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c0002 CHAPTER 2

Molecular Gerontology: Principles and Perspectives for Interventions

Suresh I.S. Rattan

INTRODUCTION

s0010

p0010 Aging research has made tremendous advances and major breakthroughs have been achieved in the understanding of aging at various levels. It is now generally believed that the biological basis of aging is well understood and a distinctive framework has been established which can facilitate formulating some general principles of aging and longevity. There are at least three main biological principles of aging and longevity which can be derived from more than fifty years of biogerontological research:

o0010 **1.** *Aging starts after essential lifespan*: Biological aging occurs during the period of survival beyond the natural lifespan of a species, termed 'essential lifespan' (ELS), in accordance with the theory of evolution of biological traits and requirements for successful reproduction (Rattan, 2000a,b; Rattan and Clark, 2005).

o0015 **2.** *Aging is a post-genetic emergent phenomenon:* Biological aging is an emergent phenomenon seen primarily in protected environments, which allow survival beyond ELS. There is no fixed and rigid genetic programme which determines the exact duration of survival of an organism, and there are no real gerontogenes whose sole function is to cause aging and to determine precisely the lifespan of an organism.

o0020 **3.** *Aging phenotype is highly heterogeneous:* The progression, rate and phenotype of aging is different in different species, organisms within a species, organs and tissues within an organism, cell types within a tissue, sub-cellular compartments within a cell type, and macromolecules within a cell.

p0030 Thus, aging is an emergent, epigenetic, and a meta-phenomenon, which is not controlled by a single mechanism. Although individually no tissue, organ or system becomes functionally exhausted even in very old organisms, it is their combined interaction and interdependence that determines the survival of the whole. The evidence that genes have a limited (about 25%) influence upon lifespan in human beings has mainly come from the studies performed on centenarians and their siblings, twins, and long living families. The value of the genetic contribution to individual lifespan was calculated from longevity studies on mono- and dizygotic twins, and it was shown that the heritability of longevity in men and women was 0.26 and 0.23, respectively (Herskind et al., 1996). This implies that the environment and the lifestyle (milieu) have more than 75% contribution in determining the lifespan of an individual. Thus a combination of genes, milieu, and chance determine the course and consequences of aging and the duration of survival of an individual, which could be modifiable (Rattan, 2007b; Rattan, 2012b). The aim of this article is to give a brief overview of the present state of knowledge with respect to the biological and molecular basis of aging, and the ongoing lines of research and strategies for slowing down aging, maintaining health, and extending health span and longevity.

Homeostasis Versus Homeodynamics

s0015

p0035 Survival and longevity are the result of various maintenance and repair mechanisms. All living systems have the intrinsic ability to respond, to counteract, and to adapt to the external and internal sources of disturbance. The traditional and dominating conceptual model to describe this property is homeostasis. However, recent enhanced understanding of the processes of biological growth, development, maturation, reproduction, and aging have led to the realization that

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the homeostasis model as an explanation is seriously incomplete. The main reason for the incompleteness of the homeostasis model is its defining principle of 'stability through constancy', which does not take into account the new themes, such as cybernetics, control theory, catastrophe theory, chaos theory, information and interaction networks, which comprise and underline the modern biology of complexity (Rattan, 2007a; Rattan, 2012b). Instead, the term homeodynamics is being increasingly used to account for the fact that, unlike machines, the internal milieu of complex biological systems is not permanently fixed, is not at equilibrium, and is a dynamic regulation and interaction among various levels of organization (Yates, 1994).

p0040 Aging, age-related diseases, and death are the final manifestations of unsuccessful homeostasis or failure of homeodynamics (Rattan, 2006; Rattan, 2012b). A wide range of molecular, cellular and physiological pathways of repair are well known, and these range from multiple pathways of nuclear and mitochondrial DNA repair to free radical counteracting mechanisms, protein turnover and repair, detoxification mechanisms, and other processes including immune and stress responses. All these processes involve numerous genes whose products and their interactions give rise to a 'homeodynamic space' or the 'buffering capacity', which is the ultimate determinant of an individual's chance and ability to survive and maintain a healthy state (Holliday, 2007; Rattan, 2006; Rattan, 2012b).

