmentation in HL-60 and U937 cells and differentiation in HL-60 cells. Blood 1992; 80: 1339-1346.
350. Greiner EF, Guppy M, Brand K. Glucose is essential for proliferation and the glycolytic enzyme induction that provokes a transition to glycolytic energy production. J Biol Chem 1994; 269: 31484-31490.
351. Griffiths SD, Clarke AR, Healy LE, Ross G, Ford AM, Hooper ML, Wyllie AH, Greaves M. Absence of p53 permits propagation of mutant cells following genotoxic damage. Oncogene 1997; 14: 523-531.
352. Grossman AD, Losick R. Extracellular control of spore formation in *Bacillus subtilis*. Proc Natl Acad Sci USA 1988; 85: 4369-4373.
353. Grundel R, Rubin H. Adaptation and selection as factors in the spontaneous transformation of NIH-3T3 cells. Carcinogenesis 1992; 13: 1873-1877.
354. Grundy FJ, Waters DA, Takova TY, Henkin TM. Identification of genes involved in utilization of acetate and acetoin in *Bacillus subtilis*. Mol Microbiol 1993; 10: 259-271.
355. Grzesiuk E. The role of mutation frequency decline and SOS repair systems in methyl methanesulfonate mutagenesis. Minireview. Acta Biochim Pol 1998; 45: 523-533.
356. Gu YZ, Hogenesch JB, Bradfield CA. The PAS superfamily: sensors of environmental and developmental signals. Annu Rev Pharmacol Toxicol 2000; 40: 519-561.
357. Guedez L, Zucali J. Bleomycin-induced differentiation of bcl-2-transfected U937 leukemia cells. Cell Growth Differ 1996; 7: 1625-1631.
358. Guttridge DC, Albanese C, Reuther JY, Pestell RG, Baldwin AS. NF-κB controls cell growth and differentiation through transcriptional regulation of cyclin D1. Mol Cell Biol 1999; 19: 5785-5799.
359. Hainaut P, Milner J. Interaction of heat-shock protein 70 with p53 translated in vitro: evidence for interaction with dimeric p53 and for a role in the regulation of p53 conformation. EMBO J 1992; 11: 3513-3520.
360. Hainaut P, Milner J. Redox modulation of p53 conformation and sequence-specific DNA binding in vitro. Cancer Res 1993; 53: 4469-4473.
361. Halappanavar SS, Rhun YL, Mounir S, Martins LM, Huot J, Earnshaw WC, Shah GM. Survival and proliferation of cells expressing caspase-uncleavable poly(ADP-ribose) polymerase in response to death-inducing DNA damage by an alkylating agent. J Biol Chem 1999; 24: 37097-37104.
362. Hall BG. Adaptive mutations in *Escherichia coli* as a model for the multiple mutational origins of tumors. Proc Natl Acad Sci USA 1995; 92: 5669-5673.
363. Hall RM, Collis CM, Kim MJ, Partridge SR, Recchia GD, Stokes HW. Mobile gene cassettes and integrons in evolution. Ann NY Acad Sci 1999; 870: 68-80.
364. Hallmann A, Godl K, Wenzl S, Sumper M. The highly efficient sex-inducing pheromone system of *Volvox*. Trends Microbiol 1998; 6: 185-189.
365. Halvorsen SW, Jiang N, Malek R. Regulation of nicotinic acetylcholine receptors on human neuroblastoma cells during differentiation. Biochem Pharmacol 1995; 50: 1665-1671.
366. Hamilton WD, Axelrod R, Tanese R. Sexual selection as an adaptation to resist parasites (a review). Proc Natl Acad Sci USA 1990; 87: 3566-3573.
367. Hancock JT. Superoxide, hydrogen peroxide and nitric oxide as signalling molecules: their production and role in disease. Br J Biomed Sci 1997; 54: 38-46.
368. Hand SC, Hardewig I. Down-regulation of cellular metabolism during environmental stress: mechanisms and implications. Annu Rev Physiol 1996; 58: 539-563.

369. Hannun YA, Luberto C. Ceramide in the eukaryotic stress response. Trends Cell Biol 2000; 10: 73-80.
370. Hansen S, Midgley CA, Lane DP, Freeman BC, Morimoto RI, Hupp TR. Modification of two distinct COOH-terminal domains is required for murine p53 activation by bacterial Hsp70. J Biol Chem 1996; 271: 30922-30928.
371. Hanson ES, Leibold EA. Regulation of iron regulatory protein 1 during hypoxia and hypoxia/reoxygenation. J Biol Chem 1998; 273: 7588-7593.
372. Harada H, Mitsuyasu T, Seta Y, Maruoka Y, Toyoshima K, Yasumoto S. Overexpression of bcl-2 protein inhibits terminal differentiation of oral keratinocytes in vitro. J Oral Pathol Med 1998; 27: 11-17.
373. Hardie DG. Roles of the AMP-activated/SNF1 protein kinase family in the response to cellular stress. Biochem Soc Symp 1999; 64: 13-27.
374. Hardie DG, Carling D. The AMP-activated protein kinase - fuel gauge of the mammalian cell? Eur J Biochem 1997; 246: 259-273.
375. Hardingham GE, Bading H. Nuclear calcium: a key regulator of gene expression. Biometals 1998; 11: 345-358.
376. Hartke A, Bouche S, Laplace JM, Benachour A, Boutibonnes P, Auffray Y. UV-inducible proteins and UV-induced cross-protection against acid, ethanol, H_2O_2 or heat treatments in *Lactococcus lactis susp lactis*. Arch Microbiol 1995; 163: 329-336.
377. Hass R. Retrodifferentiation and cell death. Crit Rev Oncogenesis 1994; 5: 359-371.
378. Hassan HM, Fridovich I. Regulation of superoxide dismutase synthesis in *Escherichia coli*: glucose effect. J Bacteriol 1977; 132: 505-510.
379. Haufel T, Dormann S, Hanusch J, Schwieger A, Bauer G. Three distinct roles for TGF-β during intercellular induction of apoptosis: a review. Anticancer Res 1999; 19: 105-111.
380. Hauge HH, Mantzilas D, Moll GN, Konings WN, Driessen AJ, Eijsink VG, Nissen-Meyer J. Plantaricin A is an amphiphilic alpha-helical bacteriocin-like pheromone which exerts antimicrobial and pheromone activities through different mechanisms. Biochemistry 1998; 37: 16026-16032.
381. Haupt Y, Maya R, Kazaz A, Oren M. Mdm2 promotes the rapid degradation of p53. Nature 1997; 387: 296-299.
382. Haussmann P, Zimmermann FK. The role of mitochondria in carbon catabolite repression in yeast. Mol Gen Genet 1976; 148: 205-211.
383. Hayakawa M, Ogawa T, Sugiyama S, Ozawa T. Hydroxyl radical and leukotoxin biosynthesis in neutrophil plasma membrane. Biochem Biophys Res Commun 1989; 161: 1077-1085.
384. Hayashi T, Sakurai M, Itoyama Y, Abe K. Oxidative damage and breakage of DNA in rat brain after transient MCA occlusion. Brain Res 1999; 832: 159-163.
385. He LS, Fox MH. Variation of heat shock protein 70 through the cell cycle in HL-60 cells and its relationship to apoptosis. Exp Cell Res 1997; 232: 64-71.
386. He Z, Xin B, Yang X, Chan C, Cao L. Nuclear factor-κB activation is involved in LMP1-mediated transformation and tumorigenesis of rat-1 fibroblasts. Cancer Res 2000; 60: 1845-1848.
387. Heininger K. A unifying hypothesis of Alzheimer's disease. I. Ageing sets the stage. Hum Psychopharmacol Clin Exp 1999; 14: 363-414.
388. Heininger K. A unifying hypothesis of Alzheimer's disease. III. Risk factors. Hum Psychopharmacol Clin Exp 2000; 15: 1-70.
389. Heininger K. A unifying hypothesis of Alzheimer's disease. IV. Causation and sequence of events. Rev Neurosci 2000; 11: 213-328.
390. Heininger K. Aging is a deprivation syndrome. Submitted.
391. Held KD. Radiation-induced apoptosis and its relationship to loss of clonogenic survival. Apoptosis 1997; 2: 265-282.
392. Hengge-Aronis R. Survival of hunger and stress: the role of rpoS in early stationary phase gene regulation in *E. coli*. Cell 1993; 72: 165-168.
393. Herceg Z, Wang ZQ. Failure of poly(ADP-ribose) polymerase cleavage by caspases leads to induction of necrosis and enhanced apoptosis. Mol Cell Biol 1999; 19: 5124-5133.
394. Herman RK, Dworkin NB. Effect of gene induction on the rate of mutagenesis of ICR-191 in *Escherichia coli*. J Bacteriol 1971; 106: 543-550.
395. Hernandez JA, Olmos E, Corpas FJ, Sevilla F, del Rio LA. Salt-induced oxidative stress in chloroplasts of pea plants. Plant Sci 1995; 105: 151-167.
396. Herrlich P, Mallick U, Ponta H, Rahmsdorf HJ. Genetic changes in mammalian cells reminiscent of an SOS response. Hum Genet 1984; 67: 360-368.
397. Hertz R, Bar-Tana J. Reductive repression in *Escherichia coli* K-12 is mediated by oxygen radicals. Arch Biochem Biophys 1986; 250: 54-62.
398. Hewitson LC, Leese HJ. Energy metabolism of the trophectoderm and inner cell mass of the mouse blastocyst. J Exp Zool 1993; 267: 337-343.
399. Heyer BS, Warsowe J, Solter D, Knowles BB, Ackerman SL. New member of the Snf1/AMPK kinase family, Melk, is expressed in the mouse egg and preimplantation embryo. Mol Reprod Dev 1997; 47: 148-156.
400. Hindle Z, Smith CP. Substrate induction and catabolite repression of the *Streptomyces coelicolor* glycerol operon are mediated through the GylR protein. Mol Microbiol 1994; 12, 737-745.
401. Hudson JJ, Taylor WD, Schindler DW. Phosphate concentrations in lakes. Nature 2000; 406: 54-56.
402. Hochman A. Programmmed cell death in prokaryotes. Crit Rev Microbiol 1997; 23: 207-214.

403. Hoeflich KP, Luo J, Rubie EA, Tsao MS, Jin O, Woodgett JR. Requirement for glycogen synthase kinase-3β in cell survival and NF-κB activation. Nature 2000; 406: 86-90.
404. Hoelzer MA, Michod RE. DNA repair and the evolution of transformation in *Bacillus subtilis*. III. Sex with damaged DNA. Genetics 1991; 128: 215-223.
405. Hoffman PF, Kaufman AJ, Halverson GP, Schrag DP. A neoproterozoic snowball earth. Science 1998; 281: 1342-1346.
406. Hoffman PF, Schrag DP. Snowball earth. Sci Am 2000; 282: 68-75.
407. Hoffmann AA, Parsons PA. Selection for increased desiccation resistance in *Drosophila melanogaster*: additive genetic control and correlated responses for other stresses. Genetics 1989; 122: 837-845.
408. Hogeweg P. Evolving mechanisms of morphogenesis: on the interplay between differential adhesion and cell differentiation. J Theor Biol 2000; 203: 317-333.
409. Hoggarth JH, Cushing KE, Mitchell JI, Ritchie DA. Induction of resistance to novobiocin in the novobiocin-producing organism *Streptomyces niveus*. FEMS Microbiol Lett 1994; 116: 131-136.
410. Holden RJ, Mooney PA. The p53 paradox in the pathogenesis of tumor progression. Med Hypotheses 1999; 52: 483-485.
411. Hollstein M, Sidransky D, Vogelstein B, Hårris CC. p53 mutations in human cancers. Science 1991; 253: 49-53.
412. Honma M, Hayashi M, Sofuni T. Cytotoxic and mutagenic responses to X-rays and chemical mutagens in normal and p53-mutated human lymphoblastoid cells. Mutat Res 1997; 374: 89-98.
413. Hoppe J, Schäfer R, Hoppe V, Sachinidis A. ATP and adenosine prevent via different pathways the activation of caspases in apoptotic AKR-2B fibroblasts. Cell Death Differ 1999; 6: 546-556.
414. Hopper AK, Hall BD. Mating type and sporulation in yeast. I. Mutations which alter mating-type control over sporulation. Genetics 1975; 80: 41-59.
415. Hopwood DA. The Leeuwenhoek lecture, 1987. Towards an understanding of gene switching in *Streptomyces*, the basis of sporulation and antibiotic production. Proc Roy Soc Lond B 1988; 235: 121-138.
416. Horiguchi T, Hayashi K, Tsubotani S, Iinuma S, Harada S, Tanida S. New naphthacenecarboxamide antibiotics, TAN-1518A and B, have inhibitory activity against mammalian DNA topoisomerase I. J Antibiot (Tokyo) 1994; 47: 545-556.
417. Horinouchi S, Kumada Y, Beppu T. Unstable genetic determinant of A-factor biosynthesis in streptomycin-producing organisms: cloning and characterization. J Bacteriol 1984; 158: 481-487.
418. Horinouchi S, Beppu T. A-factor as a microbial hormone that controls cellular differentiation and secondary metabolism in *Streptomyces griseus*. Mol Microbiol 1994; 12: 859-864.
419. Hotta K, Yamamoto H, Okami Y, Umezawa H. Resistance mechanisms of kanamycin-, neomycin-, and streptomycin-producing *Streptomycetes* to aminoglycoside antibiotics. J Antibiot (Tokyo) 1981; 34: 1175-1182.
420. Howard RS, Lively CM. Parasitism, mutation accumulation and the maintenance of sex. Nature 1994; 367: 554-557.
421. Howard RS, Lively CM. The maintenance of sex by parasitism and mutation accumulation under epistatic fitness functions. Evolution 1998; 52: 604-610.
422. Hu BR, Liu CL, Ouyang Y, Blomgren K, Siesjö BK. Involvement of caspase-3 in cell death after hypoxia-ischemia declines during brain maturation. J Cereb Blood Flow Metab 2000; 20: 1294-1300.
423. Huang Q, Alvares K, Chu RY, Bradfield CA, Reddy JK. Association of peroxisome proliferator-activated receptor and hsp72. J Biol Chem 1994; 269: 8493-8497.
424. Hubel CA. Dyslipidemia, iron, and oxidative stress in pre-eclampsia: assessment of maternal and feto-placental interactions. Semin Reprod Endocrinol 1998; 16: 75-92.
425. Huber WW, Grasl-Kraupp B, Stekel H, Gschwentner C, Lang H, Schulte-Hermann R. Inhibition instead of enhancement of lipid peroxidation by pretreatment with the carcinogenic peroxisome proliferator nafenopin in rat liver exposed to a high single dose of corn oil. Arch Toxicol 1997; 71: 575-581.
426. Huigens ME, Luck RF, Klaassen RHG, Maas MFPM, Timmermans MJTN, Stouthamer R. Infectious parthogenesis. Nature 2000; 405: 178-179.
427. Huisman GW, Kolter R. Sensing starvation: a homoserine lactone-dependent signaling pathway in *Escherichia coli*. Science 1994; 265: 537-539.
428. Huner NPA, Oquist G, Sarhan F. Energy balance and acclimation to light and cold. Trends Plant Sci 1998; 3: 224-230.
429. Hunt CR, Sim JE, Sullivan SJ, Featherstone T, Golden W, von Kapp-Herr C, Hock RA, Gomez RA, Parsian AJ, Spitz DR. Genomic instability and catalase gene amplification induced by chronic exposure to oxidative stress. Cancer Res 1998; 58: 3986-3992.
430. Hurst LD, Ellegren H. Sex biases in the mutation rate. Trends Genet 1997; 14: 446-452.
431. Hussain SP, Aguilar F, Amstad P, Cerutti P. Oxy-radical induced mutagenesis of hotspot codon-248 and codon-249 of the human p53 gene. Oncogene 1994; 9: 2277-2281.
432. Huttley GA, Jakobsen IB, Wilson SR, Easteal S. How important is DNA replication for mutagenesis? Mol Biol Evol 2000; 17: 929-937.
433. Iida A, Yamaguchi A, Hirose K. Telomerase activity in colorectal cancer and its relationship to bcl-2 expression. J Surg Oncol 2000; 73: 219-223.
434. Imai Y, Yamamoto M. The fission yeast mating pheromone P-factor: its molecular structure, gene structure,

