Syed Ibrahim Rizvi · Ufuk Çakatay
Editors

Molecular Basis and Emerging Strategies for Anti-aging Interventions

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Foreword

Is aging a disease? Are age-related diseases distinct from aging? Is aging a bad thing? Is aging a solvable medical problem?

These questions are highly divisive. To most people, it is extraordinary that the questions would even be asked, because the answers are so self-evident – but, of course, that is true both of people whose answers would be "yes" and of those whose answers would be "no." And that, itself, is unequivocally a problem – a BIG problem.

It turns out, furthermore, that the tenor of the debate around these questions varies considerably according to culture. I have lived most of my life in England, but now I live in California, where I find that there is far more agreement with my own answers to the above questions (which are "no," "no," "yes," and "yes," in case you were wondering) than elsewhere. Conversely, I find that the consensus in Asian countries is extraordinarily opposed to this way of thinking and wedded instead to the view that aging is a natural, inevitable, and welcome process that is utterly off-limits to medicine. This attitude to aging has something of a silver lining, in that it also underpins the deep-seated respect for the elderly of which Asian cultures are legitimately proud: the far better integration of the elderly in society, the encouragement to remain active late in life, and so on. But in the long run, it is a huge problem. It prevents Asian countries from contributing, to the extent that they could, to medical research efforts directed at keeping the elderly truly healthy, let alone achieving the ultimate goal of restoring them to genuinely youthful mental and physical performance.

I will lay my cards on the table here: I believe that this is the wrong kind of respect for the elderly. Even in the West, and though things are gradually improving, a seriously problematic level of ambivalence persists with regard to these questions – a degree of doubt as to the wisdom or practicality of efforts to bring aging under medical control – that powerfully limits access to funding for such work, thereby slowing it and thereby costing vast numbers of lives in the future. But this lack of enlightenment in Asia is far more severe.

This volume has the potential to help change that. The research teams that have authored these chapters are mostly based in Asia (I'm going to count Turkey as Asia for this purpose!) or originate from there, and as a result I expect (and hope) that the book will attract a strong audience in that part of the world, though without doubt it will also appeal to a worldwide audience. By providing scientists and interested

laypeople with authoritative, up-to-date information concerning the status and progress of research into aging, this book will raise the quality of debate around the questions with which I began this foreword. And there can only be one outcome of that: a broader and more crystallized understanding that aging is indeed a solvable medical problem and one to which all nations and cultures have the opportunity, and the humanitarian duty, to contribute.

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Preface

Since the dawn of civilization, man has always been fascinated by the thought of living longer. Every system of medicine around the world has tried to provide some intervention for a longer life-span. The ancient Indian text, Rigveda (> 1000 BC), mentions a drink "amrita" which can bestow immortality. However, until 1950s, scientists had little understanding of aging, which is evident from the lecture of Sir Peter Medawar delivered at University College London in 1951, entitled "An Unsolved Problem in Biology."

The last few decades have seen tremendous advances in the understanding of molecular events which underline the process of aging. It is indeed a big achievement of science that we now have a better view of the hallmarks of aging. This understanding has provided gerontologists with "targets" which can be exploited for possible anti-aging interventions.

Finding an anti-aging intervention is far more difficult than finding a cure to any disease. Aging per se is not a disease; however, with age, the body becomes predisposed to a host of ailments affecting different organs, which culminate into loss of function and ultimately death. Interestingly, while the rate of aging for a given species remains the same, the aging process is highly heterochronic.

Intervening into aging is the next frontier in contemporary medicine and will remain to be of increasing importance over time as other sources of poor health are addressed more and more successfully. Aging being a highly complex event throws up a huge array of scientific explanations, all of which provide, to some extent, convincing arguments. In the light of such variation in possible theories which explain the process of aging, the strategies being experimented for anti-aging interventions are also highly diverse.