p0045 In a normal, healthy, and young individual, the complex network of stress responses, damage control, and continuous remodeling constitute a functional homeodynamic space (Demirovic and Rattan, 2013). Since no biological system can be 100% perfect 100% of the time, there is a probability of imperfect homeodynamics giving rise to a zone of vulnerability, manifested in age-independent diseases and mortality. However, a progressive accumulation of molecular damage and its effects on the interacting molecular networks leads to the reduction in the functional homeodynamic space, and effectively increases the vulnerability zone, thus allowing for the occurrence and emergence of age-related diseases. Alzheimer's disease, cancer, cataracts, type 2 diabetes, osteoporosis, Parkinson's disease, sarcopenia, and other age-related diseases are the result of reduced homeodynamic space of the individual (Demirovic and Rattan, 2013). Thus, a progressive shrinkage of the homeodynamic space is the hallmark of aging and the cause of origin of all age-related diseases.

MOLECULAR BASIS OF AGING

s0020

p0050 At the molecular level, the theories of the mechanisms of aging are mostly centered on the accumulation of molecular damage (Rattan, 2006; Rattan, 2008c), although recently some other views, such as continuous growth leading to a kind of quasi-program of aging, have also been put forward (Blagosklonny, 2012). However, at the mechanistic level, occurrence and accumulation of damage and its consequences are the most well studied aspects of molecular gerontology.

p0055 The origin of molecular damage is mainly from three sources: (1) various chemical species such as reactive oxygen species (ROS) and free radicals (FR) formed due to external inducers of damage (for example ultra-violet rays), and as a consequence of cellular metabolism involving oxygen, metals, and other metabolites; (2) nutritional glucose and its metabolites, and their biochemical interactions with ROS and FR; and (3) spontaneous errors in biochemical processes, such as DNA duplication, transcription, post-transcriptional processing, translation, and post-translational modifications. An age-related increase in the levels of damage in various macromolecules, including DNA, RNA, proteins, carbohydrates, and lipids is well established. The biological consequences of increased levels of molecular damage can be wide ranging, including altered gene expression, genomic instability, mutations, loss of cell division potential, cell death, impaired inter-cellular communication, tissue disorganization, organ dysfunctions, and increased vulnerability to stress and other sources of disturbance (Holliday, 2007; Rattan, 2006; Rattan, 2012b).

p0060 The so-called mechanistic theories of biological aging have often focused on a single category of inducers of molecular damage as an explanation for possible mechanisms of aging (Rattan, 2006). Of these, the free radical theory and the protein error theory of aging have been the basis of most of the experimental biogerontology research. Although neither of them can be considered to be the complete theory of biological aging, their contributions in providing a solid scientific footing to experimental aging research and anti-aging interventions are highly significant.

Free Radical Theory of Aging

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p0065 The free radical theory of aging (FRTA), proposed in 1954, arose from a consideration of the aging phenomenon from the premise that a single common biochemical process may be responsible for the aging and death of all living beings (for an update, see Harman, 2006). There is abundant evidence to show that a variety of ROS and other FR are indeed involved in the occurrence of molecular damage, which can lead to structural and functional disorders, diseases, and death. The chemistry and biochemistry of FR is very well worked out, and the cellular and organismic

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consequences are well documented. However, the main criticisms raised against this theory are with respect to its lack of incorporation of the essential and beneficial role of FR in the normal functioning and survival of biological systems (Gruber et al., 2008; Halliwell, 2009). Additionally, FRTA presents FR as the universal cause of damage without taking into account the differences in the wide range of FR-counteracting mechanisms in different species. Furthermore, a large body of data showing the contrary and/or lack of predictable and expected beneficial results of antioxidant and FR-scavenging therapies have restricted the FRTA to being only a partial explanation of some of the observed changes during aging (Le Bourg and Fournier, 2004; Le Bourg, 2005; Howes, 2006).