and ability to induce gene expression and G1 arrest in the mating partner. Genes Dev 1994; 8: 328-338.
435. Imlay JA, Linn S. DNA damage and oxygen radical toxicity. Science 1988; 240: 1302-1309.
436. Ingenbleek Y, Bernstein L. The stressful condition as a nutritionally dependent adaptive dichotomy. Nutrition 1999; 15: 305-320.
437. Innes KE, Wimsatt JH. Pregnancy-induced hypertension and insulin resistance: evidence for a connection. Acta Obstet Gynecol Scand 1999; 78: 263-284.
438. Inouye K. Control of cell type proportions by a secreted factor in *Dictyostelium discoideum*. Development 1989; 107: 605-609.
439. Ishizuka H, Hanamura A, Kunimura T, Aiba H. A lowered concentration of cAMP receptor protein caused by glucose is an important determinant for catabolite repression in *Escherichia coli*. Mol Microbiol 1993; 10: 341-350.
440. Israel L. Tumour progression: random mutations or an integrated survival response to cellular stress conserved from unicellular organisms? J Theor Biol 1996; 178: 375-380.
441. Israel L. Malignant progression and resistance of cancer cells: an inducible survival program similar to the SOS system of unicellular organisms induced by environmental assaults. Bull Acad Natl Med 1998; 182: 49-57.
442. Iwahashi H, Fujii S, Obuchi K, Kaul SC, Sato A, Komatsu Y. Hydrostatic pressure is like high temperature and oxidative stress in the damage it causes to yeast. FEMS Microbiol Lett 1993; 108: 53-57.
443. Iyengar R. Gating by cyclic AMP: expanded role for an old signaling pathway. Science 1996; 271: 461-463.
444. Jaattela M. Escaping cell death: survival proteins in cancer. Exp Cell Res 1999; 248: 30-43.
445. Jaattela M, Wissing D, Kokholm K, Kallunki T, Egeblad M. Hsp70 exerts its anti-apoptotic function downstream of caspase-3-like proteases. EMBO J 1998; 17: 6124-6134.
446. Jack RW, Tagg JR, Ray B. Bacteriocins of gram-positive bacteria. Microbiol Rev 1995; 59: 171-200.
447. Jaffe K, Issa S, Daniels E, Haile D. Dynamics of the emergence of genetic resistance to biocides among asexual and sexual organisms. J Theor Biol 1997; 188: 289-299.
448. Jaffe R. First trimester utero-placental circulation: maternal-fetal interaction. J Perinat Med 1998; 26: 168-174.
449. James BW, Mauchline WS, Dennis PJ, Keevil CW, Wait R. Poly-3-hydroxybutyrate in *Legionella pneumophila*, an energy source for survival in low-nutrient environments. Appl Environ Microbiol 1999; 65: 822-827.
450. James SJ, Muskhelishvili L, Gaylor DW, Turturro A, Hart R. Upregulation of apoptosis with dietary restriction: implications for carcinogenesis and aging. Environ Health Perspect 1998; 106 (Suppl 1): 307-312.
451. Janssen-Heininger YMW, Poynter ME, Baeuerle PA. Recent advances towards understanding redox mechanisms in the activation of nuclear factor κB. Free Radical Biol Med 2000; 28: 1317-1327.
452. Jayaraman T, Marks AR. Calcium-dependent signalling in apoptosis. In: Verkhratsky A, Toescu EC, eds. Integrative Aspects of Calcium Signalling. New York: Plenum Press, 1998; 291-310.
453. Jee HJ, Ko WH. *Phytophora cactorum* can synthesize substances needed for sexual reproduction but requires a stress factor to trigger the process. Microbiology 1998; 144: 1071-1075.
454. Jeggo PA. DNA repair: PARP - another guardian angel? Curr Biol 1998; 8: R49-R51.
455. Jiang CY, Ting AT, Seed B. PPAR-γ agonists inhibit production of monocyte inflammatory cytokines. Nature 1998; 391: 82-86.
456. Jo H, Zhang R, Zhang H, McKinsey TA, Shao J, Beauchamp RD, Ballard DW, Liang P. NF-κB is required for H-ras oncogene induced abnormal cell proliferation and tumorigenesis. Oncogene 2000; 19: 841-849.
457. Joanisse DR, Storey KB. Oxidative damage and antioxidants in *Rana sylvatica*, the freeze-tolerant wood frog. Am J Physiol 1996; 40: R545-R553.
458. Johnson TM, Yu ZX, Ferrans VJ, Lowenstein RA, Finkel T. Reactive oxygen species are downstream mediators of p53-dependent apoptosis. Proc Natl Acad Sci USA 1996; 93: 11848-11852.
459. Johnston M. Feasting, fasting and fermenting. Trends Genet 1999; 15: 29-33.
460. Johnston RN, Pai SB, Pai RB. The origin of the cancer cell: oncogeny reverses phylogeny. Biochem Cell Biol 1992; 70: 831-834.
461. Joshi A, Moody ME. The cost of sex revisited: effects of male gamete output of hermaphrodites that are asexual in their female capacity. J Theor Biol 1998; 195: 533-542.
462. Josse C, Legrand-Poels S, Piret B, Sluse F, Piette J. Impairment of the mitochondrial electron chain transport prevents NF-κB activation by hydrogen peroxide. Free Radical Biol Med 1998; 25: 104-112.
463. Jost JP, Jost YC. Transient DNA demethylation in differentiating mouse myoblasts correlates with higher activity of 5-methyldeoxycytidine excision repair. J Biol Chem 1994; 269: 10040-10043.
464. Jürgensmeier JM, Panse J, Schäfer R, Bauer G. Reactive oxygen species as mediators of the transformed phenotype. Int J Cancer 1997; 70: 587-589.
465. Jürgensmeier JM, Bauer G. Interference of bcl-2 with intercellular control of carcinogenesis. Int J Cancer 1997; 71: 698-704.
466. Kahn NW, Quinn TW. Male-driven evolution among *Eoaves*? A test of the replicative division hypothesis in a heterogametic female (ZW) system. J Mol Evol 1999; 49: 750-759.

467. Kaina B, Ziouta A, Ochs K, Coquerelle T. Chromosomal instability, reproductive cell death and apoptosis induced by O-6-methylguanine in Mex^-, Mex^+ and methylation-tolerant mismatch repair compromised cells: facts and models. Mutat Res 1997; 381: 227-241.
468. Kaiser WJ, Vucic D, Miller LK. The *Drosophila* inhibitor of apoptosis D-IAP1 suppresses cell death induced by the caspase drICE. FEBS Lett 1998; 440: 243-248.
469. Kaltschmidt B, Kaltschmidt C, Hofmann TG, Hehner SP, Droge W, Schmitz ML. The pro-and anti-apoptotic function of NF-κB is determined by the nature of the apoptotic stimulus. Eur J Biochem 2000; 267: 3828-3835.
470. Kamata H, Tanaka C, Yagisawa H, Matsuda S, Gotoh Y, Nishida E, Hirata H. Suppression of nerve growth factor-induced neuronal differentiation of PC12 cells - *N*-acetylcysteine uncouples the signal transduction from Ras to the mitogen-activated protein kinase cascade. J Biol Chem 1996; 271: 33018-33025.
471. Kamata H, Hirata H. Redox regulation of cellular signalling. Cell Signal 1999; 11: 1-14.
472. Kanamura S, Kanai K, Oka M, Shugyo Y, Watanabe J. Quantitative analysis of development of mitochondrial ultrastructure in differentiating mouse hepatocytes during postnatal period. J Ultrastruct Res 1985; 93: 195-204.
473. Kanatani Y, Kasukabe T, Okabe-Kado J, Yamamoto-Yamaguchi Y, Nagata N, Motoyoshi K, Honma Y. Role of CD14 expression in the differentiation-apoptosis switch in human monocytic leukemia cells treated with 1α,25-dihydroxyvitamin D3 or dexamethasone in the presence of transforming growth factor β1. Cell Growth Differ 1999; 10: 705-712.
474. Kaplan HB, Plamann L. A *Myxococcus xanthus* cell density-sensing system required for multicellular development. FEMS Microbiol Lett 1996; 139: 89-95.
475. Karin M. Mitogen-activated protein kinase cascades as regulators of stress responses. Ann NY Acad Sci 1998; 851: 139-146.
476. Kasibhatla S, Brunner T, Genestier L, Echeverri F, Mahboubi A, Green DR. DNA damaging agents induce expression of Fas ligand and subsequent apoptosis in T lymphocytes via the activation of NF-κB and AP-1. Mol Cell 1998; 1: 543-551.
477. Kato T, Okazaki K, Murakami H, Stettler S, Fantes PA, Okayama H. Stress signal, mediated by a Hog1-like MAP kinase, controls sexual development in fission yeast. FEBS Lett 1996; 378: 207-212.
478. Kaufmann SH, Charron M, Burke PJ, Karp JE. Changes in topoisomerase-I levels and localization during myeloid maturation in vitro and in vivo. Cancer Res 1995; 55: 1255-1260.
479. Kawamura K, Fujiwara S. Advantage or disadvantage: is asexual reproduction beneficial to survival of the tunicate, *Polyandrocarpa misakiensis*? Zool Sci 2000; 17: 281-291.
480. Kawase M, Fujimura M, Morita-Fujimura Y, Chan PH. Reduction of apurinic/apyrimidinic endonuclease expression after transient global cerebral ischemia in rats. Implication of the failure of DNA repair in neuronal apoptosis. Stroke 1999; 30: 441-448.
481. Kay RR, Flatman P, Thompson CR. DIF signalling and cell fate. Semin Cell Dev Biol 1999; 10: 577-585.
482. Kelemen GH, Buttner MJ. Initiation of aerial mycelium formation in *Streptomyces*. Curr Opin Microbiol 1998; 1: 656-662.
483. Keller H, Dreyer C, Medin J, Mahfoudi A, Ozato K, Wahli W. Fatty acids and retinoids control lipid metabolism through activation of peroxisome proliferator-activated receptor-retinoid X receptor heterodimers. Proc Natl Acad Sci USA 1993; 90: 2160-2164.
484. Keller H, Givel F, Perroud M, Wahli W. Signaling cross-talk between peroxisome proliferator-activated receptor, retinoid-X receptor and estrogen receptor through estrogen response elements. Mol Endocrinol 1995; 9: 794-804.
485. Kennedy NJ, Kataoka T, Tschopp J, Budd RC. Caspase activation is required for T cell proliferation. J Exp Med 1999; 190: 1891-1895.
486. Kern SE, Kinzler KW, Bruskin A, Jarosz D, Friedman P, Prives C, Vogelstein B. Identification of p53 as a sequence-specific DNA-binding protein. Science 1991; 252: 1708-1711.
487. Kerr JFR, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 1972; 26: 239-257.
488. Keszenman DJ, Carmen Candreva E, Nunes E. Cellular and molecular effects of bleomycin are modulated by heat shock in *Saccharomyces cerevisiae*. Mutat Res 2000; 459: 29-41.
489. Khan Z, Francis GE. Contrasting pattern of DNA strand breakage and ADP-ribosylation-dependent DNA ligation during granulocyte and monocyte differentiation. Blood 1987; 69: 1114-1119.
489a. Khodarev NN, Bennett T, Shearing N, Sokolova I, Koudelik J, Walter S, Villalobos M, Vaughan ATM. LINE L1 retrotransposable element is targeted during the initial stages of apoptotic DNA fragmentation. J Cell Biochem 2000; 79: 486-495.
490. Khrapko K, Coller HA, Andre PC, Li XC, Hanekamp JS, Thilly WG. Mitochondrial mutational spectra in human cells and tissues. Proc Natl Acad Sci USA 1997; 94: 13798-13803.
491. Kibota TT, Lynch M. Estimate of the genomic mutation rate deleterious to overall fitness in *E. coli*. Nature 1996; 381: 694-696.
492. Kim DW, Sovak MA, Zanieski G, Nonet G, Romieu-Mourez R, Lau AW, Hafer LJ, Yaswen P, Stampfer M, Rogers AE, Russo J, Sonenshein GE. Activation of NF-κB/Rel occurs early during neoplastic transformation of mammary cells. Carcinogenesis 2000; 21: 871-879.

493. Kim JW, Kim SJ, Han SM, Paik SY, Hur SY, Kim YW, Lee JM, Namkoong SE. Increased glyceraldehyde-3-phosphate dehydrogenase gene expression in human cervical cancers. Gynecol Oncol 1998; 71: 266-269.
494. Kim SJ, Romeo D, Yoo YD, Park K. Transforming growth factor-β: expression in normal and pathological conditions. Horm Res 1994; 42: 5-8.
495. Kim SR, Maenhaut-Michel G, Yamada M, Yamamoto Y, Matsui K, Sofuni T, Nohmi T, Ohmori H. Multiple pathways for SOS-induced mutagenesis in *Escherichia coli*: an overexpression of dinB/dinP results in strongly enhancing mutagenesis in the absence of any exogenous treatment to damage DNA. Proc Natl Acad Sci USA 1997; 94: 13792-13797.
496. Kimpel E, Osiewacz HD. PaGrg1, a glucose-repressible gene of *Podospora anserina* that is differentially expressed during lifespan. Curr Genet 1999; 35: 557-563.
497. Kinashi H, Otten SL, Duncan JS, Hutchinson CR. Frequent loss and restoration of antibiotic production by *Streptomyces lasaliensis*. J Antibiot (Tokyo) 1988; 41: 624-637.
498. Kirk DL. The genetic program for germ-soma differentiation in *Volvox*. Annu Rev Genet 1997; 31: 359-380.
499. Kirk DL, Baran GJ, Harper JF, Huskey RJ, Huson KS, Zagris N. Stage-specific hypermutability of the regA locus of *Volvox*, a gene regulating the germ-soma dichotomy. Cell 1987; 48: 11-24.
500. Kirk MM, Stark K, Miller SM; Muller W, Taillon BE, Gruber H, Schmitt R, Kirk DL. regA, a *Volvox* gene that plays a central role in germ-soma differentiation, encodes a novel regulatory protein. Development 1999; 126: 639-647.
501. Klaidman LK, Mukherjee SK, Hutchin TP, Adams JD. Nicotinamide as a precursor for NAD^+ prevents apoptosis in the mouse brain induced by tertiary-butylhydroperoxide. Neurosci Lett 1996; 206: 5-8.
502. Kleckner N. Meiosis: How could it work? Proc Natl Acad Sci USA 1996; 93: 8167-8174.
503. Kleerebezem M, Quadri LE, Kuipers OP, de Vos WM. Quorum sensing by peptide pheromones and two-component signal-transduction systems in Gram-positive bacteria. Mol Microbiol 1997; 24: 895-904.
504. Kliewer SA, Umesono K, Noonan DJ, Heyman RA, Evans RM. Convergence of 9-cis retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. Nature 1992; 358: 771-774.
505. Knapen MFCM, Zusterzeel PLM, Peters WHM, Steegers EAP. Glutathione and glutathione-related enzymes in reproduction - a review. Eur J Obstet Gynecol Reprod Biol 1999; 82: 171-184.
506. Kolotova TY, Vasil'ev NV. High-molecular-weight DNA fragmentation and its possible role in genome rearrangements. Mol Biol 1999; 33: 123-128.
507. Kolter R, Siegele DA, Tormo AA. The stationary phase of the bacterial life cycle. Annu Rev Microbiol 1993; 47: 855-874.
508. Komarova EA, Diatchenko L, Rokhlin OW, Hill JE, Wang ZJ, Krivokrysenko VI, Feinstein E, Gudkov AV. Stress-induced secretion of growth inhibitors: a novel tumor suppressor function of p53. Oncogene 1998; 17: 1089-1096.
509. Komuves LG, Hanley K, Jiang Y, Elias PM, Williams ML, Feingold KR. Ligands and activators of nuclear hormone receptors regulate epidermal differentiaton during fetal rat skin development. J Invest Dermatol 1998; 111: 429-433.
510. Kondrashov AS. The asexual ploidy cycle and the origin of sex. Nature 1994; 370: 213-216.
511. Kondrashov AS, Turelli M. Deleterious mutations, apparent stabilizing selection and the maintenance of quantitative variation. Genetics 1992; 132: 603-618.
512. Kong Q, Lillehei KO. Antioxidant inhibitors for cancer therapy. Med Hypotheses 1998; 51: 405-409.
513. Konopka JB, Fields S. The pheromone signal pathway in *Saccharomyces cerevisiae*. Antonie Van Leeuwenhoek 1992; 62: 95-108.
514. Kordes U, Krappmann D, Heissmeyer V, Ludwig WD, Scheidereit C. Transcription factor NF-κB is constitutively activated in acute lymphoblastic leukemia cells. Leukemia 2000; 14: 399-402.
515. Korogodin VI, Korogodina VL, Fajszi C, Chepurnoy AI, Mikhova-Tsenova N, Simonyan NV. On the dependence of spontaneous mutation rates on the functional state of genes. Yeast 1991; 7: 105-117.
516. Korpelainen H. Labile sex expression in plants. Biol Rev Cambridge Phil Soc 1998; 73: 157-180.
517. Korshunov SS, Krasnikov BF, Pereverzev MO, Skulachev VP. The antioxidant functions of cytochrome c. FEBS Lett 1999; 462: 192-198.
518. Korzets A, Chagnac A, Weinstein T, Ori Y, Malachi T, Gafter U. H_2O_2 induces DNA repair in mononuclear cells: evidence for association with cytosolic Ca^{2+} fluxes. J Lab Clin Med 1999; 133: 362-369.
519. Kots YA, Sergienko EA, Bulargina TV, Severin ES. Glyceraldehyde-3-phosphate dehydrogenase activates auto-ADP-ribosylation of glyceraldehyde-3-phosphate dehydrogenase. FEBS Lett 1993; 324: 33-36.
520. Koury MJ, Bondurant MC. Erythropoietin retards DNA breakdown and prevents programmed death in erythroid progenitor cells. Science 1990; 248: 378-381.
521. Kovac L, Nelson BD, Ernster L. A method for determining the intracellular distribution of enzymes in yeast provides no evidence for the association of hexokinase with mitochondria. Biochem Biophys Res Commun 1986; 134: 285-291.
522. Kovtun Y, Chiu W-L, Tena G, Sheen J. Functional analysis of oxidative stress-activated mitogen-activated protein kinase cascade in plants. Proc Natl Acad Sci USA 2000; 97: 2940-2945.

523. Kowaltowski AJ. Alternative mitochondrial functions in cell physiopathology: beyond ATP production. Braz J Med Biol Res 2000; 33: 241-250.
524. Koyanagi-Katsuta R, Akimitsu N, Arimitsu N, Hatano T, Sekimizu K. Apoptosis of mouse embryonic stem cells induced by single cell suspension. Tissue Cell 2000; 32: 66-70.
525. Kroemer G, Dallaporta B, Resche-Rigon M. The mitochondrial death/life regulator in apoptosis and necrosis. Annu Rev Physiol 1998; 60: 619-642.
526. Kruszewski M, Green MH, Lowe JE, Szumiel I. DNA strand breakage, cytotoxicity and mutagenicity of hydrogen peroxide treatment at 4°C and 37°C in L5178Y sublines. Mutat Res 1994; 308: 233-241.
527. Kubohara Y. DIF-1, putative morphogen of *D. discoideum*, suppresses cell growth and promotes retinoic acid-induced cell differentiation in HL-60. Biochem Biophys Res Commun 1997; 236: 418-422.
528. Kubohara Y, Kimura C, Tatemoto K. Putative morphogen, DIF, of *Dictyostelium discoideum* induces apoptosis in rat pancreatic AR42J cells. Dev Growth Differ 1995; 37: 711-716.
529. Kuerbitz SJ, Plunkett BS, Walsh WV, Kastan MB. Wild-type p53 is a cell cycle checkpoint determinant following irradiation. Proc Natl Acad Sci USA 1992; 89: 7491-7495.
530. Kugu K, Ratts VS, Piquette GN, Tilly KI, Tao XJ, Martimbeau S, Aberdeen GW, Krajewski S, Reed JC, Pepe GJ, Albrecht ED, Tilly JL. Analysis of apoptosis and expression of bcl-2 gene family members in the human and baboon ovary. Cell Death Differ 1998; 5: 67-76.
531. Kuhn K, Hashimoto S, Lotz M. IL-1β protects human chondrocytes from CD95-induced apoptosis. J Immunol 2000; 164: 2233-2239.
532. Kulaeva OI, Koonin EV, McDonald JP, Randall SK, Rabinovich N, Connaughton JF, Levine AS, Woodgate R. Identification of a dinB/umuC homolog in the archeon *Sulfolobus solfataricus*. Mutat Res 1996; 357: 245-253.
533. Kumazawa T, Inouye M, Hayasaka I, Yamamura H, Murata Y. Difference in sensitivity of inner cell mass and trophectoderm to X-irradiation in mouse blastocysts. Teratology 1998; 57: 146-151.
534. Kurjan J. Pheromone response in yeast. Annu Rev Biochem 1992; 61: 1097-1129.
535. Kurrelmeyer KM, Michael LH, Baumgarten G, Taffet GE, Peschon JJ, Sivasubramanian N, Entman ML, Mann DL. Endogenous tumor necrosis factor protects the adult cardiac myocyte against ischemic-induced apoptosis in a murine model of acute myocardial infarction. Proc Natl Acad Sci USA 2000; 97: 5456-5461.
536. LaBorde JB, Pipkin JL, Hinson WG, Anson JF, Sheehan DM, Young JF, Hansen DK. Retinoic acid-induced stress protein synthesis in the mouse. Life Sci 1995; 56: 1767-1778.
537. LaCasse EC, Baird S, Korneluk RG, MacKenzie AE. The inhibitors of apoptosis (IAPs) and their emerging role in cancer. Oncogene 1998; 17: 3247-3259.
538. Ladislas R. Cellular and molecular mechanisms of aging and age related diseases. Pathol Oncol Res 2000; 6: 3-9.
539. Lander HM. An essential role for free radicals and derived species in signal transduction. FASEB J 1997; 11: 118-124.
540. Lane DP, Midgley C, Hupp T. Tumour suppressor genes and molecular chaperones. Philos Trans Roy Soc Lond B 1993; 339: 369-372.
541. Larsen AK. Involvement of DNA topoisomerases and DNA topoisomerase inhibitors in the induction of leukemia cell differentiation. Ann Oncol 1994; 5: 679-688.
542. Lassus P, Bertrand C, Zugasti O, Chambon JP, Soussi T, Mathieu-Mahul D, Hibner U. Anti-apoptotic activity of p53 maps to the COOH-terminal domain and is retained in a highly oncogenic natural mutant. Oncogene 1999; 18: 4699-4709.
543. Latruffe N, Vamecq J. Peroxisome proliferators and peroxisome proliferator activated receptors (PPARs) as regulators of lipid metabolism. Biochimie 1997; 79: 81-94.
544. Lazazzera BA. Quorum sensing and starvation: signals for entry into stationary phase. Curr Opin Microbiol 2000; 3: 177-182.
545. Leary SC, Battersby BJ, Hansford RG, Moyes CD. Interactions between bioenergetics and mitochondrial biogenesis. Biochim Biophys Acta 1998; 1365: 522-530.
546. Lebman DA, Edmiston JS. The role of TGF-β in growth, differentiation, and maturation of B lymphocytes. Microbes Infect 1999; 1: 1297-1304.
547. Lee AS. Mammalian stress response: induction of the glucose-regulated protein family. Curr Opin Cell Biol 1992; 4: 267-273.
548. Lee HC, Yin PH, Lu CY, Chi CW, Wie YH. Increase of mitochondria and mitochondrial DNA in response to oxidative stress in human cells. Biochem J 2000; 348: 425-432.
549. Lee HH, Dadgostar H, Cheng Q, Shu J, Cheng G. NF-κB-mediated up-regulation of bcl-x and bfl-1/A1 is required for CD40 survival signaling in B lymphocytes. Proc Natl Acad Sci USA 1999; 96: 9136-9141.
550. Lee J, Bruce-Keller AJ, Kruman Y, Chan SL, Mattson MP. 2-Deoxy-D-glucose protects hippocampal neurons against excitotoxic and oxidative injury: evidence for the involvement of stress proteins. J Neurosci Res 1999; 57: 48-61.
551. Lee LA, Resar LM, Dang CV. Cell density and paradoxical transcriptional properties of c-Myc and Max in cultured mouse fibroblasts. J Clin Invest 1995; 95: 900-904.
552. Lee SW, Ko YG, Bang S, Kim KS, Kim S. Death effector domain of a mammalian apoptosis mediator,

