

Review Article**Aging Is Not a Disease: Implications for Intervention**

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[Received October 10, 2013; Revised October 22, 2013; Accepted November 1, 2013]

**ABSTRACT:** Aging of biological systems occurs in spite of numerous complex pathways of maintenance, repair and defense. There are no gerontogenes which have the specific evolutionary function to cause aging. Although aging is the common cause of all age-related diseases, aging in itself cannot be considered a disease. This understanding of aging as a process should transform our approach towards interventions from developing illusory anti-aging treatments to developing realistic and practical methods for maintaining health throughout the lifespan. The concept of homeodynamic space can be a useful one in order to identify a set of measurable, evidence-based and demonstratable parameters of health, robustness and resilience. Age-induced health problems, for which there are no other clear-cut causative agents, may be better tackled by focusing on health mechanisms and their maintenance, rather than only disease management and treatment. Continuing the disease-oriented research and treatment approaches, as opposed to health-oriented and preventive strategies, are economically, socially and psychologically unsustainable.

**Key words:** longevity, stress, homeostasis, homeodynamics, hormetics, hormesis, hormetin

One's understanding of biological aging, either as a disease or as a process that increases the chances of the onset of diseases, has serious implications with respect to interventional strategies. If aging is considered as a disease, then, in an ideal condition and in principle, this could be fully treatable, and a disease-free state could be achieved. However, if aging is understood as an emergent phenomenon occurring progressively in each and every individual surviving beyond certain duration of life within the evolutionary framework, then aging cannot be considered as a disease. This latter viewpoint then transforms our approach towards aging interventions from the so-called anti-aging treatments to achieving healthy aging. This also means abandoning enemy-oriented rhetoric, such as the "war against aging", "defeating aging", and "conquering aging" etc. Instead, interventions in aging require a health-oriented approach and the use of a positive language such as maintaining health, achieving

healthy aging, and having active aging. Of course, optimal treatment and management of every disease, irrespective of age, is a social and moral imperative. But considering aging as a disease that happens to everybody is an oxymoron.

**Biological understanding of aging**

More than fifty years of modern biogerontological research has resulted in attaining certain understanding about the evolutionary and mechanistic explanations of aging and longevity, which are generally accepted by most scientists [1, 2]. For example, the emergence of the aging phenotype at the biological level mostly occurs during the survival period beyond the natural longevity of a species, termed as the essential lifespan (ELS) [3, 4], or the warranty period [5–7]. Although some biodemographers would argue that human aging begins

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even before birth [8], from birth or from the age of puberty [9, 10], biogerontologists generally support the view that aging begins after ELS, which for human species is between 40 and 50 years [11–14].

The above view-point has developed from the basic biological understanding that survival of an organism is a dynamic tug between the occurrence of damage and the processes of maintenance and repair systems (MARS), which are also the main target of evolutionary investment,

stability and selection [1, 12, 14–21]. Evolutionary natural selection operates on the longevity assurance processes [22], which effectively determine ELS or longevity of a species.

The main MARS are listed in Table 1, which comprise the longevity assurance- or ELS-assurance processes, and involve hundreds of genes and genetic networks.

**Table 1.** Biological maintenance and repair systems and their molecular mediators for longevity assurance and essential lifespan (*modified from* [23])

Biological process	Molecular mediators
Sensing and responding to intra- and extra-cellular stress	Receptors and signaling molecules, stress-responding transcription factors, chaperones, anti-oxidative enzymes, cytokines, sirtuins
Nuclear and mitochondrial DNA repair	DNA repair systems
Protein repair and degradation.	Proteasome, protein repair systems
Removal and turnover of defective macromolecules and organelles	Autophagosomes, lysosomes
Defences against reactive oxygen species and other free radicals	Antioxidants, antioxidative enzymes
Detoxification of chemicals and nutritional metabolites	Cytochrome P450, phase-I and phase-II enzymes
Innate and adaptive immune responses and apoptosis	Caspases, cytokines, antibodies
Wound healing, tissue regeneration and other higher order processes, including thermal regulation, neuro-endocrine balance, daily rhythms	Cytokines, growth factors, signaling molecules