Literature is scattered for possible anti-aging interventions. Moreover the plurality of the events which constitute the aging mechanism makes it extremely challenging to find an intervention which may be considered "anti-aging" in a holistic sense. Despite the complexities, new scientific evidence emerging with continuous research continues to present interesting targets for devising anti-aging strategies. This book is an attempt to provide a compact source of emerging anti-aging interventions which offer hope for a longer healthspan, based on our current understanding of the aging process.

A huge array of literature exists which espouses the role of dietary antioxidants as possible anti-aging agents. Although this presumption is largely due to the role of

polyphenols in counteracting oxidative damages which accompany aging, several large-scale clinical trials have failed to come up with concurring results. We however feel that the dietary efficacy of antioxidants may have cultural/geographical differences. Regions where the diet is largely deficient in antioxidants may benefit from an intervention strategy based on dietary polyphenols. Keeping this aspect in view, this book offers three chapters (Chaps. 15, 18, and 21) which provide a detailed overview of the role of polyphenols in aging.

Chapters 2, 3, and 4 highlight approaches that include noncoding RNAs, stem cell reprogramming, and tissue engineering, which have potential to provide anti-aging strategies based on highly specialized techniques. Senescent cells are known to contribute to disease onset and progression through complex cell and non-cell-autonomous effects; as a result, cellular senescence is being increasingly associated with aging. Chapters 5 and 6 deal with senotherapeutics.

The understanding of the signaling pathways has provided molecular targets which can be targeted for anti-aging effects. Chapters 9 and 10 are focused on mTOR inhibition and sirtuin modulation. Age-related diseases and frailty syndromes share some common features which converge on inflammation. Chapters 8 and 23 provide an insight into the role of inflammation in aging and anti-aging interventions based anti-inflammatory approaches.

Important topics providing anti-aging approaches based on telomerase activity, intermittent fasting, melatonin, and phytochemicals have been included in Chaps. 7, 13, 14, and 17. The activation of plasma membrane redox system (PMRS) has been suggested as a novel strategy for anti-aging intervention (Chap. 19). An interesting approach involves the use of computational methods (Chap. 12). Interventions against sarcopenia (Chap. 20) and brain injury-induced aging (Chap. 22) are also included in our book.

We would like to thank all our contributors who provided us with excellent chapters making possible the compilation of this book.

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Contents

About the Editors

Dr. Syed Ibrahim Rizvi is a professor of Biochemistry at the University of Allahabad, India. He has been a visiting professor at several universities including the University of Athens (Greece); University of Nice (France); University of Pisa; University of Milan; University of Rome (Italy); Istanbul University (Turkey); Research Centre for Natural Sciences, Budapest (Hungary); and Bangladesh University of Health Sciences, Dhaka. Prof. Rizvi is a grantee of the International Foundation for Science, Sweden. His research interests include aging mechanisms, antiaging interventions, metabolic diseases, and natural products. To date, he has published 145 research papers, 10 book chapters, and a large number of popular science articles. He has been awarded fellowships/grants by the European Molecular Biology Organization (EMBO); Federation of European Biochemical Societies (FEBS); International Cell Research Organization; Organisation for the Prohibition of Chemical Weapons (OPCW), The Hague (Netherlands); Department of Science and Technology, Government of India; and University Grants Commission, India. He has received the Young Scientist Project Award from the Department of Science and Technology, Government of India, and was conferred the Academic Excellence Award by the University of Allahabad in 2016. Prof. Rizvi serves on the editorial/review boards of several leading research journals, and his work has been highlighted in the BBC (London) and other print and TV media. Prof. Rizvi has 30 years of teaching/research experience.

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biological activity of alpha-lipoic acid. He has served as a guest editor, referee, or member of the editorial board for more than 50 journals. He has received various prestigious awards such as the top reviewer award from Elsevier Science Publishing (2008) and serves on Istanbul University's Committee on Animal Research and Ethics.