FADD, induces bacterial cell death. Mol Microbiol 2000; 35: 1540-1549.
553. Leibowitz MJ, Wickner RB. A chromosomal gene required for killer plasmid expression, mating, and spore maturation in *Saccharomyces cerevisiae*. Proc Natl Acad Sci USA 1976; 73: 2061-2065.
554. Lemasters JJ, Nieminen AL, Qian T, Trost LC, Elmore SP, Nishimura Y, Crowe RA, Cascio WE, Bradham CA, Brenner DA, Herman B. The mitochondrial permeability transition in cell death: a common mechanism in necrosis, apoptosis and autophagy. Biochim Biophys Acta 1998; 1366: 177-196.
555. Lemberger T, Staels B, Saladin R, Desvergne B, Auwerx J, Wahli W. Regulation of the peroxisome proliferator-activated receptor α gene by glucocorticoids. J Biol Chem 1994; 269: 24527-24530.
556. Lemberger T, Saladin R, Vazquez M, Assimacopoulos F, Staels B, Desvergne B, Wahli W, Auwerx J. Expression of the peroxisome proliferator-activated receptor α gene is stimulated by stress and follows a diurnal rhythm. J Biol Chem 1996; 271: 1764-1769.
557. Lengauer C, Kinzler KW, Vogelstein B. Genetic instabilities in human cancers. Nature 1998; 396: 643-649.
558. Lenski RE, Mittler JE. The directed mutation controversy and neodarwinism. Science 1993; 259: 188-194.
559. Lenski RE, Travisano M. Dynamics of adaptation and diversification: a 10,000-generation experiment with bacterial populations. Proc Natl Acad Sci USA 1994; 91: 6808-6814.
560. Lenski RE, Mongold JA, Sniegowski PD, Travisano M, Vasi F, Gerrish PJ, Schmidt TM. Evolution of competitive fitness in experimental populations of *E. coli*: What makes one genotype a better competitor than another? Antonie Van Leeuwenhoek 1998; 73: 35-47.
561. Leone TC, Weinheimer CJ, Kelly DP. A critical role for the peroxisome proliferator-activated receptor α (PPARα) in the cellular fasting response: The PPARα-null mouse as a model of fatty acid oxidation disorders. Proc Natl Acad Sci USA 1999; 96: 7473-7478.
562. Le Rhun Y, Duthu A, Ehrhart JC, Michiels F, May E, May P. Directional selection associated with clonal expansion of p53 mutant cells during neoplastic development of carcinogen-treated rat embryo lung epithelial cells. Oncogene 1994; 9: 263-271.
563. Levine AJ, Momand J, Finlay CA. The p53 tumour suppressor gene. Nature 1991; 351: 453-456.
564. Levine AJ, Wu MC, Chang A, Silver A, Attiyeh EF, Lin J, Epstein CB. The spectrum of mutations at the p53 locus. Evidence for tissue-specific mutagenesis, selection of mutant alleles, and a "gain of function" phenotype. Ann NY Acad Sci 1995; 768: 111-128.
565. Lewis KE, O'Day DH. Phagocytic specificity during sexual development in *Dictyostelium discoideum*. Can J Microbiol 1986; 32: 79-82.
566. Lewis KE, Jamieson JC. Biochemical characterization of the phagocytic giant cell receptor for *Dictyostelium discoideum* amoebae: identification by cell blotting. Biochem Biophys Res Commun 1997; 230: 505-508.
567. Lewis S, Akgün E, Jasin M. Palindromic DNA and genome stability. Further studies. Ann NY Acad Sci 1999; 870: 45-57.
568. Lewis SM. Evolution of immunoglobulin and T-cell receptor gene assembly. Ann NY Acad Sci 1999; 870: 58-67.
569. Lewis WM. The cost of sex. EXS 1987; 55: 33-57.
570. Li G, Ho VC, Mitchell DL, Trotter MJ, Tron VA. Differentiation-dependent p53 regulation of nucleotide excision repair in keratinocytes. Am J Pathol 1997; 150: 1457-1464.
571. Li NX, Karin M. Is NF-κB the sensor of oxidative stress? FASEB J 1999; 13: 1137-1143.
572. Li PF, Dietz R, von Harsdorf R. p53 regulates mitochondrial membrane potential through reactive oxygen species and induces cytochrome c-independent apoptosis blocked by Bcl-2. EMBO J 1999; 18: 6027-6036.
573. Liang BC. Evidence for association of mitochondrial DNA sequence amplification and nuclear localization in human low-grade gliomas. Mutat Res 1996; 354: 27-33.
574. Lieber MM. Environmentally responsive mutator systems: toward a unifying perspective. Riv Biol 1998; 91: 425-457.
575. Lieber MM. Adaptively responsive hypermutation and its configurational-based regulation due to global position effect. Mutat Res 2000; 449: 57-60.
576. Lin BH, Williams-Skipp C, Tao YX, Schleicher MS, Cano LL, Duke RC, Scheinman RI. NF-κB functions as both a proapoptotic and antiapoptotic regulatory factor within a single cell type. Cell Death Differ 1999; 6: 570-582.
577. Lin JH, Weigel H, Cotrina ML, Liu S, Bueno E, Hansen AJ, Hansen TW, Goldman S, Nedergaard M. Gap-junction-mediated propagation and amplification of cell injury. Nat Neurosci 1998; 1: 494-500.
578. Lindquist S. Heat-shock proteins and stress tolerance in microorganisms. Curr Opin Genet Dev 1992; 2: 748-755.
579. Linn S. DNA damage by iron and hydrogen peroxide in vitro and in vivo. Drug Metab Rev 1998; 30: 313-326.
580. Lipinski P, Drapier JC, Oliveira L, Retmanska H, Sochanowicz B, Kruszewski M. Intracellular iron status as a hallmark of mammalian cell susceptibility to oxidative stress: a study of L5178Y mouse lymphoma cell lines differentially sensitive to H_2O_2. Blood 2000; 95: 2960-2966.
581. Little JB. Radiation carcinogenesis. Carcinogenesis 2000; 21: 397-404.
582. Liu BQ, Whisler RL. Transcriptional activation and redox regulation of the tumor necrosis factor α promoter in human T cells: role of the CRE/kappa 3 promoter region. J Interferon Cytokine Res 1998; 18: 999-1007.

583. Liu GL, Kleine L, Hebert RL. Advances in the signal transduction of ceramide and related sphingolipids. Crit Rev Clin Lab Sci 1999; 36: 511-573.
584. Liu J, Ginis T, Spatz M, Hallenbeck JM. Hypoxic preconditioning protects cultured neurons against hypoxic stress via TNF-α and ceramide. Am J Physiol 2000; 278: C144-C153.
585. Liu JK, Wang XY, Shigenaga MK, Yeo HC, Mori A, Ames BN. Immobilization stress causes oxidative damage to lipid, protein, and DNA in the brain of rats. FASEB J 1996; 10: 1532-1538.
586. Liu LI, Rapoport SI, Chandrasekaran K. Regulation of mitochondrial gene expression in differentiated PC12 cells. Ann NY Acad Sci 1999; 893: 341-344.
587. Liu SK, Tessman I. groE genes affect SOS repair in *Escherichia coli*. J Bacteriol 1990; 172: 6135-6138.
588. Liu SS. Cooperation of a "reactive oxygen cycle" with the Q cycle and the proton cycle in the respiratory chain - superoxide generating and cycling mechanisms in mitochondria. J Bioenerg Biomembrane 1999; 31: 367-376.
589. Liu TZ, Hu CC, Chen YH, Stern A, Cheng JT. Differentiation status modulates transcription factor NF-κB activity in unstimulated human hepatocellular carcinoma cell lines. Cancer Lett 2000; 151: 49-56.
590. Liu WM, Chu WM, Choudary PV, Schmid CW. Cell stress and translational inhibitors transiently increase the abundance of mammalian SINE transcripts. Nucl Acid Res 1995; 23: 1758-1765.
591. Lockshin RA, Zakeri Z, Tilly JL, eds. When Cells Die. New York: Wiley-Liss, 1998.
592. Loeb KR, Loeb LA. Significance of multiple mutations in cancer. Carcinogenesis 2000; 21: 379-385.
593. Loeb LA. Cancer cells exhibit a mutator phenotype. Adv Cancer Res 1998; 72: 25-56.
594. Loft S, Poulsen HE. Cancer risk and oxidative DNA damage in man. J Mol Med 1996; 74: 297-312.
595. Loidl J. Cytological aspects of meiotic recombination. Experientia 1994; 50: 285-294.
596. Lombardo MJ, Torkelson J, Bull HJ, McKenzie GJ, Rosenberg SM. Mechanisms of genome-wide hypermutation in stationary phase. Ann NY Acad Sci 1999; 870: 275-289.
597. Long SD, Pekala PH. Regulation of GLUT4 gene expression by arachidonic acid: evidence for multiple pathways, one of which requires oxidation to prostaglandin E_2. J Biol Chem 1996; 271: 1138-1144.
598. Loomis WF, Kuspa A, Shaulsky G. Two-component signal transduction systems in eukaryotic microorganisms. Curr Opin Microbiol 1998; 1: 643-648.
599. Lorenz MG, Wackernagel W. Bacterial gene transfer by natural genetic transformation in the environment. Microbiol Rev 1994; 58: 563-602.
600. Lorimore SA, Kadhim MA, Pocock DA, Papworth D, Stevens DL, Goodhead DT, Wright EG. Chromosomal instability in the descendants of unirradiated surviving cells after α-particle irradiation. Proc Natl Acad Sci USA 1998; 95: 5730-5733.
601. LoSchiavo F, Baldan B, Compagnin D, Ganz R, Mariani P, Terzi M. Spontaneous and induced apoptosis in embryonic cell cultures of carrot (*Daucus carota* L.) in different physiological states. Eur J Cell Biol 2000; 79: 294-298.
602. Losick R, Stragier P. Crisscross regulation of cell-type-specific gene expression during development in *B. subtilis*. Nature 1992; 355: 601-604.
603. Lotem J, Peled-Kamar M, Groner Y, Sachs L. Cellular oxidative stress and the control of apoptosis by wild-type p53, cytotoxic compounds, and cytokines. Proc Natl Acad Sci USA 1996; 93: 9166-9171.
604. Louvion JF, Abbas-Terki T, Picard D. Hsp90 is required for pheromone signaling in yeast. Mol Biol Cell 1998; 9: 3071-3083.
605. Love JM, Gudas LJ. Vitamin A, differentiation and cancer. Curr Opin Cell Biol 1994; 6: 825-831.
606. Loven DP. A role for reduced oxygen species in heat induced cell killing and the induction of thermotolerance. Med Hypotheses 1988; 26: 39-50.
607. Lowin B, Hahne M, Mattmann C, Tschopp J. Cytolytic T-cell cytotoxicity is mediated through perforin and Fas lytic pathways. Nature 1994; 370: 650-652.
608. Lozano G, Elledge SJ. p53 sends nucleotides to repair DNA. Nature 2000; 404: 24-25.
609. Luft JC, Dix DJ. Hsp70 expression and function during embryogenesis. Cell Stress Chaperones 1999; 4: 162-170.
610. Lukashev ME, Werb Z. ECM signalling: orchestrating cell behaviour and misbehaviour. Trends Cell Biol 1998; 8: 437-441.
611. Lundin LG. Gene duplications in early metazoan evolution. Semin Cell Dev Biol 1999; 10: 523-530.
612. Lunec J. Introductory review: involvement of ADP-ribosylation in cellular recovery from some forms of DNA damage. Br J Cancer 1984; Suppl 6: 13-18.
613. Lynch M, Burger R, Butcher D, Gabriel W. The mutational meltdown in asexual populations. J Hered 1993; 84: 339-344.
614. Lynch MP, Nawaz S, Gerschenson LE. Evidence for soluble factors regulating cell death and cell proliferation in primary cultures of rabbit endometrial cells grown on collagen. Proc Natl Acad Sci USA 1986; 83: 4784-4788.
615. Ma K, Schicho RN, Kelly RM, Adams MWW. Hydrogenase of the hyperthermophile *Pyrococcus furiosus* is an elemental sulfur reductase or sulfhydrogenase: evidence for a sulfur-reducing hydrogenase ancestor. Proc Natl Acad Sci USA 1993; 90: 5341-5344.
616. Ma M, Eaton JW. Multicellular oxidant defense in unicellular organisms. Proc Natl Acad Sci USA 1992; 89: 7924-7928.
617. Macario AJL, Lange M, Ahring BK, De Macario EC. Stress genes and proteins in the archaea. Microbiol Mol Biol Rev 1999; 63: 923-967.

618. MacPhee DG. Mismatch repair as a source of mutations in non-dividing cells. Genetica 1996; 97: 183-195.
619. MacPhee DG. Adaptive mutability in bacteria. J Genet 1999; 78: 29-33.
620. MacPhee DG, Ambrose M. Spontaneous mutations in bacteria: chance or necessity. Genetica 1996; 97: 87-101.
621. Madhani HD, Fink GR. The control of filamentous differentiation and virulence in fungi. Trends Cell Biol 1998; 8: 348-353.
622. Maeda S, Suzuki A, Lin KH, Inagaki H, Saito T. DNA fragmentation induced in high-cell-density culture of primary rat hepatocytes is an active process dependent on energy availability, gene expression, and calmodulin. J Biochem (Tokyo) 1995; 118: 1161-1165.
623. Maehara K, Hasegawa T, Isobe KI. A NF-κB p65 subunit is indispensable for activating manganese superoxide dismutase gene transcription mediated by tumor necrosis factor-α. J Cell Biochem 2000; 77: 474-486.
624. Magiakou MA, Mastorakos G, Rabin D, Margioris AN, Dubbert B, Calogero AE, Tsigos C, Munson PJ, Chrousos GP. The maternal hypothalamic-pituitary-adrenal axis in the 3rd trimester of human pregnancy. Clin Endocrinol 1996; 44: 419-428.
625. Mallouk Y, Vayssier-Taussat M, Bonventre JV, Polla BS. Heat shock protein 70 and ATP as partners in cell homeostasis /review/. Int J Mol Med 1999; 4: 463-474.
626. Mancini M, Anderson BO, Caldwell E, Sedghinasab M, Paty PB, Hockenbery DM. Mitochondrial proliferation and paradoxical membrane depolarization during terminal differentiation and apoptosis in a human colon carcinoma cell line. J Cell Biol 1997; 138: 449-469.
627. Mandal M, Kumar R. Bcl-2 modulates telomerase activity. J Biol Chem 1997; 272: 14183-14187.
628. Manning JT. Is sex maintained to facilitate or minimise mutational advance? Heredity (Edinburgh) 1976; 36: 351-357.
629. Mantovani B. Homeostasis perturbation (physiological stress) and the mechanism of biological evolution. The possible role of active oxygen species. J Theor Biol 1995; 176: 193-194.
630. Mantymaa P, Guttorm T, Siitonen T, Saily M, Savolainen ER, Levonen AL, Kinnula V, Koistinen P. Cellular redox state and its relationship to the inhibition of clonal cell growth and the induction of apoptosis during all-trans retinoic acid exposure in acute myeloblastic leukemia cells. Haematologica 2000; 85: 238-245.
631. Marchler G, Schuller C, Adam G, Ruis H. A *Saccharomyces cerevisiae* UAS element controlled by protein kinase A activates transcription in response to a variety of stress conditions. EMBO J 1993; 12: 1997-2003.
632. Mares D, Romagnoli C, Rubini M, Fasulo MP. Cytological characterization of a giant strain of *Euglena gracilis* obtained from dark-starved cultures. Bot Acta 1993; 106: 473-479.
633. Marini A, Matmati N, Morpurgo G. Starvation in yeast increases non-adaptive mutation. Curr Genet 1999; 35: 77-81.
634. Marnett LJ. Oxyradicals and DNA damage. Carcinogenesis 2000; 21: 361-370.
635. Martin B, Garcia P, Castanie MP, Claverys JP. The recA gene of *Streptococcus pneumoniae* is part of a competence-induced operon and controls lysogenic induction. Mol Microbiol 1995; 15: 367-379.
636. Martin RJ, Hausman GJ, Hausman DB. Regulation of adipose cell development in utero. Proc Soc Exp Biol Med 1998; 219: 200-210.
637. Martins JSS. Simulated coevolution in a mutating ecology. Phys Rev E 2000; 61: R2212-R2215.
638. Martinez-Lorenzo MJ, Alava MA, Anel A, Pineiro A, Naval J. Release of preformed Fas ligand in soluble form is the major factor for activation-induced death of Jurkat T cells. Immunology 1996; 89: 511-517.
639. Martinou I, Desagher S, Eskes R, Antonsson B, Ande E, Fakan S, Martinou JC. The release of cytochrome c from mitochondria during apoptosis of NGF-deprived sympathetic neurons is a reversible event. J Cell Biol 1999; 144: 883-889.
640. Marton A, Mihalik R, Bratincsak A, Adleff V, Petak I, Vegh M, Bauer PI, Krajcsi P. Apoptotic cell death induced by inhibitors of energy conservation - Bcl-2 inhibits apoptosis downstream of a fall of ATP level. Eur J Biochem 1997; 250: 467-475.
641. Marzulli D, La Piana G, Fransvea E, Lofrumento NE. Modulation of cytochrome c-mediated extramitrochondrial NADH oxidation by contact site density. Biochem Biophys Res Commun 1999; 259: 325-330.
642. Mathupala SP, Rempel A, Pedersen PL. Aberrant glycolytic metabolism of cancer cells: a remarkable coordination of genetic, transcriptional, post-translational, and mutational events that lead to a critical role for type II hexokinase. J Bioenerg Biomembrane 1997; 29: 339-343.
643. Matin A. The molecular basis of carbon-starvation-induced general resistance in *Escherichia coli*. Mol Microbiol 1991; 5: 3-10.
644. Matsui K, Fine A, Zhu B, Marshak-Rothstein A, Ju ST. Identification of two NF-κB sites in mouse CD95 ligand (Fas ligand) promoter: functional analysis in T cell hybridoma. J Immunol 1998; 161: 3469-3473.
645. Matsumoto A, Hong SK, Ishizuka H, Horinouchi S, Beppu T. Phosphorylation of the AfsR protein involved in secondary metabolism in *Streptomyces* species by a eukaryotic-type protein kinase. Gene 1994; 146: 47-56.
646. Matsumoto H, Wang XJ, Ohnishi T. Binding between wild-type p53 and Hsp72 accumulated after UV and γ-ray irradiation. Cancer Lett 1995; 92: 127-133.
647. Matsuoka M, Nagawa F, Okazaki K, Kingsbury L, Yoshida K, Muller U, Larue DT, Winer JA, Sakano H. Detection of somatic DNA recombination in the transgenic mouse brain. Science 1991; 254: 81-86.