The traditional conceptual model to describe this characteristic of maintenance, repair and stability of the living systems is the concept of homeostasis. However, homeostasis, which means “the same state”, does not do full justice in describing the biological systems. Homeostasis fails to incorporate dynamic, constantly changing and adapting nature of biological growth, development, maturation, reproduction and aging processes. Therefore, the term homeodynamics [24], and the concept of homeodynamic space have been proposed [25–29]. Homeodynamic space, which may also be considered as the “survival ability” or the “buffering capacity” of a biological system, is the ultimate

determinant of an individual’s health, and the ability to survive and maintain a functional healthy state [6, 27–30]. At the species level, biological evolutionary processes have optimised homeodynamics and assured the longevity for a limited period of ELS, which is required for successful reproduction.

The three main characteristics of the homeodynamic space are: (1) damage control, (2) stress response (SR), and (3) constant remodeling and adaptation [27, 28]. A large number of molecular, cellular and physiological pathways and their networks, including those listed in Table 1, determine the nature and extent of the homeodynamic space. It is the progressive shrinkage of

the homeodynamic space that defines the aging process [27, 28].

At the biochemical level, shrinkage of the homeodynamic space occurs mainly due to the stochastic occurrence and semi-stochastic accumulation of molecular damage [23, 27, 28]. Various concepts put forward to explain the mechanistic basis of aging incorporate, in one or the other way, molecular damage, molecular heterogeneity and metabolic imbalance as the “cause” of aging. These concepts include virtual gerontogenes [31], system failure [16], unregulated growth-related quasi-programme [32], and metabolic instability [15, 33]. All these views directly or indirectly reject the notion of the evolution of any specific and real genes for aging, gerontogenes, which have the naturally selected function of causing aging and death of an individual. Shrinkage of the homeodynamic space, in terms of reduced ability for stress tolerance, damage control and remodeling, leads to the increased zone of vulnerability and increased probabilities of the onset and emergence of all age-related and chronic diseases [23, 27, 28]. Thus, aging is not a disease, but is a condition that allows or induces the emergence of one or more diseases in some, but not all, old people.

### Health and its maintenance

As argued above, aging occurs in spite of complex MARS, which assure survival for an evolutionarily-meaningful duration of life, ELS. There is no enemy within and no real gerontogenes exist which have the specific and naturally selected function to cause aging and death of an individual. More importantly, understanding the complexity of the aging process cautions against the simplistic engineering approaches of redesigning and other anti-aging treatments using natural or synthetic chemicals, food components and gene-modifications [14, 34–37].

Understanding of aging as the failure of MARS and the shrinkage of the homeodynamic space should transform our approach towards aging interventions from anti-aging treatments to methods of maintaining and strengthening MARS for healthy aging. Furthermore, the prevalent dominant approach of disease-directed treatments now face the challenge of how to deal with physical, mental and social health issues where there are no clear-cut causative agents such as germs, bacteria, viruses and pollutants etc. Major chronic conditions, for example, metabolic disorders, depression, dementia, malnutrition and several types of age-related cancers, are mostly due to the generalised failure and dysregulation of processes of life and their interactive networks, and not due to any specific cause(s) [38–41]. These conditions lead to the more specific diseases, such as Alzheimer’s

disease, Parkinson’s disease, diabetes-2, cataract, osteoporosis, and others, which may be open to management and therapeutic approaches.

Another important reason for the need of having aging interventions through health-oriented strategies is the ongoing debate as to whether continuing the disease-oriented approach to health is scientifically and socio-economic-politically compatible with the future of global health and economic sustainability [42–44]. Several prospective analyses have shown that the prevalent disease-management or disease-treatment approaches are economically, socially and psychologically unsustainable as compared with health-oriented and preventive strategies [6, 43–46].

But what is health? Health is often described either in the context of the absence of one or more diseases or as a vague concept of well-being, without having any objective measures for that. Although various parameters of frailty have been proposed [47–50], direct measures of health largely remain undefined. However, some attempts have been made to define health and quality of life. For example, taking into consideration the functionality of the living system as a crucial phenotype and the concept of activities of daily living (ADL), which is a well-established term [51], health could be defined as a state of COMPLETE physical and mental independence in ADL [28]. This definition of health is very much similar to the WHO’s definition as “*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity* ([www.who.int/topics/mental\\_health/en/](http://www.who.int/topics/mental_health/en/)), which is incomplete, vague, and does not clarify what is meant by “well-being” in definitive terms. Furthermore, this is an idealized state, which perhaps no one can have. Similarly, health has been defined as the ability to adapt and self manage [52], which although includes certain aspects of functionality, it still implies a kind of an idealized state of adaptation and self-management.