Protein Error Theory of Aging

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p0070 Since the spontaneous error frequency in protein translation is generally several orders of magnitude higher than that in DNA replication and RNA transcription, the role of protein errors and their feedback in biochemical pathways has been considered to be a crucial one with respect to aging. Several attempts have been made to determine the accuracy of translation in cell-free extracts, and most of the studies show that there is an age-related increase in the misincorporation of nucleotides and amino acids. It has also been shown that there is an age-related accumulation of aberrant DNA polymerases and other components of the transcriptional and translational machinery (Rattan, 2008c; Rattan, 2010).

p0075 Further evidence in support of the protein error theory of aging (PETA) comes from experiments which showed that an induction and increase in protein errors can accelerate aging in human cells and bacteria (Holliday, 1996; Rattan, 1996; Rattan, 2003; Nyström, 2002). Similarly, an increase in the accuracy of protein synthesis can slow aging and increase the lifespan in fungi (Rattan, 2008c). Therefore, it is not ruled out that several kinds of errors in various components of protein synthetic machinery, including tRNA charging, and in mitochondria do have long-term effects on cellular stability and survival (Kowald and Kirkwood, 1993a,b; Hipkiss, 2003; Holliday, 2005). However, almost all these methods have relied on indirect *in vitro* assays, and so far direct, realistic, and accurate estimates of age-related changes in errors in cytoplasmic and mitochondrial proteins, and their biological relevance, have not been made. Similarly, applying methods such as two-dimensional gel electrophoresis, which can resolve only some kinds of mis-incorporations, have so far remained insensitive and inconclusive (Rattan, 2008c). It will be necessary to combine several methods, such as electrophoresis, mass-spectrometry, protein−protein interactions and antibody-based detection of molecular heterogeneity to find out the extent of protein errors and their biological role in aging.

From FRTA and PETA to Higher Order Theories

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p0080 Both the FRTA and PETA provide molecular mechanisms for the occurrence of molecular damage. Additionally, nutritional components, especially the sugars and metal-based micronutrients can induce, enhance, and amplify the molecular damage either independently or in combination with other inducers of damage. The biological consequences of increased levels of molecular damage are wide ranging and include altered gene expression, genomic instability, mutations, molecular heterogeneity, loss of cell division potential, cell death, impaired intercellular communication, tissue disorganization, organ dysfunctions, and increased vulnerability to stress and other sources of disturbance. Historically, each of these biological consequences has been used as the basis of putting forward other theories of aging, such as replicative senescence theory, neuroendocrine theory, pineal gland theory, immunological theory and many more (Rattan, 2006; Rattan, 2008c).

GENETICS, POST-GENETICS, AND EPIGENETICS OF AGING

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p0085 Since all molecular processes in a living system are based in and regulated by genes, an attractive research strategy has been to discover genes for aging, termed gerontogenes (Rattan, 1985; Rattan, 1995; Johnson, 2002). However, the evolutionary explanation for the origins of aging and limited lifespan, as discussed above, have generally ruled out the notion of any specific genetic program involving specific gerontogenes. But a lack of specific gerontogenes, with the sole purpose of causing aging and terminating the lifespan of an individual, does not imply that genes do not or cannot influence survival, longevity, and the rate of aging.

p0090 There is ample evidence from studies performed on yeast and other fungi, nematodes, insects, rodents, and humans that mutations in various genes can either prolong or shorten the lifespan, and some of these are also the cause of premature aging syndromes in human beings (Martin, 2005; Kenyon, 2005; Kenyon, 2010; Christensen et al., 2006). Genetic linkage studies for longevity and several other studies showing an

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association between human longevity and single nucleotide polymorphisms (SNPs) in a variety of genes in various biological pathways, including heat shock response, mitochondrial functions, immune response, cholesterol metabolism, and others (Singh et al., 2004; Rattan and Singh, 2009; Yashin et al., 2012; Yashin et al., 2013). An analysis of the various functions of the genes associated with aging and longevity shows that these genes cover a wide range of biochemical pathways, such as energy metabolism, kinases, kinase receptors, transcription factors, DNA helicases, membrane glucosidases, GTP-binding protein coupled receptors, chaperones, and cell cycle check point pathways. What is clear from the identification of the genes influencing aging and longevity is that whatever their normal function and mechanism of action may be, these gerontogenes did not evolve to cause and accumulate molecular damage, to cause functional disorders, and to terminate the life of the organism.