Aging Principles and Perspectives for Intervention

1

Suresh I. S. Rattan

Abstract

The evolutionary and the biological principles of aging are now well established, and these show that aging is not determined by any specific gerontogenes. Instead, it is the imperfect maintenance and repair systems that lead to a progressive failure of homeodynamics, aging and eventual death. Gene therapy, stem cell therapy, hormonal replenishment and nutritional supplementations, tested mostly in experimental model systems, have achieved limited success for humans. The complex trait of aging requires wholistic approaches for maintaining or improving health in old age. A promising approach for health maintenance and improvement is that of mild stress-induced physiological hormesis. Physical and mental exercise, various non-nutritional food components, such as polyphenols, flavonoids and terpenoids in spices, oils and other formulations are hormetins, which have health beneficial effects through physiological hormesis. The future scenarios for aging intervention include intelligent redesigning and transhumanistic enhancements through robots and cyborgs combining both organic and biomechatronic body parts.

Keywords

Biogerontology · Gerontogenes · Healthspan · Homeostasis · Homeodynamics · Hormetin

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1.1 Introduction

Improving health, preventing aging and extending lifespan is one of the longest running dreams of human beings. While searching for an elixir for eternal life may still occupy the minds of some, modern biogerontology has shifted the focus towards developing and utilizing more realistic, rational and evidence-based approaches. Therefore, in order to fully appreciate and evaluate such approaches, it is important to have an overview and understanding of the current status of aging research, especially that of the study of the biological basis of aging. The aim of this article is threefold: (1) to provide a general review of the evolutionary, cellular and molecular bases of aging, (2) to discuss homeodynamics of survival and (3) to present a critical appraisal of various approaches towards modulating aging, including its prevention or reversion, enhancement of health and extension of healthspan.

It is now generally accepted that the biological basis of aging are well understood (Holliday 2006; Hayflick 2007a). As a result of this achievement of biogerontology, a conceptual framework and general principles of aging and longevity have been formulated. The three main biological principles of aging and longevity are summarized in Table 1.1.

In accordance with the above principles, aging is an epigenetic, emergent and a meta-phenomenon, which is affected by numerous factors. While no tissue, organ or system becomes functionally exhausted even in very old organisms, it is their collective interaction and interdependence at all levels that is decisive of overall health and survival. The contribution of genes to the lifespan of an individual is considered to be about 25%, as calculated from the longevity-correlation analyses performed on the data for the lifespan variance among siblings and monozygotic and dizygotic twins (Herskind et al. 1996). This means that non-genetic, epigenetic and environmental factors, including lifestyle, have much larger influence in determining the health, quality and the length of lifespan of an individual. This also implies that aging, healthspan and lifespan are not predetermined and can be affected by various methods of intervention.

Table 1.1 Principles of biological aging and longevity

1. *Aging starts after essential lifespan:* Biological aging is a progressive loss of physical function and fitness, which occurs during the extended period of survival beyond the natural lifespan of a species, termed "essential lifespan" (ELS) (Rattan 2000a, b; Rattan and Clark 2005)
2. *Aging is a post-genetic emergent phenomenon:* Aging phenotype is an emergent phenomenon observed in highly protected environments allowing survival beyond ELS. There is no genetic programme for determining the exact duration of survival of an individual; and there are no gerontogenes whose evolutionary function is to cause aging and limit the lifespan (Rattan 1995; Holliday and Rattan 2010)
3. *Heterogeneity of the aging phenotype:* The rate of progression and phenotype of aging are different in different species, in organisms within a species, in organs and tissues within an individual, in cell types within a tissue, in subcellular compartments within a cell type and in macromolecules within a cell (Rattan 2012a, 2016b)

1.2 Basis of Survival: Homeostasis Versus Homeodynamics

What makes living systems different from the inorganic and nonliving systems is their intrinsic ability to respond, to counteract and to adapt to the external and internal sources of disturbance. The traditional term to describe this ability is homeostasis, which, however, is not totally correct. The main reason for the incompleteness of the homeostasis model is its notion of "stability through constancy", which does not take into account the dynamic nature of information and interaction networks that underlie the complexity of the biological systems. Therefore, the term homeodynamics encompasses the fact that, unlike machines, the internal conditions of biological systems are not permanently fixed, are not at equilibrium and are under constant dynamic regulation and interaction among various levels of organization (Yates 1994).