Therefore, a pragmatic and realistic definition of health has been formulated as having ADEQUATE physical and mental independence in ADL [28]. This state of adequacy can vary widely and may be very individualistic, but it may be possible to establish it objectively by measuring a series of functional markers. In juxtaposition, a widely used phrase “quality of life” is almost entirely a subjective notion shaped by culture, surroundings and other psycho-social factors, and can be independent of any biological or other markers of health [53–55].

The pragmatic definition of health as a state of having adequate physical and mental independence in ADL requires identifying a set of measurable parameters at the most fundamental level of biological organization. Analyzing the components of the homeodynamic space

can be an objective way to quantify health at the level of cells, tissues and the body, and in turn may be accessible to interventions. In this context, the main aspects of health that need to be better understood objectively, and those which will be useful for developing evidence-based markers of health and intervention, are the following:

1. Immediate and delayed stress response profiles of cells, organisms and humans at different ages [25]. This will include developing methods for measuring resilience and robustness, in terms of biological and psychological parameters of wellness and well-being [56–58].
2. Relationship between stress tolerance, recovery, survival, immune response and longevity could be studied at different levels and ages, using a variety of systems and making use of the most comprehensive longitudinal studies examining health-related genetic and non-genetic processes [59].
3. Physiological and psychological criteria and methods to monitor health improvement (as measured by health markers and ADL discussed above) by physical, nutritional or other interventions [60–63].

### Aging interventions

One's approach towards intervention is determined by the viewpoint as to whether aging is a disease or aging is a process and a condition that increases the chances of onset of chronic diseases. Presently, there are four main streams of aging interventions: wishful thinking, piecemeal remedies, replenishing the loss of hormones, enzymes and other biomolecules, and strengthening the homeodynamics, which are discussed briefly as follows.

1. Wishful thinking, almost at the level of searching for the illusory fountain of youth, often trivializes the complexity of aging into an issue of intelligent redesigning and reverse- or forward-engineering. Several critiques of such approaches giving false hopes and impracticalities have been published [14, 34–37], with little or no effect on the proponents of those views.
2. Piecemeal remedies are the common and prevalent anti-aging or anti-disease treatments. The basic principle behind this approach is to “fix what is broke”; and this “fixing” ranges from the traditional tissue and organ repair, transplantation and replacement to targeted treatments with stem cells. Although such interventions often have life-saving effects in acute situations, these benefits are often transient, limited and require recurring interventions, with so far little evidence as being long-term aging interventions [64–67].
3. Replenishing the loss is the most widely used aging

interventional strategy, which is often based on the naïve understanding that age-related decline in the levels of enzymes, hormones or other metabolites is always harmful, and that these changes should be reset to the youthful levels. Biogerontological studies, however, have repeatedly shown that numerous age-induced changes in the immune system, hormone levels and other proteins and enzymes are the sign of constant remodeling and adaptation for survival and health [68]. For example, experimental studies on the extension of lifespan of various model systems by genetic and non-genetic means clearly show that a reduction in the levels of various hormones and their intermediates and receptors is almost always a requirement [69–71]. Exceptional longevity of naked mole rats and bats [72–75] is accompanied by reduced hormone levels and increased MARS. In humans, low levels of growth hormone and sex steroids in eunuchs and in castrated men are reported to increase their longevity [76, 77]. Supplementation with hormones, antioxidants and other such nutritional replenishments have little, none or even harmful effects in normal healthy model systems and in humans [41, 78–81].

4. Strengthening the homeodynamics is apparently the most promising aging interventions, which is based on the principles of hormesis [82, 83]. Hormesis in aging is defined as the life-supporting beneficial effects resulting from the cellular responses to single or multiple rounds of mild stress [84]. Moderate physical exercise is the paradigm for hormesis. Various other stressors that have been reported to modulate aging and prolong longevity in cells and animals include heat shock, irradiation, heavy metals, pro-oxidants, acetaldehyde, alcohols, hypergravity, polyphenols, flavonoids, and short-term and long-term dietary restriction, including intermittent fasting [82–85].