p0095 Most of these genes have well defined roles in normal metabolism, in intra- and inter-cellular signaling, and in maintenance and repair functions including stress response. It is the damage-induced changes in the regulation, structure, and/or activity of their gene products which result in their altered biological role with age. Therefore, such genes have been termed 'virtual gerontogenes' (Rattan, 1995; Rattan, 1998). Furthermore, a lack of evolutionary selection of virtual gerontogenes has given rise to the notion of post-genetics or 'post-reproductive genetics' as an explanation for different biological roles played at different ages by the same genetic variants (Franceschi et al., 2005).

s0045 Epigenetics of Aging

p0100 Although genes are the foundation of life, genes in themselves are non-functional entities. It is the wide variety of gene products, including coding and non-coding RNAs, proteins, and other macromolecules which constitute the biochemical and biophysical milieu for life to exist. 'Epigenetics' is the most commonly used term to account for and to explain the consequences of the intracellular and extracellular milieu, which establish and influence the structural and functional stability of genes. These epigenetic effects and alterations are generally not passed down from one generation to the next, but have strong deterministic effects on the health, survival, and aging of the individual.

p0105 So far, there is only scant information available about the involvement in aging of various intracellular epigenetic markers such as methylated cytosines, oxidatively modified nucleotides, alternatively spliced RNAs, and post-translationally modified proteins, including protein folding (Lund and van Lohuizen, 2004). The full spectrum of epigenetics of aging is yet to be unraveled and at present is one of the most attractive and challenging areas of research in biogerontology (Johnson et al., 2012; Heyn et al., 2012; Hannum et al., 2013). A major reason for apparent difficulties in fully understanding the epigenetics of aging is the existence of several orders higher complexity and diversity of the constituent components such as physical, chemical, biological, and environmental factors, including psychological factors in human beings. Furthermore, in order to understand how various conditions influence, regulate, and modulate the actions, interactions, and networks of gene products during aging will require new intellectual and technical tools, such as systems analysis, bioinformatics, and functional genomics involving simultaneous multiple analyses.

AGING INTERVENTIONS s0050

p0110 The biological process of aging underlies all major human diseases. Although the optimal treatment of each and every disease, irrespective of age, is a social and moral necessity, preventing the onset of age-related diseases by intervening in the basic process of aging is the best solution for improving the quality of human life in old age. According to the three principles of aging and longevity described above, having the bodies that we have developed after millions of years of evolution, occurrence of aging in the period beyond ELS, and the onset of one or more diseases before eventual death, appear to be the normal sequence of events. This viewpoint makes modulation of aging by prevention very much different from the treatment of a specific disease.

p0115 Scientific and rational anti-aging strategies aim to slow down aging, to prevent or delay the physiological decline, and to regain lost functional abilities. In order to modulate aging for achieving healthy old age and for extending lifespan, three main conditions need to be fulfilled, as represented by the equation $E = GMC^2$, where G genes and M milieu are the critical factors amenable to intervention (Rattan, 2007b).

Gene Therapy s0055

p0120 One of the earliest experimental studies which demonstrated that an induced mutation in a single gene can increase the lifespan of an organism was the discovery of the so-called *age-1* mutant in the nematode *Caenorhabditis elegans* (Friedman and Johnson, 1988a,b). Since then hundreds of putative gerontogenes or