648. Matsuyama SI, Maeda Y. Involvement of cyanide-resistant respiration in cell-type proportioning during *Dictyostelium* development. Dev Biol 1995; 172: 182-191.
649. Mattson MP. Calcium as sculptor and destroyer of neural circuitry. Exp Gerontol 1992; 27: 29-49.
650. Mayo MW, Baldwin AS. The transcription factor NF-κB: control of oncogenesis and cancer therapy resistance. Biochim Biophys Acta 2000; 1470: M55-M62.
651. McClintock B. The significance of responses of the genome to challenge. Science 1984; 226: 792.
652. McConkey DJ, Orrenius S. Signal transduction pathways in apoptosis. Stem Cells 1996; 14: 619-631.
653. McGarry JD, Brown NF. The mitochondrial carnitine palmitoyltransferase system. From concept to molecular analysis. Eur J Biochem 1997; 244: 1-14.
654. McGowan AJ, Ruiz-Ruiz MC, Gorman AM, Lopez-Rivas A, Cotter TG. Reactive oxygen intermediate(s) (ROI): common mediator(s) of poly(ADP-ribose) polymerase (PARP) cleavage and apoptosis. FEBS Lett 1996; 392: 299-303.
655. McIntosh L, Eichler T, Gray G, Maxwell D, Nickels R, Wang Y. Biochemical and genetic controls exerted by plant mitochondria. Biochim Biophys Acta 1998; 1365: 278-284.
656. McKenzie GJ, Harris RS, Lee PL, Rosenberg SM. The SOS response regulates adaptive mutation. Proc Natl Acad Sci USA 2000; 97: 6646-6651.
657. McLure KG, Lee PWK. p53 DNA binding can be modulated by factors that alter the conformational equilibrium. EMBO J 1999; 18: 763-770.
658. McMahon G, Alsina JL, Levy SB. Induction of Ca^{2+}, Mg^{2+}-dependent endonuclease activity during early stages of murine erythroleukemic cell differentiation. Proc Natl Acad Sci USA 1984; 81: 7461-7465.
659. Meacham GC, Browne BL, Zhang W, Kellermayer R, Bedwell DM, Cyr DM. Mutations in the yeast Hsp40 chaperone protein Ydj1 cause defects in Axl1 biogenesis and pro-a-factor processing. J Biol Chem 1999; 274: 34396-34402.
660. Medvedev ZA. On the immortality of the germ line: genetic and biochemical mechanism. A review. Mech Ageing Dev 1981; 17: 331-359.
661. Meissner M, Stark K, Cresnar B, Kirk DL, Schmitt R. *Volvox* germline-specific genes that are putative targets of RegA repression encode chloroplast proteins. Curr Genet 1999; 36: 363-370.
662. Melkonyan HS, Chang WC, Shapiro JP, Mahadevappa M, Fitzpatrick PA, Kiefer MC, Tomei LD, Umansky SR. SARPs: a family of secreted apoptosis-related proteins. Proc Natl Acad Sci USA 1997; 94: 13636-13641.
663. Mendrysa SM, Perry ME. The p53 tumor suppressor protein does not regulate expression of its own inhibitor, MDM2, except under conditions of stress. Mol Cell Biol 2000; 20: 2023-2030.
664. Menegazzi M, Suzuki H, Carcereri de Prati A, Tommasi M, Miwa M, Gandini G, Gerosa F. Increase of poly(ADP-ribose) polymerase mRNA levels during TPA-induced differentiation of human lymphocytes. FEBS Lett 1992; 297: 59-62.
665. Meneghini R. Iron homeostasis, oxidative stress, and DNA damage. Free Radical Biol Med 1997; 23: 783-792.
666. Mercurio F, Manning AM. NF-κB as a primary regulator of the stress response. Oncogene 1999; 18: 6163-6171.
667. Metcalf D, Nicola NA, Gough NM, Elliott M, McArthur G, Li M. Synergistic suppression: anomalous inhibition of the proliferation of factor-dependent hemopoietic cells by combination of two colony-stimulating factors. Proc Natl Acad Sci USA 1992; 89: 2819-2823.
668. Meyer-Siegler K, Mauro DJ, Seal G, Wurzer J, deRiel JK, Sirover MA. A human nuclear uracil DNA glycosylase is the 37-kDa subunit of glyceraldehyde-3-phosphate dehydrogenase. Proc Natl Acad Sci USA 1991; 88: 8460-8464.
669. Michiels C, Remacle J. Cytotoxicity of linoleic acid peroxide, malondialdehyde and 4-hydroxynonenal towards human fibroblasts. Toxicology 1991; 66: 225-234.
670. Miele L, Osborne B. Arbiter of differentiation and death: Notch signaling meets apoptosis. J Cell Physiol 1999; 181: 393-409.
671. Mielke K, Herdegen T. JNK and p38 stress kinases - degenerative effectors of signal transduction cascades in the nervous system. Prog Neurobiol 2000; 61: 45-60.
672. Miguelez EM, Hardisson C, Manzanal MB. Hyphal death during colony development in *Streptomyces antibioticus*: morphological evidence for the existence of a process of cell deletion in a multicellular prokaryote. J Cell Biol 1999; 145: 515-525.
673. Miho Y, Kouroku Y, Fujita E, Mukasa T, Urase K, Kasahara T, Isoai A, Momoi MY, Momoi T. BFGF inhibits the activation of caspase-3 and apoptosis of P19 embryonal carcinoma cells during neuronal differentiation. Cell Death Differ 1999; 6: 463-470.
674. Miranda S, Foncea R, Guerrero J, Leighton F. Oxidative stress and upregulation of mitochondrial biogenesis genes in mitochondrial DNA-depleted HeLa cells. Biochem Biophys Res Commun 1999; 258: 44-49.
675. Mizushima N, Noda T, Yoshimori T, Tanaka Y, Ishii T, George MD, Klionsky DJ, Ohsumi M, Ohsumi Y. A protein conjugation system essential for autophagy. Nature 1998; 395: 395-398.
676. Modrich P, Lahue R. Mismatch repair in replication fidelity, genetic recombination, and cancer biology. Annu Rev Biochem 1996; 65: 101-133.
677. Mohanty S, Firtel RA. Control of spatial patterning and cell-type proportioning in *Dictyostelium*. Semin Cell Dev Biol 1999; 10: 597-607.

678. Molica S, Mannella A, Dattilo A, Levato D, Iuliano F, Peta A, Consarino C, Magro S. Differential expression of Bcl-2 oncoprotein and Fas antigen on normal peripheral blood and leukemic bone marrow cells: a flow cytometric analysis. Haematologica 1996; 81: 302-309.
679. Molina y Vedia L, McDonald B, Reep B, Brune B, Di Silvio M, Billiar TR, Lapetina EG. Nitric oxide-induced S-nitrosylation of glyceraldehyde-3-phosphate dehydrogenase inhibits enzymatic activity and increases endogenous ADP-ribosylation. J Biol Chem 1992; 267: 24929-24932.
680. Mongold JA. DNA repair and the evolution of transformation in *Haemophilus influenzae*. Genetics 1992; 132: 893-898.
681. Moody CS, Hassan HM. Mutagenicity of oxygen free radicals. Proc Natl Acad Sci USA 1982; 79: 2855-2859.
682. Moore TDE, Edman JC. The alpha-mating type locus of *Cryptococcus neoformans* contains a peptide pheromone gene. Mol Cell Biol 1993; 13: 1962-1970.
683. Morgenegg G, Winkler GC, Hubscher U, Heizmann CW, Mous J, Kuenzle CC. Glyceraldehyde-3-phosphate dehydrogenase is a nonhistone protein and a possible activator of transcription in neurons. J Neurochem 1986; 47: 54-62.
684. Morioka K, Tone S, Mukaida M, Takano-Ohmuro H. The apoptotic and nonapoptotic nature of the terminal differentiation of erythroid cells. Exp Cell Res 1998; 240: 206-217.
685. Morowitz HJ. Energy Flow in Biology. New York: Academic Press, 1968.
686. Morris JM, Gopaul NK, Endresen MJR, Knight M, Linton EA, Dhir S, Anggard EE, Redman CWG. Circulating markers of oxidative stress are raised in normal pregnancy and pre-eclampsia. Br J Obstet Gynaecol 1998; 105: 1195-1199.
687. Morrison DA. Streptococcal competence for genetic transformation: regulation by peptide pheromones. Microb Drug Resist 1997; 3: 27-37.
688. Moshinsky DJ, Wogan GN. UV-induced mutagenesis of human p53: analysis using a double-selection method in yeast. Environ Mol Mutagen 2000; 35: 31-38.
689. Mothersill C, Seymour C. Survival of human epithelial cells irradiated with cobalt 60 as microcolonies or single cells. Int J Radiat Biol 1997; 72: 597-606.
690. Mothersill C, Seymour C. Cell-cell contact during gamma irradiation is not required to induce a bystander effect in normal human keratinocytes: evidence for release during irradiation of a signal controlling survival into the medium. Radiat Res 1998; 149: 256-262.
691. Mothersill C, Stamato TD, Perez ML, Cummins R, Mooney R, Seymour CB. Involvement of energy metabolism in the production of 'bystander effects' by radiation. Br J Cancer 2000; 82: 1740-1746.
692. Moyes CD, Mathieu-Costello OA, Tsuchiya N, Filburn C, Hansford RG. Mitochondrial biogenesis during cellular differentiation. Am J Physiol 1997; 272: C1345-C1351.
693. Msadek T. When the going gets tough: survival strategies and environmental signaling networks in *Bacillus subtilis*. Trends Microbiol 1999; 7: 201-207.
694. Mueller DM, Getz GS. Steady state analysis of mitochondrial RNA after growth of yeast *Saccharomyces cerevisiae* under catabolite repression and derepression. J Biol Chem 1986; 261: 11816-11822.
695. Murata JI, Tada M, Iggo RD, Sawamura Y, Shinohe Y, Abe H. Nitric oxide as a carcinogen: analysis by yeast functional assay of inactivating p53 mutations induced by nitric oxide. Mutat Res 1997; 379: 211-218.
696. Mustea I, Muresian T. Crabtree effect in some bacterial cultures. Cancer 1967; 20: 1499-1501.
697. Nadin BM, Mah CS, Scharff JR, Ratner AI. The regulative capacity of prespore amoebae as demonstrated by fluorescence-activated cell sorting and green fluorescent protein. Dev Biol 2000; 217: 173-178.
698. Nagata S, Golstein P. The Fas death factor. Science 1995; 267: 1449-1456.
699. Nagata S. Fas ligand-induced apoptosis. Annu Rev Genet 1999; 33: 29-55.
700. Nagy K, Pasti G, Bene L, Zs-Nagy I. Induction of granulocytic maturation in HL-60 human leukemia cells by free radicals: a hypothesis of cell differentiation involving hydroxyl radicals. Free Radical Res Commun 1993; 19: 1-15.
701. Nakano MM, Magnuson R, Myers A, Curry J, Grossman AD, Zuber P. srfA is an operon required for surfactin production, competence development, and efficient sporulation in *Bacillus subtilis*. J Bacteriol 1991; 173: 1770-1778.
702. Nakano S, Ueo H, Bruce SA, Ts'o PO. A contact-insensitive subpopulation in Syrian hamster cell cultures with a greater susceptibility to chemically induced neoplastic transformation. Proc Natl Acad Sci USA 1985; 82: 5005-5009.
703. Nakashima RA, Scott LJ, Pedersen PL. The role of mitochondrial hexokinase binding in the abnormal energy metabolism of tumor cell lines. Ann NY Acad Sci 1986; 488: 438-450.
704. Nanjundiah V, Saran S. The determination of spatial pattern in *Dictyostelium discoideum*. J Biosci 1992; 17: 353-394.
705. Nantes IL, Faljoni-Alario F, Vercesi AE, Santos KE, Bechara EJH. Liposome effect on the cytochrome c-catalyzed peroxidation of carbonyl substrates to triplet species. Free Radical Biol Med 1998; 25: 546-553.
706. Nasar F, Jankowski C, Nag DK. Long palindromic sequences induce double-strand breaks during meiosis in yeast. Mol Cell Biol 2000; 20: 3449-3458.
707. Nathan DF, Vos MH, Lindquist S. Identification of SSF1, CNS1, and HCH1 as multicopy suppressors of a *Saccharomyces cerevisiae* Hsp90 loss-of-function

mutation. Proc Natl Acad Sci USA 1999; 96: 1409-1414.
708. Nathan I, Dizdaroglu M, Bernstein L, Junker U, Lee C, Muegge K, Durum SK. Induction of oxidative DNA damage in U937 cells by TNF or anti-Fas stimulation. Cytokine 2000; 12: 881-887.
709. Nelson MA. Mating systems in ascomycetes: a romp in the sac. Trends Genet 1996; 12: 69-74.
710. Ni HT, LaPorte DC. Response of a yeast glycogen synthase gene to stress. Mol Microbiol 1995; 16: 1197-1205.
711. Ni X, Westpheling J. Direct repeat sequences in the *Streptomyces* chitinase-63 promoter direct both glucose repression and chitin induction. Proc Natl Acad Sci USA 1997; 94: 13116-13121.
712. Nicieza RG, Huergo J, Connolly BA, Sanchez J. Purification, characterization, and role of nucleases and serine proteases in *Streptomyces* differentiation. Analogies with the biochemical processes described in late steps of eukaryotic apoptosis. J Biol Chem 1999; 274: 20366-20375.
713. Nielsen KM. Barriers to horizontal gene transfer by natural transformation in soil bacteria. APMIS 1998; 106 (Suppl 84): 77-84.
714. Nilsen-Hamilton M. Transforming growth factor-β and its actions on cellular growth and differentiation. Curr Top Dev Biol 1990; 24: 95-136.
715. Ninio J. Transient mutators: a semiquantitative analysis of the influence of translation and transcription errors on mutation rates. Genetics 1991; 129: 957-962.
716. Nishikawa S, Endo T. The yeast JEM1p is a DnaJ-like protein of the endoplasmic reticulum membrane required for nuclear fusion. J Biol Chem 1997; 272: 12889-12892.
717. Nor JE, Christensen J, Mooney DJ, Polverini PJ. Vascular endothelial growth factor (VEGF)-mediated angiogenesis is associated with enhanced endothelial cell survival and induction of Bcl-2 expression. Am J Pathol 1999; 154: 375-384.
718. North S, Hainaut P. p53 and cell-cycle control. A finger in every pie. Pathol Biol 2000; 48: 255-270.
719. Northcutt RG. Ontogeny and phylogeny: a re-evaluation of conceptual relationships and some applications. Brain Behav Evol 1990; 36: 116-140.
720. Nosseri C, Coppola S, Ghibelli L. Possible involvement of poly(ADP-ribose) polymerase in triggering stress-induced apoptosis. Exp Cell Res 1994; 212: 367-373.
721. Nunoshiba T. Two-stage gene regulation of the superoxide stress response soxRS system in *Escherichia coli*. Crit Rev Eukaryot Gene Expr 1996; 6: 377-389.
722. Nyström T. To be or not to be: the ultimate decision of the growth-arrested bacterial cell. FEMS Microbiol Rev 1998; 21: 283-290.
723. Nyström T, Gustavsson N. Maintenance energy requirement: what is required for stasis survival of *Escherichia coli*? Biochim Biophys Acta 1998; 1365: 225-231.
724. Ochi K, Penyige A, Barabas G. The possible role of ADP-ribosylation in sporulation and streptomycin production by *Streptomyces griseus*. J Gen Microbiol 1992; 138: 1745-1750.
725. O'Connell J, Bennett MW, O'Sullivan GC, Collins JK, Shanahan F. The Fas counterattack: cancer as a site of immune privilege. Immunol Today 1999; 20: 46-52.
726. O'Day DH, Lewis KE. Diffusible mating-type factors induce macrocyst development in *Dictyostelium discoideum*. Nature 1975; 254: 431-432.
727. O'Day DH, Lydan MA. The regulation of membrane fusion during sexual development in *Dictyostelium discoideum*. Biochem Cell Biol 1989; 67: 321-326.
728. O'Halloran TV. Transition metals in control of gene expression. Science 1993; 261: 715-725.
729. Ohashi M, Iwase M, Nagumo M. Changes in susceptibility to Fas-mediated apoptosis during differentiation of HL-60 cells. J Leukoc Biol 2000; 67: 374-380.
730. Ohmori T, Maeda Y. The developmental fate of *Dictyostelium discoideum* cells depends greatly on the cell-cycle position at the onset of starvation. Cell Differ 1987; 22: 11-18.
731. Ohno S. The one ancestor per generation rule and three other rules of mitochondrial inheritance. Proc Natl Acad Sci USA 1997; 94: 8033-8035.
732. Ohsako S, Bunick D, Hayashi Y. Immunocytochemical observation of the 90-kD heat shock protein (HSP90): high expression in primordial and pre-meiotic germ cells of male and female rat gonads. J Histochem Cytochem 1995; 43: 67-76.
733. Ohsumi Y. Molecular mechanism of autophagy in yeast, *Saccharomyces cerevisiae*. Philos Trans Roy Soc Lond B 1999; 354: 1577-1580.
734. Ohsumi Y, Anraku Y. Specific induction of Ca^{2+} transport activity in MATa cells of *Saccharomyces cerevisiae* by a mating pheromone, alpha factor. J Biol Chem 1985; 260: 10482-10486.
735. Ohtsuki T, Matsumoto M, Kuwabara K, Kitagawa K, Suzuki K, Taniguchi N, Kamada T. Influence of oxidative stress on induced tolerance to ischemia in gerbil hippocampal neurons. Brain Res 1992; 599: 246-252.
736. Okazaki N, Okazaki K, Watanabe Y, Kato-Hayashi M, Yamamoto M, Okayama H. Novel factor highly conserved among eukaryotes controls sexual development in fission yeast. Mol Cell Biol 1998; 18: 887-895.
737. Oleinick NL, Balasubramaniam U, Xue L, Chiu S. Nuclear structure and the microdistribution of radiation damage in DNA. Int J Radiat Biol 1994; 66: 523-529.
738. Oleskin AV, Botvinko IV, Tsavkelova EA. Colonial organization and intercellular communication in microorganisms. Microbiology 2000; 69: 249-265.
739. Oliver FJ, de la Rubia G, Rolli V, Ruiz-Ruiz MC, de Murcia G, Murcia JM. Importance of poly(ADP-ribose) polymerase and its cleavage in apoptosis. Lesson from an uncleavable mutant. J Biol Chem 1998; 273: 33533-33539.