All such conditions, which can bring about biologically beneficial effects by causing mild stress, and in turn stimulating various defense pathways, are termed as hormetins [62, 84, 86]. Hormetins are categorized as: (1) physical hormetins, such as physical exercise, heat and radiation; (2) psychological or mental hormetins, such as increased brain activity through appropriate cognitive games and challenges, including solving puzzles, focused attention and meditation; and (3) biological and nutritional hormetins, such as micronutrients, phytochemicals in spices and other natural and synthetic food sources. Discovering novel hormetins as modulators of aging and longevity is a developing area of research, which is also drawing attention of the aesthetic, health-care and food industry [87, 88]. There are, however,

several issues regarding the dose, timing, frequency and specificity of various stresses are yet to be resolved by proper research and careful testing.

### Concluding remarks

Most of the biomedical research is so far dominated and supported by disease-directed thinking. Some biogerontologists have also succumbed to these pressures of disease-dominated world-view to the extent that they consider aging as another disease. Although “aging is a disease” kind of rhetoric may have some role to play in attracting the attention of big business and investors, it totally disregards the scientific history and understanding of biogerontology. Furthermore, a lack of interdisciplinary health discussion among scientists and other scholars has allowed the growth of numerous self-proclaimed anti-aging specialists and longevity-gurus, generating a lot of confusion, false promises, muddled thinking, and impractical and even harmful interventions [14, 34–37].

More than fifty years of biogerontological and other research on life processes and lifestyle-related diseases has shown that the issues of aging, quality of life and longevity cannot be successfully approached with disease-oriented thinking. Therefore, a change and a paradigm shift is required in thinking, approaching and developing strategies towards understanding health, maintaining health, extending the health-span, and enhancing public- and social-health.

### Acknowledgement

Laboratory of Cellular Ageing is financially partially supported by a research grant from LVMH Recherche, Saint Jean de Braye, France.

### References

- [1] Holliday R (2006). Aging is no longer an unsolved problem in biology. *Ann NY Acad Sci*, 1067:1-9.
- [2] Hayflick L (2007). Biological aging is no longer an unsolved problem. *Ann NY Acad Sci*, 1100:1-13.
- [3] Rattan SIS (2000). Biogerontology: the next step. *Ann NY Acad Sci*, 908:282-290.
- [4] Rattan SIS (2006). Theories of biological aging: genes, proteins and free radicals. *Free Rad Res*, 40:1230-1238.
- [5] Carnes BA (2007). Senescence viewed through the lens of comparative biology. *Ann N Y Acad Sci*, 1114:14-22.
- [6] Carnes BA (2011). What is lifespan regulation and why does it exist? *Biogerontology*, 12:367-374.
- [7] Carnes BA, Olshansky SJ, Grahn D (2003). Biological evidence for limits to the duration of life. *Biogerontology*, 4:31-45.
- [8] Mentis AF, Kararizou E (2010). Does ageing originate in utero? *Biogerontology*, 11:725-729.
- [9] Gavrilov LA, Gavrilova NS (2011). Mortality Measurement at Advanced Ages: A Study of the Social Security Administration Death Master File. *N Am Actuar J*, 15:432-447.
- [10] Gavrilov LA, Gavrilova NS (2012). Biodemography of exceptional longevity: early-life and mid-life predictors of human longevity. *Biodemography Soc Biol*, 58:14-39.
- [11] Carnes BA, Witten TM (2013). How long must humans live? *J Gerontol Bio Sci*, in press, doi:10.1093/gerona/glt164:
- [12] Hayflick L (2007). Entropy explains aging, genetic determinism explains longevity, and undefined terminology explains misunderstanding both. *PLoS Genet*, 3:e220.
- [13] Holliday R (2009). Genes and the evolution of longevity. *Biogerontology*, 10:1-2.
- [14] Holliday R, Rattan SIS (2010). Longevity mutants do not establish any "new science" of ageing. *Biogerontology*, 11:507-511.
- [15] Demetrius L (2013). Boltzmann, Darwin and directionality theory. *Physics Reports*, 530:1-85.
- [16] Gavrilov LA, Gavrilova NS (2001). The reliability theory of aging and longevity. *J Theor Biol*, 213:527-545.
- [17] Gladyshev VN (2013). The origin of aging: imperfectness-driven non-random damage defines the aging process and control of lifespan. *Trends Genet*, 29:506-512.
- [18] Holliday R (2007). *Ageing: the paradox of life*. Dordrecht, The Netherlands, Springer.
- [19] Kirkwood TBL. *Time of Our Lives*. London, Weidenfeld & Nicolson, (1999).
- [20] Wensink M (2013). Age-specificity and the evolution of senescence: a discussion. *Biogerontology*, 14:99-105.
- [21] Wensink MJ, van Heemst D, Rozing MP, Westendorp RG (2012). The maintenance gap: a new theoretical perspective on the evolution of aging. *Biogerontology*, 13:197-201.
- [22] Martin GM (2007). Modalities of gene action predicted by the classical evolutionary theory of aging. *Ann NY Acad Sci*, 1100:14-20.
- [23] Rattan SIS (2008). Increased molecular damage and heterogeneity as the basis of aging. *Biol Chem*, 389:267-272.
- [24] Yates FE (1994). Order and complexity in dynamical systems: homeodynamics as a generalized mechanics for biology. *Math Comput Model*, 19:49-74.
- [25] Demirovic D, Rattan SIS (2013). Establishing cellular stress response profiles as biomarkers of homeodynamics, health and hormesis. *Exp Gerontol*, 48:94-98.
- [26] Rattan SIS (2010). Targeting the age-related occurrence, removal, and accumulation of molecular damage by hormesis. *Ann N Y Acad Sci*, 1197:28-32.
- [27] Rattan SIS (2012). Biogerontology: from here to where? The Lord Cohen Medal Lecture-2011. *Biogerontology*, 13:83-91.