The property of homeodynamics of the living systems is founded in a wide range of maintenance and repair processes at all levels of organization (Table 1.2). All these processes are governed by hundreds of survival-assurance genes, which give rise to a "homeodynamic space", as the ultimate determinant of an individual's chance and ability to survive and maintain health (Rattan 2006, 2012a). Aging, age-related diseases and eventual death are the result of a failure of homeodynamics. This fact is also reflected in the definition of aging as a progressive shrinkage of the homeodynamic space (Rattan 2006, 2012a).

1.3 Genetics and Epigenetics of Aging

Since all molecular processes in living systems are based in and regulated by genes and gene products, discovering genes for aging has been an important theme in biogerontology. However, evolutionary theories of aging and longevity discount the notions of any specific genes for aging (Kowald and Kirkwood 2016).

Table 1.2 Main maintenance and repair pathways in biological systems arranged from molecular to whole body level

Nuclear and mitochondrial DNA repair
Anti-oxidative enzymes and free radical scavengers
Degradation of damaged DNA and RNA
Protein repair
Degradation of damaged proteins
Degradation of damaged organelles
Programmed cell death – apoptosis
Intracellular stress responses
Detoxification of harmful chemicals and metabolites
Immune responses
Wound healing and tissue regeneration
Other higher-order defences, thermal regulation, neuroendocrine balance and circadian rhythms

Furthermore, the strong heterogeneity of the aging phenotype is indicative of the fact that the progression of aging is neither programmed nor deterministic but mostly mediated by stochastic events (Holliday 2007, 2009). On the other hand, aging does appear to have a genetic component, and the role of genes in aging is indicated by (1) an apparent limit to lifespan within a species (Carnes et al. 2003; Dong et al. 2016), (2) some heritability of lifespan as evident from studies on twins (Tan et al. 2013), (3) presence of human genetic mutants of premature aging syndromes (Kipling et al. 2004; Martin et al. 2007) and (4) association of some gene polymorphisms with extreme longevity (de Magalhaes 2014b).

In order to resolve the paradox of stochastic nature of the progression of the aging and the genetic aspects of longevity, a novel view about the nature of aging genes, termed gerontogenes, has been put forward, and a modified term "virtual gerontogenes" has been suggested implying the altered state of survival genes as giving the appearance of being the real aging genes (Rattan 1985, 1995). This notion of virtual genes also applies to several so-called disease-causing genes. For example, the Werner gene, which is considered to "cause" the premature aging syndrome, is in reality a DNA helicase gene whose normal role in DNA replication and repair prevents the emergence of the Werner's syndrome, and it is only when this gene is altered by mutation that the disease phenotype emerges (Goldstein et al. 1990). The same applies to most of the so-called oncogenes, which are cancer-causing only when they are mutated and cannot perform their normal function (Tacutu et al. 2011).

The nature of virtual gerontogenes is considered to be of two types: (1) genes with mutations already present at the time of fertilization and birth and that manifest any deleterious effects after the period of growth, development and maturation (Partridge 2001; de Magalhaes 2012) and (2) the antagonistic pleiotropic genes, which were selected for survival benefits during early development but which can have potentially harmful effects in post-reproductive life when they are no longer under the force of natural selection (Kirkwood and Rose 1991; Holliday and Rattan 2010).