740. Omichinski JG, Trainor C, Evans T, Gronenborn AM, Clore GM, Felsenfeld G. A small single-"finger" peptide from the erythroid transcription facor GATA-1 binds specifically to DNA as a zinc or iron complex. Proc Natl Acad Sci USA 1993; 90: 1676-1680.
741. Oohata AA. Factors controlling prespore cell differentiation in *Dictyostelium discoideum*: minute amounts of differentiation-inducing factor promote prespore cell differentiation. Differentiation 1995; 59: 283-288.
742. Ooi K, Yahara T. Genetic variation of geminiviruses: comparison between sexual and asexual host plant populations. Mol Ecol 1999; 8: 89-97.
743. Orrenius S, Burkitt MJ, Kass GE, Dypbukt JM, Nicotera P. Calcium ions and oxidative cell injury. Ann Neurol 1992; 32 (Suppl): S33-S42.
744. Ota T, Hanada K, Hashimoto I. The effect of cold stress on UVB injury in mouse skin and cultured keratinocytes. Photochem Photobiol 1996; 64: 984-987.
745. O'Toole GA, Gibbs KA, Hager PW, Phibbs PV Jr, Kolter R. The global carbon metabolism regulator Crc is a component of a signal transduction pathway required for biofilm development by *Pseudomonas aeruginosa*. J Bacteriol 2000; 182: 425-431.
746. Pagie L, Hogeweg P. Colicin diversity: a result of eco-evolutionary dynamics. J Theor Biol 1999; 196: 251-261.
747. Paidhungat M, Garrett S. A homolog of mammalian, voltage-gated calcium channels mediates yeast pheromone-stimulated Ca^{2+} uptake and exacerbates the cdc1(Ts) growth defect. Mol Cell Biol 1997; 17: 6339-6347.
748. Pancholi V, Fischetti VA. Glyceraldehyde-3-phosphate dehydrogenase on the surface of group A streptococci is also an ADP-ribosylating enzyme. Proc Natl Acad Sci USA 1993; 90: 8154-8158.
749. Pandey P, Nakazawa A, Ito Y, Datta R, Kharbanda S, Kufe D. Requirement for caspase activation in monocytic differentiation of myeloid leukemia cells. Oncogene 2000; 19: 3941-3947.
750. Pantopoulos K, Hentze MW. Rapid responses to oxidative stress mediated by iron regulatory protein. EMBO J 1995; 14: 2917-2924.
751. Papadopoulos D, Schneider D, Meier-Eiss J, Arber W, Lenski RE, Blot M. Genomic evolution during a 10,000-generation experiment with bacteria. Proc Natl Acad Sci USA 1999; 96: 3807-3812.
752. Paquin C, Adams J. Frequency of fixation of adaptive mutations is higher in evolving diploid than haploid yeast populations. Nature 1983; 302: 495-500.
753. Paradis E, Douillard H, Koutroumanis M, Goodyer C, LeBlanc A. Amyloid β peptide of Alzheimer's disease downregulates bcl-2 and upregulates bax expression in human neurons. J Neurosci 1996; 16: 7533-7539.
754. Parchment RE. The implications of a unified theory of programmed cell death, polyamines, oxyradicals and histogenesis in the embryo. Int J Dev Biol 1993; 37: 75-83.
755. Parikh VS, Morgan MM, Scott R, Clements LS, Butow RA. The mitochondrial genotype can influence nuclear gene expression in yeast. Science 1987; 235: 576-580.
756. Parks D, Bolinger R, Mann K. Redox state regulates binding of p53 to sequence-specific DNA, but not to non-specific or mismatched DNA. Nucl Acid Res 1997; 25: 1289-1295.
757. Parro V, Mellado RP. Effect of glucose on agarase overproduction by *Streptomyces*. Gene 1994; 145: 49-55.
758. Parsons PA. Stress-resistance genotypes, metabolic efficiency and interpreting evolutionary change. EXS 1997; 83: 291-305.
759. Partridge L, Hurst LD. Sex and conflict. Science 1998; 281: 2003-2008.
760. Pattus F, Massotte D, Wilmsen HU, Lakey J, Tsernoglou D, Tucker A, Parker MW. Colicins: prokaryotic killer-pores. Experientia 1990; 46: 180-192.
761. Paul A, Wilson S, Belham CM, Robinson CJM, Scott PH, Gould GW, Plevin R. Stress-activated protein kinases: activation, regulation and function. Cell Signal 1997; 9: 403-410.
762. Paumen MB, Ishida Y, Muramatsu M, Yamamoto M, Honjo T. Inhibition of carnitine palmitoyltransferase I augments sphingolipid synthesis and palmitate-induced apoptosis. J Biol Chem 1997; 272: 3324-3329.
763. Peacock JW, Benchimol S. Mutation of the endogenous p53 gene in cell transformed by HPV-16 E7 and EJ c-ras confers a growth advantage involving an autocrine mechanism. EMBO J 1994; 13: 1084-1092.
764. Pecci L, Montefoschi G, Cavallini D. Some new details of the copper-hydrogen peroxide interaction. Biochem Biophys Res Commun 1997; 235: 264-267.
765. Peck JR. A ruby in the rubbish: beneficial mutations, deleterious mutations and the evolution of sex. Genetics 1994; 137: 597-606.
766. Peck JR, Barreau G, Heath SC. Imperfect genes, Fisherian mutation and the evolution of sex. Genetics 1997; 145: 1171-1199.
767. Peitsch MC, Müller C, Tschopp J. DNA fragmentation during apoptosis is caused by frequent single-strand cuts. Nucl Acid Res 1993; 21: 4206-4209.
768. Peluso JJ. Putative mechanism through which N-cadherin-mediated cell contact maintains calcium homeostasis and thereby prevents ovarian cells from undergoing apoptosis. Biochem Pharmacol 1997; 54: 847-853.
769. Pennisi E. A genomic battle of the sexes. Science 1998; 281: 1984-1985.
770. Perry EK, Piggott MA, Court JA, Johnson M, Perry RH. Transmitters in the developing and senescent human brain. Ann NY Acad Sci 1993; 695: 69-72.
771. Peruski LF Jr. Expression of heat shock protein D48.5 of *Escherichia coli* is subject to modulation by catabolite repression. Microbiol Res 1996; 151: 273-280.
772. Peterkofsky A. Cyclic nucleotides in bacteria. Adv Cyclic Nucleotide Res 1976; 7: 1-48.

773. Peters J, Jagger J. Inducible repair of near-UV radiation lethal damage in *E. coli*. Nature 1981; 289: 194-195.
774. Peterson SL, Stevenson PM. Changes in catalase activity and concentration during ovarian development and differentiation. Biochim Biophys Acta 1992; 1135: 207-214.
775. Petit MA, Bedale W, Osipiuk J, Lu C, Rajagopalan M, McInerney P, Goodman MF, Echols H. Sequential folding of UmuC by the Hsp70 and Hsp60 chaperone complexes of *Escherichia coli*. J Biol Chem 1994; 269: 23824-23829
776. Pfeifer GP, Holmquist GP. Mutagenesis in the p53 gene. Biochim Biophys Acta 1997; 1333: M1-M8.
777. Pieper AA, Verma A, Zhang J, Snyder SH. Poly(ADP-ribose) polymerase, nitric oxide and cell death. Trends Pharmacol Sci 1999; 20: 171-181.
778. Pierce GB, Lewellyn AL, Parchment RE. Mechanism of programmed cell death in the blastocyst. Proc Natl Acad Sci USA 1989; 86: 3654-3658.
779. Pierre JL, Fontecave M. Iron and activated oxygen species in biology: the basic chemistry. Biometals 1999; 12: 195-199.
780. Pinkoski MJ, Brunner T, Green DR, Lin T. Fas and Fas ligand in gut and liver. Am J Physiol 2000; 278: G354-G366.
781. Pinter E, Reece EA, Leranth CZ, Sanyal MK, Hobbins JC, Mahoney MJ, Naftolin F. Yolk sac failure in embryopathy due to hyperglycemia: ultrastructural analysis of yolk sac differentiation associated with embryopathy in rat conceptuses under hyperglycemic conditions. Teratology 1986; 33: 73-84.
782. Piper PW. Molecular events associated with acquisition of heat tolerance by the yeast *Saccharomyces cerevisiae*. FEMS Microbiol Rev 1993; 11: 339-355.
783. Poccia F, Piselli P, Vendetti S, Bach S, Amendola A, Placido R, Colizzi V. Heat shock protein expression on the membrane of T cells undergoing apoptosis. Immunology 1996; 88: 6-12.
784. Podack ER. How to induce involuntary suicide: the need for dipeptidyl peptidase I. Proc Natl Acad Sci USA 1999; 96: 8312-8314.
785. Poltronieri P, Yokota T, Koyama Y, Hanai S, Uchida K, Miwa M. PARP cleavage in the apoptotic pathway in S2 cells from *Drosophila melanogaster*. Biochem Cell Biol 1997; 75: 445-449.
786. Polyak K, Li Y, Zhu H, Lengauer C, Willson JK, Markowitz SD, Trush MA, Kinzler KW, Vogelstein B. Somatic mutations of the mitochondrial genome in human colorectal tumours. Nat Genet 1998; 20: 291-293.
787. Pope MK, Green B, Westpheling J. The bldB gene encodes a small protein required for morphogenesis, antibiotic production, and catabolite control in *Streptomyces coelicolor*. J Bacteriol 1998; 180: 1556-1562.
788. Pope MK, Green BD, Westpheling J. The bld mutants of *Streptomyces coelicolor* are defective in the regulation of carbon utilization, morphogenesis and cell-cell signalling. Mol Microbiol 1996; 19: 747-756.
789. Porter AG. Protein translocation in apoptosis. Trends Cell Biol 1999; 9: 394-401.
790. Poynter ME, Daynes RA. Peroxisome proliferator-activated receptor α activation modulates cellular redox status, represses nuclear factor κB signaling, and reduces inflammatory cytokine production in aging. J Biol Chem 1998; 273: 32833-32841.
791. Poyton RO, McEwen JE. Crosstalk between nuclear and mitochondrial genomes. Annu Rev Biochem 1996; 65: 563-607.
792. Prapong T, Hsu W, Martens C, Uemura E. The effect of β-amyloid on cyclic AMP and glucose uptake by cultured hippocampal neurons. Soc Neurosci Abstr 1998; 24: 1458.
793. Print CG, Loveland KL. Germ cell suicide: new insights into apoptosis during spermatogenesis. Bioessays 2000; 22: 423-430.
794. Quarmby LM. Signal transduction in the sexual life of *Chlamydomonas*. Plant Mol Biol 1994; 26: 1271-1287.
795. Quesada P, Atorino L, Cardone A, Ciarcia G, Farina B. Poly(ADP-ribosyl)ation system in rat germinal cells at different stages of differentiation. Exp Cell Res 1996; 226: 183-190.
796. Quillet-Mary A, Jaffrezou JP, Mansat V, Bordier C, Naval J, Laurent G. Implication of mitochondrial hydrogen peroxide generation in ceramide-induced apoptosis. J Biol Chem 1997; 272: 21388-21395.
797. Rabin BS. Stress, Immune Function, and Health: The Connection. New York: Wiley-Liss & Sons, 1999.
798. Radicella JP, Park PU, Fox MS. Adaptive mutation in *Escherichia coli*: a role for conjugation. Science 1995; 268: 418-420.
799. Radman M, Matic I, Halliday JA, Taddei F. Editing DNA replication and recombination by mismatch repair: from bacterial genetics to mechanisms of predisposition to cancer in humans. Philos Trans Roy Soc Lond B 1995; 347: 97-103.
800. Radman M, Matic I, Taddei F. Evolution of evolvability. Ann NY Acad Sci 1999; 870: 146-155.
801. Raff MC. Social controls on cell survival and cell death. Nature 1992; 356: 397-400.
802. Raff M. Cell suicide for beginners. Nature 1998; 396: 119-122.
803. Ragg SJ, Kaga S, Berg KA, Ochi A. The mitogen-activated protein kinase pathway inhibits ceramide-induced terminal differentiation of a human monoblastic leukemia cell line, U937. J Immunol 1998; 161: 13390-1398.
804. Rahman MS, Humayun MZ. SOS and UVM pathways have lesion-specific additive and competing effects on mutation fixation at replication-blocking DNA lesions. J Bacteriol 1999; 181: 1515-1523.
805. Ramana CV, Boldogh I, Izumi T, Mitra S. Activation of apurinic/apyrimidinic endonuclease in human cells by reactive oxygen species and its correlation with their

adaptive response to genotoxicity of free radicals. Proc Natl Acad Sci USA 1998; 95: 5061-5066.
806. Ramenghi U, Bonissoni S, Migliaretti G, DeFranco S, Bottarel F, Gambaruto C, DiFranco D, Priori R, Conti F, Dianzani I, Valesini G, Merletti F, Dianzani U. Deficiency of the Fas apoptosis pathway without Fas gene mutations is a familial trait predisposing to development of autoimmune diseases and cancer. Blood 2000; 95: 3176-3182.
807. Ramirez CD, Sleiman RJ, Catchpoole DR, Stewart BW. Morphological and molecular evidence of differentiation during etoposide-induced apoptosis in human lymphoblastoid cells. Cell Death Differ 2000; 7: 548-555.
808. Ranade N, Vining LC. Accumulation of intracellular carbon reserves in relation to chloramphenicol biosynthesis by *Streptomyces venezuelae*. Can J Microbiol 1993; 39: 377-383.
809. Randle PJ. Regulatory interactions between lipids and carbohydrates: the glucose fatty acid cycle after 35 years. Diabetes Metab Rev 1998; 14: 263-283.
810. Raoul C, Pettmann B, Henderson CE. Active killing of neurons during development and following stress: a role for $p75^{NTR}$ and Fas? Curr Opin Neurobiol 2000; 10: 111-117.
811. Rasco JF, Hood RD. Enhancement of the teratogenicity of all-trans-retinoic acid by maternal restraint stress in mice as a function of treatment timing. Teratology 1995; 51: 63-70.
812. Rath PC, Aggarwal BB. TNF-induced signaling in apoptosis. J Clin Immunol 1999; 19: 350-364.
813. Rauth S, Kichina J, Green A. Inhibition of growth and induction of differentiation of metastatic melanoma cells in vitro by genistein: chemosensitivity is regulated by cellular p53. Br J Cancer 1997; 75: 1559-1566.
814. Ravati A, Ahlemeyer B, Becker A, Krieglstein J. Preconditioning-induced neuroprotection is mediated by reactive oxygen species. Brain Res 2000; 866: 23-32.
815. Ravi R, Bedi A, Fuchs EJ, Bedi A. CD95 (Fas)-induced caspase-mediated proteolysis of NF-κB. Cancer Res 1998; 58: 882-886.
816. Redfield RJ. Evolution of bacterial transformation: is sex with dead cells ever better than no sex at all? Genetics 1988; 119: 213-221.
817. Redfield RJ. Male mutation rates and the cost of sex for females. Nature 1994; 369: 145-147.
818. Redfield RJ, Schrag MR, Dean AM. The evolution of bacterial transformation: sex with poor relations. Genetics 1997; 146: 27-38.
819. Reed JC. Bcl-2 and the regulation of programmed cell death. J Cell Biol 1994; 24: 1-6.
820. Reed JC. Bcl-2 family proteins and the hormonal control of cell life and death in normalcy and neoplasia. Vitam Horm 1997; 53: 99-138.
821. Reed JC. Dysregulation of apoptosis in cancer. J Clin Oncol 1999; 17: 2941-2953.
822. Remacle J, Raes M, Toussaint O, Renard P, Rao G. Low levels of reactive oxygen species as modulators of cell function. Mutat Res 1995; 316: 103-122.
823. Ren JG, Zheng RL, Shi YM, Gong B, Li JF. Apoptosis, redifferentiation and arresting proliferation simultaneously triggered by oxidative stress in human hepatoma cells. Cell Biol Int 1998; 22: 41-49.
824. Renault E, Sarrazin S, Deschatrette J. Evidence for interactions between rat hepatoma cell apoptosis and differentiation. Biochem Genet 1998; 36: 1-13.
825. Reynier P, Chretien MF, Savagner F, Larcher G, Rohmer V, Barriere P, Malthiery Y. Long PCR analysis of human gamete mtDNA suggests defective mitochondrial maintenance in spermatozoa and supports the bottleneck theory for oocytes. Biochem Biophys Res Commun 1998; 252: 373-377.
826. Reza Fazeli M, Cove JH, Baumberg S. Physiological factors affecting streptomycin production by *Streptomyces griseus* ATCC 12475 in batch and continuous culture. FEMS Microbiol Lett 1995; 126: 55-61.
827. Ricca A, Biroccio A, Del Bufalo D, Mackay AR, Santoni A, Cippitelli M. bcl-2 over-expression enhances NF-κB activity and induces mmp-9 transcription in human MCF7(ADR) breast-cancer cells. Int J Cancer 2000; 86: 188-196.
828. Rice SA, Oliver JD. Starvation response of the marine barophile CNPT-3. Appl Environ Microbiol 1992; 58: 2432-2437.
829. Rice WR. Male fitness increases when females are eliminated from gene pool: implications for the Y chromosome. Proc Natl Acad Sci USA 1998; 95: 6217-6221.
830. Richards B, Zhang H, Phear G, Meuth M. Conditional mutator phenotypes in hMSH2-deficient tumor cell lines. Science 1997; 277: 1523-1526.
831. Richter C, Schweizer M, Cossarizza A, Franceschi C. Control of apoptosis by the cellular ATP level. FEBS Lett 1996; 378: 107-110.
832. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation. Nature 1998; 391: 79-82.
833. Ridley M. Evolution. Cambridge, MA: Blackwell Science, 1996.
834. Rigobello MP, Scutari G, Friso A, Barzon E, Artusi S, Bindoli A. Mitochondrial permeability transition and release of cytochrome c induced by retinoic acids. Biochem Pharmacol 1999; 58: 665-670.
835. Riley MA. Molecular mechanisms of bacteriocin evolution. Annu Rev Genet 1998; 32: 255-278.
836. Rink H, Partke HJ. Giant cells from *Saccharomyces uvarum* grown after X-irradiation. Radiat Environ Biophys 1975; 12: 119-125.
837. Ripley LS. Predictability of mutant sequences. Relationships between mutational mechanisms and mutant specificity. Ann NY Acad Sci 1999; 870: 159-172.