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longevity genes have been reported in *C. elegans*, *Drosophila* and rodents, which when mutated result in the extension of average and maximum lifespan of the organism. The methods used for the identification of such genes include induction of mutations and deletions by irradiation and chemical mutagens, alterations in gene expression by knockout, homologous recombination, or by gene addition, and reduction in gene expression by RNAi-induced abrogation of translation. It is important to realize that in almost all such cases longevity extension had occurred when one or multiple interventions resulted in the reduction or total inhibition of the activity of one or more genes (Rattan and Singh, 2009). Some of the main pathways whose 'loss of function' is shown to associate with extended period of survival are: (i) energy generation and utilization in mitochondrial respiratory chain; (ii) nutrition and hormonal sensing and signaling including insulin/insulin-like growth factor-1 and its target forkhead transcription factor FOXO, transcriptional silencing by sirtuin-mediated histone deacetylase; and (iii) translational interference through target of rapamycin (TOR). Similarly, there are other examples which show that several mutant mice strains with defects in growth hormone (GH) pathways including deficiencies of GH levels and GH receptor have extended lifespans. Application of RNAi technology will further identify numerous genes whose normal levels of activities are lifespan restricting (Rattan and Singh, 2009; Kenyon, 2010; Holliday and Rattan, 2010). Studies have also been performed in which the effects of adding one or multiple copies of various genes, leading to the increased expression of their gene products, has resulted in the extension of lifespan. Some such transgenic manipulations in model systems include the addition of gene(s) for one of the protein elongation factors, antioxidant genes superoxide dismutase and catalase, sirtuin, forkhead trascription factor FOXO, heat shock proteins (HSP), heat shock factor (HSF), protein repair methyltransferase and klotho, which is an inhibitor of insulin and IGF1 signaling (Rattan and Singh, 2009).

p0125 Although these studies have demonstrated longevity-extending effects of various genes in controlled laboratory conditions, there is very little information available on the basic process of aging in terms of the rate and extent of occurrence and accumulation of macromolecular damage and its physiological consequences in these animals. There is also almost no information available as to what is the physiological price paid for inactivating such genes whose normal function is a part of the general metabolism and signaling. There is some evidence that laboratory-protected longevity mutants in *C. elegans* have reduced Darwinian fitness when competing with the wild type worms under nutritionally challenging conditions. Similarly, klotho-induced insulin resistance and the paradox of the insulin/IGF-1 signaling pathways in longevity extension seriously question the practicality of such gene manipulations in humans (Rincon et al., 2004; Van Voorhies et al., 2006; Unger, 2006).

p0130 Another system in which genetic interventions have been tried as potential anti-aging therapies is the Hayflick system of limited proliferative lifespan of normal diploid differentiated cells in culture (Rattan, 2008a). Almost all the genetic interventions by transient or permanent transfection and ectopic expression of various genes on this model system have focused on extending the replicative lifespan of cells by bypassing the cell cycle check-points (Campisi and d'Adda di Fagagna, 2007; Collado et al., 2007). One of the most widely used genetic interventions in indefinitely extending the replicative lifespan of normal cells has been the ectopic expression of telomerase in a wide variety of cells (Simonsen et al., 2002; Davis and Kipling, 2005). However, continuous proliferation by such genetically modified non-aging cells often leads to their genomic instability, transformation, and cancer-forming activity (Wang et al., 2000; Serakinci et al., 2004). In the case of animals, whereas telomerase negative mice show reduced lifespan and some other abnormalities after six-generations (Lansdorp, 1997), overexpression of telomerase in the skin increases myc-induced hyperplasia (Flores et al., 2006) without any extension of lifespan.

p0135 Considering that the molecular cause of aging is the progressive accumulation of macromolecular damage and increased molecular heterogeneity, there are at least three major targets for anti-aging genetic interventions: (1) increasing the repair of damaged macromolecules, for example DNA repair pathways; (2) increasing the removal of damaged macromolecules, for example proteasomal and lysosomal pathways; and (3) decreasing the source of damaging agents, for example ROS, other FR, and reactive sugar metabolites. Whereas the first two targets basically imply achieving genetic enhancement or genetic improvement, the third target requires resetting the metabolic pathways.

p0140 All of the above targets for anti-aging interventions involve hundreds of genes and gene products, whose expression and action are evolutionarily highly regulated in a cell-type-specific manner. Although there are several approaches in development for gene-based enhancement of physical strength, endurance, appearance, and memory, there are serious technical limitations and ethical and safety concerns that remain to be resolved. Preventing or treating one or more age-related diseases by gene therapy, including stem cells, are at best piecemeal treatments which are often temporary or become unsuccessful since these are