- [28] Rattan SIS (2013). Healthy ageing, but what is health? *Biogerontology*, *in press* DOI 10.1007/s10522-013-9442-7
- [29] Rattan SIS, Demirovic D (2009). Hormesis and aging. In: Mattson MP, Calabrese E, editors. *Hormesis: a revolution in biology, toxicology and medicine*. New York, Springer: 153-175.
- [30] Rattan SIS (2007). Homeostasis, homeodynamics, and aging. In: Birren J, editor. *Encyclopedia of Gerontology*. UK, Elsevier Inc.: 696-699.
- [31] Rattan SIS (1995). Gerontogenes: real or virtual? *FASEB J*, 9:284-286.
- [32] Blagosklonny MV (2012). Cell cycle arrest is not yet senescence, which is not just cell cycle arrest: terminology for TOR-driven aging. *Aging (Albany NY)*, 4:159-165.
- [33] Demetrius L (2004). Calorie restriction, metabolic rate and entropy. *J Gerontol Biol Sci*, 59A:902-915.
- [34] Le Bourg E (2000). Gerontologists and the media: false hopes and fantasies can be hazardous for science. *Biogerontology*, 1:371-372.
- [35] Le Bourg E (2013). Obsolete ideas and logical confusions can be obstacles for biogerontology research. *Biogerontology*, 14:221-227.
- [36] Olshansky SJ, Carnes BA (2012). Science fact versus SENS foreseeable. *Gerontology*, 59:190-192.
- [37] Warner H, Anderson J, Austad S, Bergamini E, Bredesen D, Butler R et al. (2005). Science fact and the SENS agenda. What can we reasonably expect from ageing research? *EMBO Rep*, 6:1006-8.
- [38] O'Neill D (2013). 2012 - That was the year that was. *Age Ageing*,
- [39] Tacutu R, Budovsky A, Yanai H, Fraifeld VE (2011). Molecular links between cellular senescence, longevity and age-related diseases - a systems biology perspective. *Aging (Albany NY)*, 3:1178-1191.
- [40] Walter S, Atzmon G, Demerath EW, Garcia ME, Kaplan RC, Kumari M et al. (2011). A genome-wide association study of aging. *Neurobiol Aging*, 32:2109 e15-28.
- [41] Watson J (2013). Oxidants, antioxidants and the current incurability of metastatic cancers. *Open Biol*, 3:120144.
- [42] Farrelly C (2008). A tale of two strategies. *EMBO Rep*, 9:92-95.
- [43] Olshansky SJ, Biggs S, Achenbaum WA, Davison GC, Fried L, Gutman G et al. (2011). The global agenda council on the ageing society: policy principles. *Global Policy*, 2:97-105.
- [44] Vaupel JW (2010). Biodemography of human ageing. *Nature*, 464:536-542.
- [45] Carnes BA, Olshansky SJ, Hayflick L (2012). Can Human Biology Allow Most of Us to Become Centenarians? *J Gerontol A Biol Sci Med Sci*,
- [46] Goldman DP, Cutler D, Rowe JW, Michaud PC, Sullivan J, Peneva D et al. (2013). Substantial health and economic returns from delayed aging may warrant a new focus for medical research. *Health Aff (Millwood)*, 32:1698-1705.
- [47] Fulop T, Larbi A, Witkowski JM, McElhaney J, Loeb M, Mitnitski A et al. (2010). Aging, frailty and age-related diseases. *Biogerontology*, 11:547-563.