838. Rispe C, Pierre JS. Coexistence between cyclical parthenogens, obligate parthenogens, and intermediates in a fluctuating environment. J Theor Biol 1998; 195: 97-110.
839. Rivedal E, Mikaisen S, Sanner T. Morphological transformation and effect on gap junction intercellular communication in Syrian hamster embryo cells as screening test for carcinogens devoid of mutagenic activity. Toxicol Vitro 2000; 14: 185-192.
840. Robertson KA, Hill DP, Xu Y, Liu L, Van Epps S, Hockenbery DM, Park JR, Wilson TM, Kelley MR. Down-regulation of apurinic/apyrimidinic endonuclease expression is associated with the induction of apoptosis in differentiating myeloid leukemia cells. Cell Growth Differ 1997; 8: 443-449.
841. Robson AJ, Bergstrom CT, Pritchard JK. Risky business: sexual and asexual reproduction in variable environments. J Theor Biol 1999; 197: 541-556.
842. Rochard P, Cassar-Malek I, Marchal S, Wrutniak C, Cabello G. Changes in mitochondrial activity during avian myoblast differentiation: influence of triiodothyronine or v-erb A expression. J Cell Physiol 1996; 168: 239-347.
843. Roche E, Prentki M. Calcium regulation of immediate-early response genes. Cell Calcium 1994; 16: 331-338.
844. Rock FL, Hardiman G, Timans JC, Kastelein RA, Bazan JF. A family of human receptors structurally related to *Drosophila* Toll. Proc Natl Acad Sci USA 1998; 95: 588-593.
845. Rockabrand D, Livers K, Austin T, Kaiser R, Jensen D, Burgess R, Blum P. Roles of DnaK and RpoS in starvation-induced thermotolerance of *Escherichia coli*. J Bacteriol 1998; 180: 846-854.
846. Rodriguez-Zaragoza S. Ecology of free-living amebas. Crit Rev Microbiol 1994; 20: 225-241.
847. Roemer K. Mutant p53: gain-of-function oncoproteins and wild-type p53 inactivators. Biol Chem 1999; 380: 879-887.
848. Rogers MB. Life-and-death decisions influenced by retinoids. Curr Top Dev Biol 1997; 35: 1-46.
849. Romslo I. Energy-dependent accumulation of iron by isolated rat liver mitochondria. IV. Relationship to the energy state of the mitochondria. Biochim Biophys Acta 1975; 387: 69-79.
850. Ronai Z. Glycolytic enzymes as DNA binding proteins. Int J Biochem 1993; 25: 1073-1076.
851. Rong P, Bennie AM, Epa WR, Barrett GL. Nerve growth factor determines survival and death of PC12 cells by regulation of the bcl-x, bax, and caspase-3 genes. J Neurochem 1999; 72: 2294-2300.
852. Rose ML, Rivera CA, Bradford BU, Graves LM, Cattley RC, Schoonhoven R, Swenberg JA, Thurman RG. Kupffer cell oxidant production is central to the mechanism of peroxisome proliferators. Carcinogenesis 1999; 20: 27-33.
853. Rosenzweig RF, Sharp RR, Treves DS, Adams J. Microbial evolution in a simple unstructured environment: genetic differentiation in *Escherichia coli*. Genetics 1994; 137: 903-917.
854. Ruiz T, Villanueva JR, Rodriguez L. Influence of carbon catabolite repression on the G1 arrest of *Saccharomyces cerevisiae* MATa cells by alpha factor. J Gen Microbiol 1984; 130: 337-342.
855. Ruiz-Gines JA, Lopez-Ongil S, Gonzalez-Rubio M, Gonzalez-Santiago L, Rodriguez-Puyol M, Rodriguez-Puyol D. Reactive oxygen species induce proliferation of bovine aortic endothelial cells. J Cardiovasc Pharmacol 2000; 35: 109-113.
856. Ryan KM, Ernst MK, Rice NR, Vousden KH. Role of NF-κB in p53-mediated programmed cell death. Nature 2000; 404: 892-897.
857. Sabapathy K, Klemm M, Jaenisch R, Wagner EF. Regulation of ES cell differentiation by functional and conformational modulation of p53. EMBO J 1997; 16: 6217-6229.
858. Saeki K, Yuo A, Kato M, Miyazono K, Yazaki Y, Takaku F. Cell density-dependent apoptosis in HL-60 cells, which is mediated by an unknown soluble factor, is inhibited by transforming growth factor beta 1 and overexpression of bcl-2. J Biol Chem 1997; 272: 20003-20010.
859. Saga Y, Yanagisawa K. Macrocyst development in *Dictyostelium discoideum*. 1. Induction of synchronous development by giant cells and biochemical analysis. J Cell Sci 1982; 55: 341-352.
860. Sahu SC. Oncogenes, oncogenesis, and oxygen radicals. Biomed Environ Sci 2000; 3: 183-201.
861. Sakahira H, Enari M, Nagata S. Cleavage of CAD inhibitor in CAD activation and DNA degradation during apoptosis. Nature 1998; 391: 96-99.
862. Sakurai H, Miyoshi H, Toriumi W, Sugita T. Functional interactions of transforming growth factor β-activated kinase 1 with IκB kinases to stimulate NF-κB activation. J Biol Chem 1999; 274: 10641-10648.
863. Salles B, Weinstock GM. Mutation of the promoter and LexA binding sites of cea, the gene encoding colicin E1. Mol Gen Genet 1989; 215: 483-489.
864. Salvioli S, Dobrucki J, Moretti L, Troiano L, Fernandez MG, Pinti M, Pedrazzi J, Franceschi C, Cossarizza A. Mitochondrial heterogeneity during staurosporine-induced apoptosis in HL60 cells: analysis at the single cell and single organelle level. Cytometry 2000; 40: 189-197.
865. Samejima K, Villa P, Earnshaw WC. Role of factors downstream of caspases on nuclear disassembly during apoptotic execution. Philos Trans Roy Soc Lond B 1999; 354: 1591-1598.
866. Samejima Y, Meruelo D. Bystander killing induces apoptosis and is inhibited by forskolin. Gene Ther 1995; 2: 50-58.
867. Sanchez Y, Lindquist SL. HSP104 required for induced thermotolerance. Science 1990; 248: 1112-1115.

868. Sandau KB, Brune B. Up-regulation of Bcl-2 by redox signals in glomerular mesangial cells. Cell Death Differ 2000; 7: 118-125.
869. Sandhu JK, Birnboim HC. Mutagenicity and cytotoxicity of reactive oxygen and nitrogen species in the MN-11 murine tumor cell line. Mutat Res 1997; 379: 241-252.
870. Sandona D, Gastaldello S, Rizzuto R, Bisson R. Expression of cytochrome c oxidase during growth and development of *Dictyostelium*. J Biol Chem 1995; 270: 5587-5593.
871. Sarge KD. Male germ cell-specific alteration in temperature set-point of the cellular stress response. J Biol Chem 1995; 270: 18745-18748.
872. Sassone-Corsi P. CREM: a master-switch governing male germ cell differentiation and apoptosis. Semin Cell Dev Biol 1998; 9: 475-482.
873. Satoh MS, Lindahl T. Role of poly(ADP-ribose) formation in DNA repair. Nature 1992; 356: 356-358.
874. Savickiene J, Gineitis A, Stigbrand T. Modulation of apoptosis of proliferating and differentiating HL-60 cells by protein kinase inhibitors: suppression of PKC or PKA differently affects cell differentiation and apoptosis. Cell Death Differ 1999; 6: 698-709.
875. Sawa A, Khan AA, Hester LD, Snyder SH. Glyceraldehyde-3-phosphate dehydrogenase: nuclear translocation participates in neuronal and nonneuronal death. Proc Natl Acad Sei USA 1997; 94: 11669-11674.
876. Saxena M, Williams S, Tasken K, Mustelin T. Crosstalk between cAMP-dependent kinase and MAP kinase through a protein tyrosine phosphatase. Nat Cell Biol 1999; 1: 305-311.
877. Scarpulla RC. Nuclear control of respiratory chain expression in mammalian cells. J Bioenerg Biomembrane 1997; 29: 109-119.
878. Schaap P, Nebl T, Fisher PR. A slow sustained increase in cytosolic Ca^{2+} levels mediates stalk gene induction by differentiation-inducing factor in *Dictyostelium*. EMBO J 1996; 15: 5177-5183.
879. Scheffler IE. Mitochondria. New York: Wiley-Liss, 1999.
880. Scheffler IE, de la Cruz BJ, Prieto S. Control of mRNA turnover as a mechanism of glucose repression in *Saccharomyces cerevisiae*. Int J Biochem Cell Biol 1998; 30: 1175-1193.
881. Schelling JR, Nkemere N, Kopp JB, Cleveland RP. Fas-dependent fratricidal apoptosis is a mechanism of tubular epithelial cell deletion in chronic renal failure. Lab Invest 1998; 78: 813-824.
882. Schett G, Steiner CW, Groger M, Winkler S, Graninger W, Smolen J, Xu QB, Steiner G. Activation of Fas inhibits heat-induced activation of HSF1 and up-regulation of hsp70. FASEB J 1999; 13: 833-842.
883. Schierwater B, Hadrys H. Environmental factors and mutagenesis in the hydroid *Eleutheria dichotoma*. Invert Reprod Dev 1998; 34: 139-148.
884. Schmalhausen EV, Muronetz VI. An uncoupling of the processes of oxidation and phosphorylation in glycolysis. Biosci Rep 1997; 17: 521-527.
885. Schmidt H, Grune T, Müller R, Siems WG, Wauer RR. Increased levels of lipid peroxidation products malondialdehyde and 4-hydroxynonenal after perinatal hypoxia. Pediatr Res 1996; 40: 15-20.
886. Schopf JW. Disparate rates, differing fates: tempo and mode of evolution changed from the Precambrian to the Phanerozoic. Proc Natl Acad Sci USA 1994; 91: 6735-6742.
887. Schraufstatter IU, Hyslop PA, Hinshaw DB, Spragg RG, Sklar LA, Cochrane CG. Hydrogen peroxide-induced injury of cells and its prevention by inhibitors of poly(ADP-ribose) polymerase. Proc Natl Acad Sci USA 1986; 83: 4908-4912.
888. Schroeder S, Bischoff J, Lehmann LE, Hering R, von Spiegel T, Putensen C, Hoeft A, Stuber F. Endotoxin inhibits heat shock protein 70 (HSP70) expression in peripheral blood mononuclear cells of patients with severe sepsis. Intens Care Med 1999; 25: 52-57.
889. Schulte-Hermann R, Grasl-Kraupp B, Bursch W. Dose-response and threshold effects in cytotoxicity and apoptosis. Mutat Res 2000; 464: 13-18.
890. Schulze-Osthoff K, Walczak H, Droge W, Krammer PH. Cell nucleus and DNA fragmentation are not required for apoptosis. J Cell Biol 1994; 127: 15-20.
891. Schwaegerle KE, McIntyre H, Swingley C. Quantitative genetics and the persistence of environmental effects in clonally propagated organisms. Evolution 2000; 54: 452-461.
892. Schwartz D, Goldfinger N, Kam Z, Rotter V. p53 controls low DNA damage-dependent premeiotic checkpoint and facilitates DNA repair during spermatogenesis. Cell Growth Differ 1999; 10: 665-675.
893. Schwartz JL, Rotmensch J, Giovanazzi S, Cohen MB, Weichselbaum RR. Faster repair of DNA double-strand breaks in radioresistant human tumor cells. Int J Radiat Oncol Biol Phys 1988; 15: 907-912.
894. Schwartz JL, Jordan R, Sedita BA, Swenningson MJ, Banath JP, Olive PL. Different sensitivity to cell killing and chromosome mutation-induction by gamma-rays in 2 human lymphoblastoid cell lines derived from a single donor: possible role of apoptosis. Mutagenesis 1995; 10: 227-233.
895. Schwartz MW, Baskin DG, Kaiyala KJ, Woods SC. Model for the regulation of energy balance and adiposity by the central nervous system. Am J Clin Nutr 1999; 69: 584-596.
896. Schwertner HA, Torres L, Jackson WG, Maldonado HA, Whitson JD, Troxler RG. Cortisol and the hypercholesterolemia of pregnancy and labor. Atherosclerosis 1987; 67: 237-244.
897. Scott RE, Estervig DN, Tzen CY, Minoo P, Maercklein PB, Hoerl BJ. Nonterminal differentiation represses the neoplastic phenotype in spontaneously and simian virus

40-transformed cells. Proc Natl Acad Sci USA 1989; 86: 1652-1656.
898. Seetharam S, Seidman MM. Modulation of ultraviolet light mutational hotspots by cellular stress. J Mol Biol 1992; 228: 1031-1036.
899. Selye H. The Stress of Life. Revised edition. New York: McGraw Hill Book Co., 1975.
900. Seul KH, Tadros PN, Beyer EC. Mouse connexin40: gene structure and promoter analysis. Genomics 1997; 46: 120-126.
901. Seymour CB, Mothersill C. Delayed expression of lethal mutations and genomic instability in the progeny of human epithelial cells that survived in a bystander-killing environment. Radiat Oncol Invest 1997; 5: 106-110.
902. Shall S. The function of poly(ADP-ribosylation) in DNA breakage and rejoining. Mol Cell Biochem 1994; 138: 71-75.
903. Shapiro IM, Debolt K, Hatori M, Iwamoto M, Pacifici M. Retinoic acid induces a shift in the energetic state of hypertrophic chondrocytes. J Bone Miner Res 1994; 9: 1229-1237.
904. Shapiro JA, Dworkin M, eds. Bacteria as Multicellular Organisms. New York: Oxford University Press, 1997.
905. Sharma N, Fitt PS. Induction of error-free DNA repair in *Escherichia coli* by thiamine deprivation. Mutat Res 1990; 243: 165-171.
906. Shaulsky G, Loomis WF. Cell type regulation in response to expression of ricin A in *Dictyostelium*. Dev Biol 1993; 160: 85-98.
907. Shaulsky G, Loomis WF. Mitochondrial DNA replication but no nuclear DNA replication during development of *Dictyostelium*. Proc Natl Acad Sci USA 1995; 92: 5660-5663.
908. Shay JW, Werbin H. New evidence for the insertion of mitochondrial DNA into the human genome: significance for cancer and aging. Mutat Res 1992; 275: 227-235.
909. Shen HM, Chia SE, Ong CN. Evaluation of oxidative DNA damage in human sperm and its association with male infertility. J Androl 1999; 20: 718-723.
910. Shikazono N, Watanabe H, Tanaka A, Tano S, Tsutsumi N, Hirai A. Reduced rejoining ability of DNA strand breaks with differentiation in barley root cells. Mutat Res 1995; 337: 41-48.
911. Shikone T, Billig H, Hsueh AJW. Experimentally-induced cryptorchidism increases apoptosis in rat testis. Biol Reprod 1994; 51: 865-872.
912. Shimazaki K, Ishida A, Kawai N. Increase in bcl-2 oncoprotein and the tolerance to ischemia-induced neuronal death in the gerbil hippocampus. Neurosci Res 1994; 20: 95-99.
913. Shimkets LJ. Social and developmental biology of the myxobacteria. Microbiol Rev 1990; 54: 473-501.
914. Shiinmin LC, Chang BH, Li WH. Male-driven evolution of DNA sequences. Nature 1993; 362: 745-747.
915. Shinohara Y, Sagawa I, Ichihara J, Yamamoto K, Terao K, Terada H. Source of ATP for hexokinase-catalyzed glucose phosphorylation in tumor cells: dependence on the rate of oxidative phosphorylation relative to that of extramitochondrial ATP generation. Biochim Biophys Acta 19997; 1319: 319-330.
916. Shufran KA, Peters DC, Webster JA. Generation of clonal diversity by sexual reproduction in the greenbug, *Schizapis graminum*. Insect Mol Biol 1997; 6: 203-209.
917. Sidotide-Fraisse C, Rincheval V, Risler Y, Mignotte B, Vayssiere JL. TNF-α activates at least two apoptotic signaling cascades. Oncogene 1998; 17: 1639-1651.
918. Siemankowski LM, Morreale J, Briehl MM. Antioxidant defenses in the TNF-treated MCF-7 cells: selective increase in MnSOD. Free Radical Biol Med 1999; 26: 919-924.
919. Siemens TV, Nichols DL, Zitomer RS. Effect of mitochondrial functions on synthesis of yeast cytochrome c. J Bacteriol 1980; 142 499-507.
920. Simpson GG. Tempo and Mode in Evolution. New York: Columbia University Press, 1944.
921. Singh JK, Dasgupta A, Adayev T, Shahmehdi SA, Hammond D, Banerjee P. Apoptosis is associated with an increase in saturated fatty acid containing phospholipids in the neuronal cell line, HN2-5. Biochim Biophys Acta 1996; 1304: 171-178.
922. Sirover MA. New insights into an old protein: the functional diversity of mammalian glyceraldehyde-3-phosphate dehydrogenase. Biochim Biophys Acta 1999; 1432: 159-184.
923. Sivan E, Homko CJ, Whittaker PG, Reece EA, Chen X, Boden G. Free fatty acids and insulin resistance during pregnancy. J Clin Endocrinol Metab 1998; 83: 2338-2342.
924. Sjöblom T, Lahdetie J. Expression of p53 in normal and gamma-irradiated rat testis suggests a role for p53 in meiotic recombination and repair. Oncogene 1996; 12: 2499-2505.
925. Sjöblom T, West A, Lahdetie J. Apoptotic response of spermatogenic cells to the germ cell mutagens etoposide, adriamycin, and diepoxybutane. Environ Mol Mutagen 1998; 31: 133-148.
926. Skromne I, Sanchez O, Aguirre J. Starvation stress modulates the expression of the *Aspergillus nidulans* brlA regulatory gene. Microbiology 1995; 141: 21-28.
927. Skulachev VP. Cytochrome c in the apoptotic and antioxidant cascades. FEBS Lett 1998; 423: 275-280.
928. Skulachev VP. Phenoptosis: programmed death of an organism. Biochemistry (Mosc) 1999; 64: 1418-1426.
929. Small WC, Brodeur RD, Sandor A, Fedorova N, Li GY, Butow RA, Srere PA. Enzymatic and metabolic studies on retrograde regulation mutants of yeast. Biochemistry 1995; 34: 5569-5576.
930. Smith BT, Walker GC. Mutagenesis and more: umuDC and the *Escherichia coli* SOS response. Genetics 1998; 148: 1599-1610.