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overshadowed by the systemic aging of the whole body. Ideally, gene therapy for the process of aging requires a significant and 'intelligent' redesigning already at the level of the zygote for better maintenance and survival of the body without having to trade-off with growth, development, and reproduction. The chances of such an 'intelligently redesigned' and directed evolution to succeed in competition with the Darwinian natural selection from much larger random variations and combinations are practically none.

s0060 Manipulating the Milieu

p0145 The second parameter M in the equation $E = GMC^2$ represents milieu – the environment in which living systems operate and survive. The milieu in which genes and gene products function ranges from the intracellular molecular and ionic milieu to all other levels of organization including cellular, physiological, psychological, and societal. Almost all the ongoing work on aging modulation and intervention at present is aimed at modifying the milieu by either replenishing those enzymes, hormones and other molecules, such as antioxidants and micronutrients, whose levels are reported to decrease during aging. Although some of these approaches have been shown to have some clinical benefits in the treatment of some diseases in the elderly, none of these really modulate the aging process itself. However, another approach for aging intervention that has been drawing a lot of attention and has significant potential is that of mild stress-induced hormesis, discussed below.

s0065 HORMETICS, HORMESIS, AND HORMETINS

p0150 A promising strategy to slow down aging and prevent or delay the onset of age-related diseases is that of mild stress-induced hormesis. The consequences of stress can be both harmful and beneficial depending on the intensity, duration, and frequency of the stress, and on the price paid in terms of energy utilization and other metabolic disturbances. However, the most important aspect of biological stress response (SR) is that it is not monotonic with respect to the dose of the stressor. SR is almost always characterized by a nonlinear biphasic relationship. Several meta-analyses performed on a large number of papers published in the fields of toxicology, pharmacology, medicine, and radiation biology have led to the conclusion that the most fundamental shape of the dose response is neither threshold nor linear, but is U- or inverted U-shaped, depending on the endpoint being measured. This phenomenon of biphasic dose response is termed hormesis (Calabrese et al., 2007), and the study and science of hormesis is termed hormetics (Rattan, 2012a).

p0155 The key conceptual features of hormesis are the disruption, the modest overcompensation, and the re-establishment of homeodynamics. Hormesis in aging is characterized by the life-supporting beneficial effects resulting from the cellular responses to single or multiple rounds of mild stress. It is important to note that although the hormetic zone is usually small, both with respect to the dose and the effect, its biological consequences are cumulative, amplified, and physiologically significant (Rattan, 2008b,d; Demirovic and Rattan, 2013).

p0160 All such conditions which bring about biologically beneficial effects by initially causing low level molecular damage, and then lead to the activation of one or more SR pathways and thereby strengthens the homeodynamics, are termed hormetins (Rattan, 2008b,d). Hormetins may be further categorized as: (1) Hormetin-P, physical hormetins, such as exercise, thermal shock, and irradiation; (2) Hormetin-M, mental hormetins, such as mental challenge and focused attention or meditation; and (3) Hormetin-N, nutritional and biological hormetins, such as infections, micronutrients, spices, and some oils and fatty acids.

p0165 An example of stress-induced hormesis is the well-documented beneficial effects of moderate exercise as a hormetin, which initially increases the production of FR, acids, and aldehydes. Another frequent observation in studies of hormesis is that a single hormetic agent, such as heat shock (HS) or exercise, can strengthen the overall homeodynamics of cells and enhance other abilities, such as tolerance to other stresses, by initiating a cascade of processes resulting in a biological amplification and eventual beneficial effects (Rattan, 2008b,d; Demirovic and Rattan, 2013).

p0170 Various mild stresses that have been reported to delay aging and prolong longevity in cells and animals include temperature shock, irradiation, heavy metals, pro-oxidants, acetaldehyde, alcohols, hypergravity, exercise, and food restriction (Le Bourg and Rattan, 2008). Aging modulatory and other effects of hormesis have also been reported for human cells. For example, using a regimen of repeated mild HS given to cultured normal human skin fibroblasts, keratinocytes, endothelial cells, and telomerase-immortalized bone marrow mesenchymal stem cells, a variety of hormetic effects have been reported. These effects include slowing down of cellular aging, extension of cellular replicative lifespan, maintenance of youthful morphology, reduction in molecular damage, and improvement in differentiation, wound healing, and angiogenesis. Other hormetic conditions, which