There is a large body of evidence showing that the genes involved in the maintenance and repair pathways are the main determinants of species' longevity (Rattan 2015a). Experimental extension of lifespan of various organisms and comparative studies of species with widely varying lifespans provide such evidence. Such genes are commonly known as the longevity assurance genes (LAG) or vitagenes that determine the ELS of a species (Rattan 2007). These longevity assurance genetic pathways include the efficiency of deoxyribonucleic acid (DNA) repair (Rattan 1989; Park et al. 2011), the fidelity of genetic information transfer (Kirkwood et al. 1984), the efficiency of protein degradation (Schmidt and Finley 2013), cellular responsiveness to stress (Kapahi et al. 1999) and the capacity to protect from free radical- and oxidation-induced molecular damage (Jones 2015). A very important understanding to emerge from the above studies is that the diversity of genes associated with aging and longevity of different organisms implies that there is no single and universal pathway affecting these phenotypes. It seems that whereas from an evolutionary point of view the genes involved in repair and maintenance pathways are important as the LAG, each species has also evolved additional species-specific

pathways of aging. Such genetic pathways have been termed as public and private pathways, respectively (Martin 2007).

In addition to the genetic aspects of aging and longevity, there is a lot of interest in understanding the epigenetic aspects of aging (Pal and Tyler 2016; Sen et al. 2016). Methylated cytosines, oxidatively modified nucleotides, alternatively spliced RNAs and post-translationally modified proteins, including protein folding, comprise the main intracellular epigenetic markers (Lund and van Lohuizen 2004). Since the full spectrum of epigenetics of aging is yet to be unraveled, it 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 the apparent difficulties in fully understanding the epigenetics of aging is the existence of several orders higher complexity and diversity of the constituting components, such as physical, chemical, biological and environmental factors, including psychological factors in human beings. Furthermore, a lot of epigenetic modifications can occur reversibly on a daily basis, depending on several lifestyle factors (Gensous et al. 2017; Chaleckis et al. 2016).

1.4 Molecular Mechanisms of Aging

The theories of the molecular mechanisms of aging are mostly centred on the occurrence and accumulation of damage (Yin and Chen 2005; Rattan 2006, 2008b). Although other views, such as continuous growth leading to a kind of quasi-programme (Blagosklonny 2012), and progressive increase in entropy (Hayflick 2007b) are also discussed as the mechanisms of aging, the occurrence and accumulation of molecular damage are the most studied aspects of molecular gerontology.

There are three main types of sources for the origin of macromolecular damage:

1. Chemical species (e.g. reactive oxygen species (ROS) and other free radicals (FR)) formed due to external inducers of oxidative damage and as a consequence of cellular metabolism involving oxygen, metals and other metabolites (Forman 2016).
2. Nutritional glucose and its metabolites and their biochemical interactions with ROS and FR (Nedic et al. 2015; Tanase et al. 2016).
3. Spontaneous errors in biochemical processes, such as DNA duplication, transcription, post-transcriptional processing, translation and post-translational modifications (Nyström 2002).

An age-related increase in the levels of various types of macromolecular damage, including DNA, RNA, protein, carbohydrates and lipid damage, is well documented (Holliday 2007; Rattan 2006, 2012a). Often, the mechanistic theories of biological aging have focused on a single category of damage inducers as a universal explanation. For example, the free radical theory of aging (FRTA), proposed by Denham Harman in 1954, is based on the premise that a single biochemical process

of FR-induced damage may be responsible for the aging and death of all living beings (for an update, see Harman 2006). In support of this idea, there is a significant amount of evidence that shows that ROS and other FR are indeed involved in the occurrence of damage and can lead to structural and functional disorders, diseases and death. However, a lack of incorporation of the essential role of FR in the normal functioning and survival of biological systems has raised several points of criticism about FRTA (Gruber et al. 2008; Halliwell 2009). Furthermore, FRTA presents FR as the ultimate cause of damage while ignoring the fact that there are large differences in the range of FR-counteracting mechanisms in different species (Vina et al. 2013; Jones 2015). In addition, contrary and/or lack of beneficial results of antioxidant and FR-scavenging therapies as predicted by FRTA have restricted FRTA to being only a partial explanation of aging (Le Bourg and Fournier 2004; Le Bourg 2005; Howes 2006).