931. Sniegowski PD, Gerrish PJ, Lenski RE. Evolution of high mutation rates in experimental populations of *E. coli*. Nature 1997; 387: 703-705.
932. Sohal RS, Allen RG. Oxidative stress as a causal factor in differentiation and aging: a unifying hypothesis. Exp Gerontol 1990; 25: 499-522.
933. Sohur US, Dixit MN, Chen CL, Byrom MW, Kerr LA. Rel/NF-κB represses bcl-2 transcription in pro-B lymphocytes. Gene Expr 1999; 8: 219-229.
934. Soloff BL, Nagle WA, Moss AJ Jr, Henle KJ, Crawford JT. Apoptosis induced by cold shock in vitro is dependent on cell growth phase. Biochem Biophys Res Commun 1987; 145: 876-883.
935. Solomon JM, Grossman AD. Who's competent and when: regulation of natural genetic competence in bacteria. Trends Genet 1996; 12: 150-155.
936. Solov'yan VT, Andreev IO, Kolotova TY, Pogribniy PV, Tarnavsky DT, Kunakh VA. The cleavage of nuclear DNA into high molecular weight DNA fragments occurs not only during apoptosis but also accompanies changes in functional activity of the non-apoptotic cells. Exp Cell Res 1997; 235: 130-137.
937. Sommer S, Bailone A, Devoret R. The appearance of the UmuD'C protein complex in *Escherichia coli* switches repair from homologous recombination to SOS mutagenesis. Mol Microbiol 1993; 10: 963-971.
938. Son WY, Hwang SH, Han CT, Lee JH, Kim S, Kim YC. Specific expression of heat shock protein HspA2 in human male germ cells. Mol Hum Reprod 1999; 5: 1122-1126.
939. Sonenshein GE. Rel/NF-κB transcription factors and the control of apoptosis. Semin Cancer Biol 1997; 8: 113-119.
940. Sovak MA, Arsura M, Zanieski G, Kavanagh KT, Sonenshein GE. The inhibitory effects of transforming growth factor β1 on breast cancer cell proliferation are mediated through regulation of aberrant nuclear factor-κB/Rel expression. Cell Growth Differ 1999; 10: 537-544.
941. Srivastava DK, Shukla OP. Organic nutrients & catabolite repression of encystation of *Acanthamoeba culbertsoni*. Indian J Exp Biol 1983; 21: 455-457.
942. Stanley SM. Clades versus clones in evolution: why we have sex. Science 1975; 190: 382-383.
943. Steele DF, Butler CA, Fox TD. Expression of a recoded nuclear gene inserted into yeast mitochondrial DNA is limited by mRNA-specific translational activation. Proc Natl Acad Sci USA 1996; 93: 5253-5257.
944. Steele RJC, Thompson AM, Hall PA, Lane DP. The p53 tumour suppressor gene. Br J Surg 1998; 85: 1460-1467.
945. Steels EL, Learmonth RP, Watson K. Stress tolerance and membrane lipid unsaturation in *Saccharomyces cerevisiae* grown aerobically or anaerobically. Microbiology 1994; 140: 569-576.
946. Stefanelli C, Stanic I, Bonavita F, Flamigni F, Pignatti C, Guarnieri C, Caldarera CM. Inhibition of glucocorticoid-induced apoptosis with 5-aminoimidazole-4-carboxamide ribonucleoside, a cell-permeable activator of AMP-activated protein kinase. Biochem Biophys Res Commun 1998; 243: 821-826.
947. Stepp SE, Mathew PA, Bennett M, de Saint Basile G, Kumar V. Perforin: more than just an effector molecule. Immunol Today 2000; 21: 254-256.
948. St John JC, Sakkas D, Barratt CLR. A role for mitochondrial DNA and sperm survival. J Androl 2000; 21: 189-199.
949. Stoika RS, Korchinsky AG. Effect of hyperthermia on autocrine functions in tumor and normal cells. Exp Oncol 1995; 17: 277-286.
950. Stoler DL, Chen N, Basik M, Kahlenberg MS, Rodriguez-Bigas MA, Petrelli NJ, Anderson GR. The onset and extent of genomic instability in sporadic colorectal tumor progression. Proc Natl Acad Sci USA 1999; 96: 15121-15126.
951. Storey KB. Metabolic adaptations supporting anoxia tolerance in reptiles. Recent advances. Comp Biochem Physiol 1996; 113: 23-35.
952. Styrud J, Eriksson UJ. In vitro effects of glucose and growth factors on limb bud and mandibular arch chondrocytes maintained at various serum concentrations. Teratology 1991; 44: 65-75.
953. Su JH, Satou T, Anderson AJ, Cotman CW. Up-regulation of Bcl-2 is associated with neuronal DNA damage in Alzheimer's disease. NeuroReport 1996; 7: 437-440.
954. Subramanian M, Pusphendran CK, Tarachand U, Devasagayam TP. Gestation confers temporary resistance to peroxidation in the maternal brain. Neurosci Lett 1993; 155: 151-154.
955. Sudilovsky O, Gunter R. Induction of enzymes by glucagon, glucose repression, adenosine 3′,5′-monophosphate concentration during carcinogenesis and in Morris 6918A hepatoma. Cancer Res 1975; 35: 1069-1074.
956. Suga H, Koyanagi M, Hoshiyama D, Ono K, Iwabe N, Kuma K, Miyata T. Extensive gene duplication in the early evolution of animals before the parazoan-eumetazoan split demonstrated by G proteins and protein tyrosine kinases from sponge and hydra. J Mol Evol 1999; 48: 646-653.
957. Sugito K, Yamane M, Hattori H, Hayashi Y, Tohnai I, Ueda M, Tsuchida N, Ohtsuka K. Interaction between hsp70 and hsp40, eukaryotic homologs of DnaK and DnaJ, in human cells expressing mutant-type p53. FEBS Lett 1995; 358: 161-164.
958. Suhara T, Fukuo K, Sugimoto T, Morimoto S, Nakahashi T, Hata S, Shimizu M, Ogihara T. Hydrogen peroxide induces up-regulation of Fas in human endothelial cells. J Immunol 1998; 160: 4042-4047.
959. Surette MG, Miller MB, Bassler BL. Quorum sensing in *Escherichia coli*, *Salmonella typhimurium*, and *Vibrio harveyi*: a new family of genes responsible for

autoinducer production. Proc Natl Acad Sei USA 1999; 96: 1639-1644.
960. Susin SA, Lorenzo HK, Zamzami N, Marzo I, Snow BE, Brothers GM, Mangion J, Jacotot E, Costantini P, Loeffler M, Larochette N, Goodlett DR, Aebersold R, Siderovski DP, Penninger JM, Kroemer G. Molecular characterization of mitochondrial apoptosis-inducing factor. Nature 1999; 397: 441-446.
961. Suzukawa K, Miura K, Mitsushita J, Resau J, Hirose K, Crystal R, Kamata T. Nerve growth factor-induced neuronal differentiation requires generation of Rac1-regulated reactive oxygen species. J Biol Chem 2000; 275: 13175-13178.
962. Suzuki A, Tsutomi Y. Bcl-2 accelerates the neuronal differentiation: new evidence approaching to the biofunction of bcl-2 in the neuronal system. Brain Res 1998; 801: 59-66.
963. Suzuki H, Kumagai T, Goto A, Sugiura T. Increase in intracellular hydrogen peroxide and upregulation of a nuclear respiratory gene evoked by impairment of mitochondrial electron transfer in human cells. Biochem Biophys Res Commun 1998; 249: 542-545.
964. Svensater G, Sjogreen B, Hamilton IR. Multiple stress responses in *Streptococcus mutans* and the induction of general and stress-specific proteins. Microbiology 2000; 146: 107-117.
965. Taddei F, Matic I, Radman M. cAMP-dependent SOS induction and mutagenesis in resting bacterial populations. Proc Natl Acad Sci USA 1995; 92: 11736-11740.
966. Taddei F, Radman M, Maynard-Smith J, Toupance B, Gouyon PH, Godelle B. Role of mutator alleles in adaptive evolution. Nature 1997; 387: 700-702.
967. Taddei F, Vulic M, Radman M, Matic I. Genetic variability and adaptation to stress. EXS 1997; 83: 271-290.
968. Takahashi E, Yamada M, Saito M, Kuboyama M, Ogasa K. Differentiation of cultured Friend leukemia cells induced by short-chain fatty acids. Gann 1975; 66: 577-580.
969. Takami M, Preston SL, Behrman HR. Eicosatetraynoic and eicosatriynoic acids, lipoxygenase inhibitors, block meiosis via antioxidant action. Am J Physiol 2000; 278: C646-C650.
970. Takasu M, Tada Y, Wang JO, Tagawa M, Takenaga K. Resistance to apoptosis induced by microenvironmental stresses is correlated with metastatic potential in Lewis lung carcinoma. Clin Exp Metastasis 1999; 17: 409-416.
971. Takatsuka J, Takahashi N, de Luca LM. Retinoic acid metabolism and inhibition of cell proliferation: an unexpected liaison. Cancer Res 1996; 56: 675-678.
972. Takenaka K, Nagafuji K, Harada M, Mizuno S, Miyamoto T, Makino S, Gondo H, Okamura T, Niho Y. In vitro expansion of hematopoietic progenitor cells induces functional expression of Fas antigen (CD95). Blood 1996; 88: 2871-2877.
973. Tamai KT, Monaco L, Nantel F, Zazopoulos E, Sassone-Corsi P. Coupling signalling pathways to transcriptional control: nuclear factors responsive to cAMP. Recent Prog Horm Res 1997; 52, 121-139.
974. Tan MJ, Li SJ, Swaroop MJ, Guan KL, Oberley LW, Sun Y. Transcriptional activation of the human glutathione peroxidase promoter by p53. J Biol Chem 1999; 274: 12061-12066.
975. Tan Y, Riley MA. Rapid invasion by colicinogenic *Escherichia coli* with novel immunity functions. Microbiology 1996; 142: 2175-2180.
976. Tanaka H, Arakawa H, Yamaguchi T, Shiraishi K, Fukuda S, Matsui K, Takei Y, Nakamura Y. A ribonucleotide reductase gene involved in a p53-dependent cell-cycle checkpoint for DNA damage. Nature 2000; 404: 42-49.
977. Tangye SG, Raison RL. Human cytokines suppress apoptosis of leukaemic $CD5^+$ B cells and preserve expression of bcl-2. Immunol Cell Biol 1997; 75: 127-135.
978. Tatsumi-Miyajima J, Kupper JH, Takebe H, Burkle A. Trans-dominant inhibition of poly(ADP-ribosyl)ation potentiates alkylation-induced shuttle-vector mutagenesis in Chinese hamster cells. Mol Cell Biochem 1999; 193: 31-35.
979. Taub ML, Syracuse JA, Cai JW, Fiorella P, Subjeck JR. Glucose deprivation results in the induction of glucose-regulated proteins and domes in MDCK monolayers in hormonally defined serum-free medium. Exp Cell Res 1989; 182: 105-113.
980. Taylor BL, Zhulin IB. PAS domains: internal sensors of oxygen, redox potential, and light. Microbiol Mol Biol Rev 1999; 63: 479-506.
981. Teixeira CC, Shapiro IM, Hatori M, Rajpurohit R, Koch C. Retinoic acid modulation of glutathione and cysteine metabolism in chondrocytes. Biochem J 1996; 314: 21-26.
982. Theodoridis GC, Anne A, Stark L. On evolutive systems and the initial evolution of structure and function. J Theor Biol 1996; 178: 61-88.
983. Thiagalingam S, Kinzler KW, Vogelstein B. PAK1, a gene that can regulate p53 activity in yeast. Proc Natl Acad Sci USA 1995; 92: 6062-6066.
984. Thieffry D, Sarkar S. Forty years under the central dogma. Trends Biochem Sci 1998; 23: 312-316.
985. Thies RL, Autor AP. Reactive oxygen injury to cultured pulmonary artery endothelial cells: mediation by poly (ADP-ribose) polymerase activation causing NAD depletion and altered energy balance. Arch Biochem Biophys 1991; 286: 353-363.
986. Thomas GH. High male:female ratio of germ-line mutations: an alternative explanation for postulated gestational lethality in males in X-linked dominant disorders. Am J Hum Genet 1996; 58: 1364-1368.
987. Thompson AR, Chen SH. Germ line origins of de novo mutations in hemophilia B families. Hum Genet 1994; 94: 299-302.

988. Thompson MA, Rosenthal MA, Ellis SL, Friend AJ, Zorbas MI, Whitehead RH, Ramsay RG. c-Myb down-regulation is associated with human colon cell differentiation, apoptosis, and decreased Bcl-2 expression. Cancer Res 1998; 58: 5168-5175.
989. Thorne SH, Williams HD. Cell-density-dependent starvation survival of *Rhizobium leguminosarum bv. phaseoli*: identification of the role of an *N*-acyl homoserine lactone in adaptation to stationary-phase survival. J Bacteriol 1999; 181: 981-990.
990. Tichy M, Vermaas W. In vivo role of catalase-peroxidase in *Synechocystis sp. strain PCC 6803*. J Bacteriol 1999; 181: 1875-1882.
991. Toft NJ, Winton DJ, Kelly J, Howard LA, Dekker M, te Riele H, Arends MJ, Wyllie AH, Margison GP, Clarke AR. Msh2 status modulates both apoptosis and mutation frequency in the murine small intestine. Proc Natl Acad Sci USA 1999; 96: 3911-3915.
992. Tomkins GM. The metabolic code. Science 1975; 189: 760-763.
993. Torriglia A, Perani P, Courtois Y. L-DNase II: a new link in apoptotic pathways. Med Sci 1999; 15: 253-259.
994. Tortosa P, Dubnau D. Competence for transformation: a matter of taste. Curr Opin Microbiol 1999; 2: 588-592.
995. Tournier C, Hess P, Yang DD, Xu J, Turner TK, Nimnual A, Bar-Sagi D, Jones SN, Flavell RA, Davis RJ. Requirement of JNK for stress-induced activation of the cytochrome c-mediated death pathway. Science 2000; 288: 870-874
996. Trejo JL, Rua C, Cuchillo I, Machin C. Calbindin-D28k- and astroglial protein-immunoreactivities, and ultrastructural differentiation in the prenatal rat cerebral cortex and hippocampus are affected by maternal adrenalectomy. Brain Res Dev Brain Res 1998; 108: 161-177.
997. Trobner W, Piechocki R. Selection against hypermutability in *Escherichia coli* during long term evolution. Mol Gen Genet 1984; 198: 177-178.
998. Trombe MC. Calcium signaling in *Streptococcus pneumoniae*: implication of the kinetics of calcium transport. Microb Drug Resist 1999; 5: 247-252.
999. Trosko JE. Hierarchical and cybernetic nature of biologic systems and their relevance to homeostatic adaptation to low-level exposures to oxidative stress-inducing agents. Environ Health Perspect 1998; 106 (Suppl 1): 331-333.
1000. Trosko JE, Goodman JI. Intercellular communication may facilitate apoptosis: implications for tumor promotion. Mol Carcinogen 1994; 11: 8-12.
1001. Trosko JE, Inoue T. Oxidative stress, signal transduction, and intercellular communication in radiation carcinogenesis. Stem Cells 1997; 15 (Suppl 2): 59-67.
1002. Trosko JE, Ruch RJ. Cell-cell communication in carcinogenesis. Front Biosci 1998; 3: D208-236.
1003. Turpaev KT. Nitric oxide in intercellular communication. Mol Biol 1998; 32: 475-484.
1004. Trucco C, Rolli V, Oliver FJ, Flatter E, Masson M, Dantzer F, Niedergang C, Dutrillaux B, Menissier-de Murcia J, de Murcia G. A dual approach in the study of poly(ADP-ribose) polymerase: in vitro random mutagenesis and generation of deficient mice. Mol Cell Biochem 1999; 193: 53-60.
1005. Tuchman M, Matsuda I, Munnich A, Malcolm S, Strautnieks S, Briede T. Proportions of spontaneous mutations in males and females with ornithine transcarbamylase deficiency. Am J Med Genet 1995; 55: 67-70.
1006. Tuynder M, Godfrine S, Cornelis JJ, Rommelaere J. Dose-dependent induction of resistance to terminal differentiation in X-ray irradiated cultures of normal human keratinocytes. Proc Natl Acad Sci USA 1991; 88: 2638-2642.
1007. Tyler DD. The Mitochondrion in Health and Disease. New York: VCH Publishers, 1992.
1008. Uchida K, Shiraishi M, Naito Y, Torii Y, Nakamura Y, Osawa T. Activation of stress signaling pathways by the end product of lipid peroxidation. 4-Hydroxy-2-nonenal is a potential inducer of intracellular peroxide production. J Biol Chem 1999; 274: 2234-2242.
1009. Ueda N, Walker PD, Hsu SM, Shah SV. Activation of a 15-kDa endonuclease in hypoxia/reoxygenation injury without morphologic features of apoptosis. Proc Natl Acad Sci USA 1995; 92: 7202-7206.
1010. Ueki T, Inouye S. A new sigma factor, SigD, essential for stationary phase is also required for multicellular differentiation in *Myxococcus xanthus*. Genes Cells 1998; 3: 371-385.
1011. Ueno H, Kondo E, Yamamoto-Honda R, Tobe K, Nakamoto T, Sasaki K, Mitani K, Furusaka A, Tanaka T, Tsujimoto Y, Kadowaki T, Hirai H. Association of insulin receptor substrate proteins with Bcl-2 and their effects on its phosphorylation and antiapoptotic function. Mol Biol Cell 2000; 11: 735-746.
1012. Uhal BD, Joshi I, True AL, Mundle S, Raza A, Pardo A, Selman M. Fibroblasts isolated after fibrotic lung injury induce apoptosis of alveolar epithelial cells in vitro. Am J Physiol 1995; 13: L819-L828.
1013. Uhlmann EJ, D'Sa-Eipper C, Subramanian T, Wagner AJ, Hay N, Chinnadurai G. Deletion of a nonconserved region of Bcl-2 confers a novel gain of function: suppression of apoptosis with concomitant cell proliferation. Cancer Res 1996; 56: 2506-2509.
1014. Ulery TL, Jang SH, Jaehning, JA. Glucose repression of yeast mitochondrial transcription: kinetics of derepression and role of nuclear genes. Mol Cell Biol 1994; 14: 1160-1170.
1015. Ullrich O, Siems WG, Lehmann K, Huser H, Ehrlich W, Grune T. Inhibition of poly(ADP-ribose) formation by 4-hydroxynonenal in primary cultures of rabbit synovial fibroblasts. Biochem J 1996; 315: 705-708.
1016. Umeyama T, Lee PC, Ueda K, Horinouchi S. An AfsK/AfsR system involved in the response of aerial mycelium