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have been shown to have anti-aging effects in human cells are irradiation, mechanical stretching, and electromagnetic field shock (Rattan, 2008b,d; Demirovic and Rattan, 2013).

p0175 Nutritional hormetins, especially those derived from plant and animal sources, including oils and fatty acids, have generated much scientific interest for their beneficial health effects (Canuelo et al., 2012; Hamel et al., 2008; Niki et al., 2005). This is because of the realization that not all chemicals found in plants are beneficial for animals in a simple and straightforward manner. Instead, they cause molecular damage by virtue of their electrochemical properties and have a typical biphasic hormetic dose response. Some examples of nutritional hormetins involving heat shock response (HSR) are phenolic acids, polyphenols, flavanoids, ferulic acid geranylgeranyl, rosmarinic acid, kinetin, zinc, and the extracts of tea, dark chocolate, saffron, and spinach, components of olive oil and other fatty acids (Rattan, 2008b,d; Canuelo et al., 2012; Hamel et al., 2008; Niki et al., 2005).

p0180 Hormesis may also provide an explanation for the health beneficial effects of numerous other foods and food components such as garlic, Gingko, and other fruits and vegetables (Everitt et al., 2006; Hayes, 2005; Hayes, 2007; Ferrari, 2004; Gurib-Fakim, 2006). Understanding the hormetic and interactive mode of action of natural and processed foods is a challenging field of research, and has great potential in developing nutritional and other lifestyle modifications for aging intervention and therapies. However, not all pathways of SR respond to every stressor, and although there may be some overlap, generally these pathways are quite specific. The specificity of the response is mostly determined by the nature of the damage induced by the stressor and the variety of downstream effectors involved. Yet, the major pathways of SR can be used as the screening platform for discovering, testing, and monitoring the effects of novel hormetins. For example, it may be possible to develop multi-hormetin formulations as drugs and nutriceuticals whose mode of action is through hormetic pathways by mild stress-induced stimulation of homeodynamic processes.

p0185 Finally, while the G and M components of the $E = GMC^2$ formula for eternal life are being taken care of by various experimental approaches, the third factor C represents chance, which is the probability of stochastic events leading to a cascade of error-catastrophe in complex interacting systems. Recent developments in our understanding of complex networks at all levels of organization from molecular to societal and global networks have highlighted the vulnerability of all strong and weak links, and have reasserted the significance of chance events which are not amenable to regulation and manipulation. In the context of modulating aging, repeated mild stress-induced hormesis increases the boundaries of the homeodynamic space thus giving cells and organisms wider margins for metabolic fluctuation and adaptation. Slowing down the shrinkage of the homeodynamic space hormetically will reduce the probability of occurrence and emergence of various diseases in old age, and thus extend the health span.

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NON-PRINT ITEM

Abstract

Aging is well understood in evolutionary and biological terms, and a distinctive framework has been established upon which general principles of aging and longevity can be formulated. These principles of aging can be the basis for developing effective aging interventional strategies for prevention and therapies. Aging and longevity are not determined by any specific gerontogenes, but are the result of imperfect maintenance and repair. At the cellular and molecular levels aging is characterized by the progressive failure of homeodynamics, unregulated growth, accumulation of macromolecular damage, increased molecular heterogeneity, altered cellular functioning, and reduced stress tolerance and ability to adapt. Novel approaches for testing and developing effective means of intervention, prevention, and modulation of aging incorporate means to minimize the occurrence and accumulation of molecular damage, and to strengthen the homeodynamics of the organism. Gene therapy, stem cell therapy, hormonal replenishment, nutritional supplementation, and other natural and synthetic molecules demonstrate varying degrees of promise and success as aging interventions. Another powerful strategy for achieving healthy aging and for preventing age-related diseases is that of mild stress-induced hormesis by physical, mental, and nutritional hormetins including exercise, polyphenols, flavonoids, and oils and fatty acids. A combination of different approaches for aging interventions aims to extend the health span and improve the quality of life.

Keywords: biogerontology; gerontogenes; homeostasis; homeodynamics; hormetics; hormesis; hormetins