The biological consequences of increased levels of molecular damage are wide-ranging and include mutations, altered gene expression, cell cycle arrest, cell death, loss of intercellular communication, disorganization of the tissues, dysfunctioning of the organs, reduced stress tolerance and reduced ability to adapt (Rattan 2008b): Each of these biological consequences has, historically, been used as the basis of developing other so-called theories of aging, such as pineal gland theory, neuroendocrine theory, immunological theory, replicative senescence theory, etc. However, at present, the occurrence and accumulation of molecular damage as the basis of age-related failure of homeodynamics are considered as a unified explanation for biological aging (Rattan 2006, 2008b).

1.5 Aging Interventions: Treatment, Prevention or Management

One's approach towards intervention in aging can be influenced by one's understanding of aging either being a disease that needs to be treated or being a condition emerging from the basic life processes, which can be modulated to some extent. Since aging is an emergent phenotype due to the failure of homeodynamics and not due to the action of any life-limiting and death-causing mechanisms, it changes aging interventional approach from "anti-aging" to "healthy aging". Aging occurs in spite of the presence of complex pathways of maintenance, repair and defence, and there is no "enemy within" that needs to be eliminated. Even the diseases of old age, such as Alzheimer, Parkinson, type 2 diabetes and cancers, have no simple causative agents except for the life processes themselves.

Table 1.3 presents the rationale behind the present and future strategies for aging interventions, which are briefly discussed below.

Table 1.3 The present and future strategies for aging intervention

Strategy	Interventions
Piecemeal remedy – "fix what is broken"	Cosmetics, tissue and organ repair, organ transplantation, senescent cell removal, young blood/plasma transfusion, stem cells
Replenishment and supplementation	Hormones, nutritional supplements with synthetic and natural molecules including antioxidants, vitamins and phytochemicals
Strengthening the homeodynamics	Hormesis through nutritional hormetins, food physical activity, immunological challenge and social and cognitive engagement
Gene therapy and intelligent redesigning	Gene therapy, genetic and bodily enhancements, trans-humanistic cyborgs and robotics

1.5.1 Piecemeal Remedies

One of the most common and prevalent biomedical approaches to aging intervention is the so-called piecemeal remedies. The basic logic behind this approach is to "fix what is broke"; and it ranges from cosmetics to the tissue/organ repair or transplantation, targeted treatments with stem cells, and rejuvenation with young blood/plasma transfusion (Goodell and Rando 2015; Rebo et al. 2016; Castellano et al. 2015). More recently, elimination of senescent cells by potential senolytic compounds is becoming an increasingly appealing approach (Naylor et al. 2013; Cortese and Santostasi 2016; He and Sharpless 2017; de Keizer 2017). Although such interventions often have life-saving effects in acute situations, these benefits are often transient, limited and require recurring interventions (Kyriazis 2014).

1.5.2 Replenishment and Supplementation

One of the most widely used aging interventional strategies, tested mostly in animal model systems, is that of replenishing the loss. However, the naïve premise of this approach is that age-related decline in the levels of hormones, enzymes and other metabolites is always harmful and that these declined levels should be brought back to the youthful levels. This view almost totally ignores the biogerontological understanding that many changes occurring during aging are often the sign of remodelling and adaptation for survival and health (Davies 2016; Martin et al. 2015). For example, a reduction in the levels of various hormones and their intermediates and receptors seems to be a co-requirement for the extension of lifespan of organisms, as determined by genetic and non-genetic interventions (Rattan and Sharma 2017). Similarly, unexpectedly long-living naked mole rats and bats generally have much lower levels of hormones than short-lived species (Gorbunova et al. 2014; Brunet-Rossinni and Austad 2004). Furthermore, some claims have been made that the increased longevity of eunuchs and castrated men could be due to their low levels of growth hormone and sex steroids (Min et al. 2012). Therefore,

several biogerontologists have cautioned that hormonal and nutritional supplementation as replenishments may have little, none or even harmful effects in normal healthy situations (Le Bourg 2005; Rizvi and Jha 2011; Sadowska-Bartosz and Bartosz 2014; Conti et al. 2016; Vaiserman et al. 2016).