formation to glucose in *Streptomyces griseus*. Microbiology 1999; 145: 2281-2292.
1017. Umezawa K, Iked Y, Uchihata Y, Naganawa H, Kondo S. Chloptosin, an apoptosis-inducing dimeric cyclohexapeptide produced by *Streptomyces*. J Org Chem 2000; 65: 459-463.
1018. Uren AG, Pakusch M, Hawkins CJ, Puls KL, Vaux DL. Cloning and expression of apoptosis inhibitory protein homologs that function to inhibit apoptosis and/or bind tumor necrosis factor receptor-associated factors. Proc Natl Acad Sci USA 1996; 93: 4974-4978.
1019. Uren AG, Coulson EJ, Vaux DL. Conservation of baculovirus inhibitor of apoptosis repeat proteins (BIRPs) in viruses, nematodes, vertebrates and yeasts. Trends Biochem Sci 1998; 23: 159-162.
1020. Uren AG, Beilharz T, O'Connell MJ, Bugg SJ, van Driel R, Vaux DL, Lithgow T. Role for yeast inhibitor of apoptosis (IAP)-like proteins in cell division. Proc Natl Acad Sci USA 1999; 96: 10170-10175.
1021. Urushihara H. Choice of partners: sexual cell interactions in *Dictyostelium discoideum*. Cell Struct Funct 1996; 21: 231-236.
1022. Vago P, Humbert G, Lenoir M. Amikacin intoxication induces apoptosis and cell proliferation in rat organ of Corti. NeuroReport 1998; 9: 431-436.
1023. Vanden Heuvel JP. Peroxisome proliferator-activated receptors: a critical link among fatty acids, gene expression and carcinogenesis. J Nutr 1999; 129: 575-580.
1024. Van Antwerp DJ, Martin SJ, Verma IM, Green DR. Inhibition of TNF-α-induced apoptosis by NF-κB. Trends Cell Biol 1998; 8: 107-111.
1025. Varga M, Kashefi K, Blunt-Harris EL, Lovley DR. Microbiological evidence for FeIII reduction on early Earth. Nature 1998; 395: 65-67.
1026. Varnes ME, Chiu SM, Xue LY, Oleinick NL. Photodynamic therapy-induced apoptosis in lymphoma cells: translocation of cytochrome c causes inhibition of respiration as well as caspase activation. Biochem Biophys Res Commun 1999; 255: 673-679.
1027. Vasilenko TI, Tovarova II, Khokhlov AS. Effect of the A-factor on the adenylate level in *Streptomyces griseus*. Prikl Biokhim Mikrobiol 1983; 19: 356-361.
1028. Vayssiere JL, Petit PX, Risler Y, Mignotte B. Commitment to apoptosis is associated with changes in mitochondrial biogenesis and activity in cell lines conditionally immortalized with simian virus 40. Proc Natl Acad Sci USA 1994; 91: 11752-11756.
1029. Velculescu VE, El-Deiry WS. Biological and clinical importance of the p53 tumor suppressor gene. Clin Chem 1996; 42: 858-868.
1030. Velicer GJ, Kroos L, Lenski RE. Loss of social behaviors by *Myxococcus xanthus* during evolution in an unstructured habitat. Proc Natl Acad Sci USA 1998; 95: 12376-12380.
1031. Venetianer A, Pirity M, Hever-Szabo A. The function of heat-shock proteins in stress tolerance. Cell Biol Int 1994; 18: 605-615.
1032. Venters HD, Dantzer R, Kelley KW. A new concept in neurodegeneration: TNFα is a silencer of survival signals. Trends Neurosci 2000; 23: 175-180.
1033. Verkerke-van Wijk I, Kim JY, Brandt R, Devreotes PN, Schaap P. Functional promiscuity of gene regulation by serpentine receptors in *Dictyostelium discoideum*. Mol Cell Biol 1998; 18: 5744-5749.
1034. Vessey DA, Lee KH, Boyer TD. Differentiation-induced enhancement of the ability of cultured human keratinocytes to suppress oxidative stress. J Invest Dermatol 1995; 104: 355-358.
1035. Vidal-Puig AJ, Considine RV, Jimenez-Linan M, Werman A, Pories WJ, Caro JF, Flier JS. Peroxisome proliferator-activated receptor gene expression in human tissues. Effects of obesity, weight loss, and regulation by insulin and glucocorticoids. J Clin Invest 1997; 99: 2416-2422.
1036. Villani G, Greco M, Papa S, Attardi G. Low reserve of cytochrome c oxidase capacity in vivo in the respiratory chain of a variety of human cell types. J Biol Chem 1998; 273: 31829-31836.
1037. Virolle MJ, Gagnat J. Sequences involved in growth-phase-dependent expression and glucose repression of a *Streptomyces* α-amylase gene. Microbiology 1994; 140: 1059-1067.
1038. Voellmy R. Transduction of the stress signal and mechanisms of transcriptional regulation of heat shock/stress protein gene expression in higher eukaryotes. Crit Rev Eukaryot Gene Expr 1994; 4: 357-401.
1039. Vogt M, Bauer MK, Ferrari D, Schulze-Osthoff K. Oxidative stress and hypoxia/reoxygenation trigger CD95 (APO-1/Fas) ligand expression in microglial cells. FEBS Lett 1998; 429: 67-72.
1040. von Borstel RC, Higgins JA. Janus carcinogens and mutagens. Mutat Res 1998; 402: 321-329.
1041. von Wangenheim KH, Peterson HP. Control of cell proliferation by progress in differentiation: clues to mechanisms of aging, cancer causation and therapy. J Theor Biol 1998; 193: 663-678.
1042. Vorobyeva NV, Sherman MYU, Glagolev AN. Bacterial chemotaxis controls the catabolite repression of flagellar biogenesis. FEBS Lett 1982; 143: 233-236.
1043. Vossen RC, van Dam-Mieras MC, Hornstra G, Zwaal RF. Differential effects of endothelial cell fatty acid modification on the sensitivity of their membrane phospholipids to peroxidation. Prostagland Leuk Essent Fatty Acid 1995; 52: 341-347.
1044. Vrijenhoek RC. Clonal organisms and the benefits of sex. Adv Mol Ecol 1998; 306: 151-172.
1045. Vulic M, Lenski RE, Radman M. Mutation, recombination, and incipient speciation of bacteria in the laboratory. Proc Natl Acad Sci USA 1999; 96: 7348-7351.
1046. Wachsman JT. The beneficial effects of dietary restriction: reduced oxidative damage and enhanced apoptosis. Mutat Res 1996; 350: 25-34.

1047. Waddell BJ. The placenta as hypothalamus and pituitary: possible impact and fetal adrenal function. Reprod Fertil Dev 1993; 5: 479-497.
1048. Waddell BJ, Atkinson HC. Production rate, metabolic clearance rate and uterine extraction of corticosterone during rat pregnancy. J Endocrinol 1994; 143: 183-190.
1049. Walbot V. Reactivation of mutator transposable elements of maize by ultraviolet light. Mol Gen Genet 1992; 234: 353-360.
1050. Walker DR, Bond JP, Tarone RE, Harris CC, Makalowski W, Boguski MS, Greenblatt MS. Evolutionary conservation and somatic mutation hotspot maps of p53: correlation with p53 protein structural and functional features. Oncogene 1999; 18: 211-218.
1051. Walker JC. Atmospheric constraints on the evolution of metabolism. Orig Life 1980; 10: 93-104.
1052. Walker LSK, McLeod JD, Boulougouris G, Patel YI, Ellwood CN, Hall ND, Sansom DM. Lack of activation induced cell death in human T blasts despite CD95L up-regulation: protection from apoptosis by MEK signalling. Immunology 1999; 98: 569-575.
1053. Walsh K, Perlman H. Cell cycle exit upon myogenic differentiation. Curr Opin Genet Dev 1997; 7: 597-602.
1054. Walsh SW. Maternal-placental interactions of oxidative stress and antioxidants in preeclampsia. Semin Reprod Endocrinol 1998; 16: 93-104.
1055. Wang CY, Mayo MW, Korneluk RG, Goeddel DV, Baldwin AS Jr. NF-κB antiapoptosis: induction of TRAF1 and TRAF2 and c-IAP1 and c-IAP2 to suppress caspase-8 activation. Science 1998; 281: 1680-1683.
1056. Wang J, Lenardo MJ. Roles of caspases in apoptosis, development, and cytokine maturation revealed by homozygous gene deficiencies. J Cell Sci 2000; 113: 753-757.
1057. Wang WG, Passaniti A. Extracellular matrix inhibits apoptosis and enhances endothelial cell differentiation by a NF κB-dependent mechanism. J Cell Biochem 1999; 73: 321-331.
1058. Wang X, Manganaro F, Schipper HM. A cellular stress model for the sequestration of redox-active glial iron in the aging and degenerating nervous system. J Neurochem 1995; 64: 1868-1877.
1059. Wang XJ, Ohnishi T. p53-dependent signal transduction induced by stress. J Radiat Res 1997; 38: 179-194.
1060. Watanabe Y, Inaba T, Shimano H, Gotoda T, Yamamoto K, Mokuno H, Sato H, Yazaki Y, Yamada N. Induction of LDL receptor-related protein during the differentiation of monocyte-macrophages. Possible involvement in the atherosclerotic process. Arterioscler Thromb 1994; 14: 1000-1006.
1061. Watson AJ. The cell biology of blastocyst development. Mol Reprod Dev 1992; 33: 492-504.
1062. Watson RWG, Rotstein OD, Parodo J, Bitar R, Hackam D, Marshall JC. Granulocytic differentiation of HL-60 cells results in spontaneous apoptosis mediated by increased caspase expression. FEBS Lett 1997; 412: 603-609.
1063. Watson RW, Rotstein OD, Parodo J, Bitar R, Marshall JC. The IL-1β-converting enzyme (caspase-1) inhibits apoptosis of inflammatory neutrophils through activation of IL-1β. J Immunol 1998; 161: 957-962.
1064. Watson RW, O'Neill A, Brannigen AE, Coffey R, Marshall JC, Brady HR, Fitzpatrick JM. Regulation of Fas antibody induced neutrophil apoptosis is both caspase and mitochondrial dependent. FEBS Lett 1999; 453: 67-71.
1065. Watson SP, Clements MO, Foster SJ. Characterization of the starvation-survival response of *Staphylococcus aureus*. J Bacteriol 1998; 180: 1750-1758.
1066. Watt R, Piper PW. UBI4, the polyubiquitin gene of *Saccaromyces cerevisiae*, is a heat shock gene that is also subject to catabolite derepression control. Mol Gen Genet 1997; 253: 439-447.
1067. Waxman D, Peck JR. Sex and adaptation in a changing environment. Genetics 1999; 153: 1041-1053.
1068. Waxman S, Huang Y, Scher BM, Scher M. Enhancement of differentiation and cytotoxicity of leukemia cells by combinations of fluorinated pyrimidines and differentiation inducers: development of double-strand breaks. Biomed Pharmacother 1992; 46: 183-192.
1069. Weber GF. Final common pathways in neurodegenerative diseases: regulatory role of the glutathione cycle. Neurosci Biobehav Rev 1999; 23: 1079-1086.
1070. Webster KA, Gunning P, Hardeman E, Wallace DC, Kedes L. Coordinate reciprocal trends in glycolytic and mitochondrial transcript accumulations during the in vitro differentiation of human myoblasts. J Cell Physiol 1990; 142: 566-573.
1071. Whitfield JF, Bird RP, Chakravarthy BR, Isaacs RJ, Morley P. Calcium - cell cycle regulator, differentiator, killer, chemopreventor, and maybe, tumor promoter. J Cell Biochem 1995; Suppl 22: 74-91.
1072. Widmann C, Gibson S, Jarpe MB, Johnson GL. Mitogen-activated protein kinase: conservation of a three-kinase module from yeast to human. Physiol Rev 1999; 79: 143-180.
1073. Wilhelm S, Wagner H, Hacker G. Activation of caspase-3-like enzymes in non-apoptotic T cells. Eur J Immunol 1998; 28: 891-900.
1074. Williams GC. Sex and Evolution. Princeton: Princeton University Press, 1975.
1075. Williams GT, Critchlow MR, Hedge VL, O'Hare KB. Molecular failure of apoptosis: inappropriate cell survival and mutagenesis? Toxicol Lett 1998; 102-103: 485-489.
1076. Williams J. Morphogenesis in *Dictyostelium*: new twists to a not-so-old tale. Curr Opin Gen Dev 1995; 5; 426-431.
1077. Williams J, Hopper N, Early A, Traynor D, Harwood A, Abe T, Simon MN, Veron M. Interacting signaling pathways regulating prestalk cell differentiation and movement during the morphogenesis of *Dictyostelium*. Development 1993; Suppl: 1-7.

1078. Willnow TE, Hilpert J, Armstrong SA, Rohlmann A, Hammer RE, Burns DK, Herz J. Defective forebrain development in mice lacking gp330/megalin. Proc Natl Acad Sci USA 1996; 93: 8460-8464.
1079. Wintersberger U, Wintersberger E. Poly ADP-ribosylation - a cellular emergency reaction? FEBS Lett 1985; 188: 189-191.
1080. Winton DJ, Brooks RA. Analysis of DNA damage and repair accompanying differentiation in the intestinal crypt. Philos Trans Roy Soc Lond B 1998; 353: 895-902.
1081. Wojtczak L. The Crabtree effect: a new look at the old problem. Acta Biochim Pol 1996; 43: 361-368.
1082. Wray GA, Levinton JS, Shapiro LH. Molecular evidence for deep Pre-Cambrian divergences among metazoan phyla. Science 1996; 274: 568-573.
1083. Wright BE, Longacre A, Reimers JM. Hypermutation in derepressed operons of *Escherichia coli* K12. Proc Natl Acad Sci USA 1999; 96: 5089-5094.
1084. Wu LJ, Randers-Pehrson G, Xu A, Waldren CA, Geard CR, Yu Z, Hei TK. Targeted cytoplasmic irradiation with α particles induces mutations in mammalian cells. Proc Natl Acad Sci USA 1999; 96: 4959-4964.
1085. Wu MX, Ao Z, Prasad KV, Wu R, Schlossman SF. IEX-1L, an apoptosis inhibitor involved in NF-κB-mediated cell survival. Science 1998; 281: 998-1001.
1086. Wu P, Inskeep K, Bowker-Kinley MM, Popov KM, Harris RA. Mechanism responsible for inactivation of skeletal muscle pyruvate dehydrogenase complex in starvation and diabetes. Diabetes 1999; 48: 1593-1599.
1087. Xia F, Liber HL. The tumor suppressor p53 modifies mutational processes in a human lymphoblastoid cell line. Mutat Res 1997; 373: 87-97.
1088. Xu Y, Krishnan A, Wan XS, Majima H, Yeh CC, Ludewig G, Kasarskis EJ, St. Clair DK. Mutations in the promoter reveal a cause for the reduced expression of the human manganese superoxide dismutase gene in cancer cells. Oncogene 1999; 18: 93-102.
1089. Yamashita N, Hoshida S, Taniguchi N, Kuzuya T, Hori M. Whole-body hyperthermia provides biphasic cardioprotection against ischemia/reperfusion injury in the rat. Circulation 1998; 98: 1414-1421.
1090. Yamashita N, Shin-ya K, Furihata K, Hayakawa Y, Seto H. New ravidomycin analogues, FE35A and FE35B, apoptosis inducers produced by *Streptomyces rochei*. J Antibiot (Tokyo) 1998; 51: 1105-1108.
1091. Yao A, Rubin AL, Rubin H. Progressive state selection of cells in low serum promotes high density growth and neoplastic transformation in NIH 3T3 cells. Cancer Res 1990; 50: 5171-5176.
1092. Yarmolinsky MB. Programmed cell death in bacterial populations. Science 1995; 267: 836-837.
1093. Yasbin RE, Cheo D, Bayles KW. The SOB system of *Bacillus subtilis*: a global regulon involved in DNA repair and differentiation. Res Microbiol 1991; 142: 885-892.
1094. Yavin E, Billia DM. Apoptotic death in cerebral hemisphere cells is density dependent and modulated by transient oxygen and glucose deprivation. J Neurosci Res 1997; 47: 471-478.
1095. Yehiely F, Oren M. The gene for the rat heat shock cognate, hsc70, can suppress oncogene-mediated transformation. Cell Growth Differ 1992; 3: 803-809.
1096. Yeldandi AV, Rao MS, Reddy JK. Hydrogen peroxide generation in peroxisome proliferator-induced oncogenesis. Mutat Res 2000; 448: 159-177.
1097. Yermolaieva O, Brot N, Weissbach H, Heinemann SH, Hoshi T. Reactive oxygen species and nitric oxide mediate plasticity of neuronal calcium signaling. Proc Natl Acad Sci USA 2000; 97: 448-453.
1098. Yin Y, Stahl BC, DeWolf WC, Morgentaler A. p53-mediated germ cell quality control in spermatogenesis. Dev Biol 1998; 204: 165-171.
1099. Yokoo T, Kitamura M. IL-1β depresses expression of the 70-kilodalton heat shock protein and sensitizes glomerular cells to oxidant-initiated apoptosis. J Immunol 1997; 159: 2886-2892.
1100. Yonei S, Yokota R, Sato Y. The distinct role of catalase and DNA repair systems in protection against hydrogen peroxide in *Escherichia coli*. Biochem Biophys Res Commun 1987; 143: 638-644.
1101. You M, Ku PT, Hrdlickova R, Bose HR Jr. ch-IAP1, a member of the inhibitor-of-apoptosis protein family, is a mediator of the antiapoptotic activity of the v-Rel oncoprotein. Mol Cell Biol 1997; 17: 7328-7341.
1102. Yu Z, Luo H, Fu W, Mattson MP. The endoplasmic reticulum stress-responsive protein GRP78 protects neurons against excitotoxicity and apoptosis: suppression of oxidative stress and stabilization of calcium homeostasis. Exp Neurol 1999; 155: 302-314.
1103. Zambrano MM, Siegele DA, Almiron M, Tormo A, Kolter R. Microbial competition: *Escherichia coli* mutants that take over stationary phase cultures. Science 1993; 259: 1757-1760.
1104. Zambrano MM, Kolter R. *Escherichia coli* mutants lacking NADH dehydrogenase I have a competitive disadvantage in stationary phase. J Bacteriol 1993; 175: 5642-5647.
1105. Zanke BW, Boudreau K, Rubie E, Winnett E, Tibbles LA, Zon L, Kyriakis J, Liu FF, Woodgett JR. The stress-activated protein kinase pathway mediates cell death following injury induced by cisplatinum, UV irradiation or heat. Curr Biol 1996; 6: 606-613.
1106. Zatyka M, Thomas CM. Control of genes for conjugative transfer of plasmids and other mobile elements. FEMS Microbiol Rev 1998; 21: 291-319.
1107. Zeuner A, Eramo A, Peschle C, De Maria R. Caspase activation without death. Cell Death Differ 1999; 6: 1075-1080.
1108. Zeyl C, Bell G. The advantage of sex in evolving yeast populations. Nature 1997; 388: 465-468.
1109. Zhan Q, Kontny U, Iglesias M, Alamo I Jr, Yu K, Hollander MC, Woodworth CD, Fornace AJ Jr. Inhibi-

tory effect of Bcl-2 on p53-mediated transactivation following genotoxic stress. Oncogene 1999; 18: 297-304.

1110. Zhang J, Dawson VL, Dawson TM, Snyder SH. Nitric oxide activation of poly(ADP-ribose) synthetase in neurotoxicity. Science 1994; 263: 687-689.

1111. Zhang J, Rosenberg HF, Nei M. Positive Darwinian selection after gene duplication in primate ribonuclease genes. Proc Natl Acad Sci USA 1998; 95: 3708-3713.

1112. Zhang KZ, Westberg JA, Holtta E, Andersson LC. Bcl-2 regulates neural differentiation. Proc Natl Acad Sci USA 1996; 93: 5404-4508.

1113. Zhou HN, Randers-Pehrson G, Waldren CA, Vannais D, Hall EJ, Hei TK. Induction of a bystander mutagenic effect of α particles in mammalian cells. Proc Natl Acad Sci USA 2000; 97: 2099-2104.

1114. Zinser ER, Kolter R. Mutations enhancing amino acid catabolism confer a growth advantage in stationary phase. J Bacteriol 1999; 181: 5800-5807.