- [48] Hubbard RE, Woodhouse KW (2010). Frailty, inflammation and the elderly. *Biogerontology*, 11:635-641.
- [49] Mitnitski A, Song X, Rockwood K (2013). Assessing biological aging: the origin of deficit accumulation. *Biogerontology*, 14. *in press*.
- [50] Montesanto A, Lagani V, Martino C, Dato S, De Rango F, Berardelli M et al. (2010). A novel, population-specific approach to define frailty. *Age* 32:385-395.
- [51] Engberg H, Christensen K, Andersen-Ranberg K, Vaupel JW, Jeune B (2008). Improving activities of daily living in danish centenarians--but only in women: a comparative study of two birth cohorts born in 1895 and 1905. *J Gerontol A Biol Sci Med Sci*, 63:1186-1192.
- [52] Huber M, Knottnerus JA, Green L, van der Horst H, Jadad AR, Kromhout D et al. (2011). How should we define health? *BMJ*, 343:d4163.
- [53] Franco OH, Karnik K, Osborne G, Ordovas JM, Catt M, van der Ouderaa F (2009). Changing course in ageing research: The healthy ageing phenotype. *Maturitas*, 63:13-19.
- [54] Richter J, Schwarz M, Bauer B (2008). Personality characteristics determine health-related quality of life as an outcome indicator of geriatric inpatient rehabilitation. *Curr Gerontol Geriatr Res*, Article ID 474618; doi:10.1155/2008/474618:8.
- [55] Steptoe A, Leigh ES, Kumari M (2011). Positive affect and distressed affect over the day in older people. *Psychol Aging*, 26:956-965.
- [56] Byerley LO, Leamy L, Tam SW, Chou CW, Ravussin E (2010). Development of a serum profile for healthy aging. *Age*, 32:497-507.
- [57] Kitano H (2007). Towards a theory of biological robustness. *Mol Syst Biol*, 3:137.
- [58] Kriete A (2013). Robustness and aging- a systems-level perspective. *Biosystems*, 112:37-48.
- [59] Yashin AI, Arbeevev KG, Wu D, Arbeevev LS, Kulminski A, Akushevich I et al. (2013). How lifespan associated genes modulate aging changes: lessons from analysis of longitudinal data. *Front Genet*, 4:3.
- [60] Rattan SI (2012). Rationale and methods of discovering hormetins as drugs for healthy ageing. *Expert Opin Drug Discov*, 7:439-448.
- [61] Rattan SIS (2004). Aging, anti-aging, and hormesis. *Mech Age Dev*, 125:285-289.
- [62] Rattan SIS (2008). Hormesis in aging. *Ageing Res Rev*, 7:63-78.
- [63] Rattan SIS (2008). Principles and practice of hormetic treatment of aging and age-related diseases. *Hum Exp Toxicol*, 27:151-157.
- [64] Fuchs E, Chen T (2013). A matter of life and death: self-renewal in stem cells. *EMBO Rep*, 14:39-48.
- [65] Kuranda K, Vargaftig J, de la Rochere P, Dosquet C, Charron D, Bardin F et al. (2011). Age-related changes in human hematopoietic stem/progenitor cells. *Aging Cell*, 10:542-546.
- [66] Rodgerson DO, Harris AG (2011). A comparison of stem cells for therapeutic use. *Stem Cell Rev*, 7:782-796.

- [67] Seppet E, Paasuke M, Conte M, Capri M, Franceschi C (2011). Ethical aspects of aging research. *Biogerontology*, 12:491-502.
- [68] Franceschi C, Valensin S, Bonafè M, Paolisso G, Yashin AI, Monti D et al. (2000). The network and the remodeling theories of aging: historical background and new perspectives. *Exp Gerontol*, 35:879-896.
- [69] Bartke A, Westbrook R (2012). Metabolic characteristics of long-lived mice. *Front Genet*, 3:288.
- [70] Fontana L, Partridge L, Longo VD (2010). Extending healthy life span--from yeast to humans. *Science*, 328:321-326.
- [71] Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013). The hallmarks of aging. *Cell*, 153:1194-1217.
- [72] Kim EB, Fang X, Fushan AA, Huang Z, Lobanov AV, Han L et al. (2011). Genome sequencing reveals insights into physiology and longevity of the naked mole rat. *Nature*, 479:223-227.
- [73] Perez VI, Buffenstein R, Masamsetti V, Leonard S, Salmon AB, Mele J et al. (2009). Protein stability and resistance to oxidative stress are determinants of longevity in the longest-living rodent, the naked mole-rat. *Proc Natl Acad Sci U S A*, 106:3059-3064.
- [74] Brunet-Rossini AK, Austad SN (2004). Ageing studies on bats: a review. *Biogerontology*, 5:211-222.
- [75] Seim I, Fang X, Xiong Z, Lobanov AV, Huang Z, Ma S et al. (2013). Genome analysis reveals insights into physiology and longevity of the Brandt's bat *Myotis brandtii*. *Nat Commun*, 4:2212.
- [76] Hamilton JB, Mestler GE (1969). Mortality and survival: comparison of eunuchs with intact men and women in a mentally retarded population. *J Gerontol*, 24:395-411.
- [77] Min KJ, Lee CK, Park HN (2012). The lifespan of Korean eunuchs. *Curr Biol*, 22:R792-793.
- [78] Gutteridge JM, Halliwell B (2010). Antioxidants: Molecules, medicines, and myths. *Biochem Biophys Res Commun*, 393:561-564.
- [79] Hayes DP (2008). Adverse effects of nutritional inadequacy and excess: a hormetic model. *Am J Clin Nutr*, 88:578S-581S.
- [80] Le Bourg E (2005). Antioxidants and aging in human beings. In: Rattan SIS, editors. *Aging Interventions and Therapies*. Singapore, World Scientific Publishers: 85-107.
- [81] Wick G (2002). 'Anti-aging' medicine: does it exist? A critical discussion of 'anti-aging health products'. *Exp Gerontol*, 37:1137-1140.
- [82] Le Bourg E, Rattan SIS, Eds. *Mild stress and healthy aging: applying hormesis in aging research and interventions*. Dordrecht, The Netherlands, Springer; 2008.
- [83] Rattan SIS, Le Bourg E, Eds. *Hormesis in health and disease*. Boca Raton, CRC Press; 2013.
- [84] Rattan SIS, Demirovic D (2010). Hormesis can and does work in humans. *Dose Response*, 8:58-63.
- [85] Singh R, Lakhanpal D, Kumar S, Sharma S, Kataria H, Kaur M et al. (2011). Late-onset intermittent fasting dietary restriction as a potential intervention to retard age-associated brain function impairments in male rats. *Age (Dordr)*.
- [86] Rattan SIS, Fernandes RA, Demirovic D, Dymek B, Lima CF (2009). Heat stress and hormetin-induced hormesis in human cells: effects on aging, wound healing, angiogenesis and differentiation. *Dose Response*, 7:93-103.
- [87] Argyropoulou A, Aligiannis N, Trougakos IP, Skaltsounis AL (2013). Natural compounds with anti-ageing activity. *Nat Prod Rep*, 30:1412-1437.
- [88] Rattan SIS, Kryzch V, Schnebert S, Perrier E, Carine Nizard C (2013). Hormesis-based anti-aging products: a case study of a novel cosmetic. *Dose Response*, 11:99-108.