1.5.3 Strengthening the Homeodynamics

Biogerontologists are increasingly realizing that "single-molecule, single-target" oriented approaches for aging intervention are severely limited because these neglect the highly dynamic, interactive and networking nature of life. Therefore, whole body level holistic or more accurately "wholistic" (in order to distinguish science-based approaches from the "everything goes" holistic claims) approaches are being tested and developed as promising aging interventions. Food, physical activity and mental engagement come under such wholistic interventions, which strengthen the homeodynamics (Rattan 2015b, 2017). One such wholistic interventionary approach is that of hormesis.

Physiological hormesis in health maintenance and improvement is defined as the life-supporting beneficial effects resulting from the cellular and organismic responses to repeated and transient exposure to mild stress (Le Bourg and Rattan 2008; Mattson and Calabrese 2010; Rattan 2014). Moderate physical exercise is the paradigm for stress-induced physiological hormesis (Sen et al. 2000; Radak et al. 2005; Williamson and Pahor 2010). Other stress inducers which have been shown to affect aging of cells and animals include acetaldehyde, alcohols, dietary restriction, flavonoids, heat shock, heavy metals, hypergravity, intermittent fasting, infections, irradiation, pro-oxidants, polyphenols and terpenoids (Le Bourg and Rattan 2008; Mattson and Calabrese 2010; Rattan 2014; Weis et al. 2017). An important observation in studies of physiological hormesis is that a single stressor, such as heat shock or exercise, can strengthen the overall homeodynamics and enhance other abilities, such as adaptability, cognition, immune response, memory, resilience and overall robustness. These systemic and wholistic effects are generally achieved by initiating a cascade of processes that result in a biological amplification of effects.

All such conditions, which bring about health beneficial effects by initially causing low-level stress, are termed as hormetins (Rattan and Demirovic 2009, 2010a, b). Hormetins can be further categorized as (1) physical hormetins, such as heat, radiation and physical exercise; (2) nutritional hormetins, such as phytochemicals in spices, micronutrients and other natural and synthetic food components; and (3) psychological or mental hormetins, such as brain exercise through cognitive games and challenges, including solving puzzles, social engagement, focused attention and meditation (Brewer et al. 2011; Stark 2012; Duraimani et al. 2015).

The molecular basis of hormesis lies in the activation of stress response pathways on exposure to single or multiple rounds of mild stress (Rattan 2008a; Demirovic et al. 2014). Whereas severe and chronic stress results in the weakening of homeodynamics and can lead to functional impairments, diseases and death,

transient and mild stress strengthens the homeodynamic ability of a biological system (Demirovic and Rattan 2013). It is important to recount that although the measurable effects after a single round of mild stress exposure are usually small, a repeated exposure results in the biological consequences which are cumulative, amplified and physiologically significant, as exemplified by the health beneficial effects of repeated moderate exercise.

It should also be pointed out that several so-called antioxidants, including numerous plant components, some vitamins and micronutrients, are actually stress-inducing hormetins and that their biological effects as being antioxidants are not due to the compounds themselves being direct antioxidants (Panossian 2017; Qi et al. 2017; Linnane et al. 2007; Mocchegiani et al. 2011; Martucci et al. 2017; Li et al. 2017; Camandola and Mattson 2017; Pallauf et al. 2016). Discovering novel hormetins is a developing area of research, which is also drawing significant attention of the aesthetic, healthcare and food industry (Rattan 2012b; Rattan et al. 2013).

Some possibilities of discovering novel hormetins by activating different SR pathways are food-restriction mimetics and other inducers of autophagy (Ingram and Roth 2015; Darzynkiewicz et al. 2014), antidiabetic drug metformin (Barzilai et al. 2012; Campbell et al. 2017), DNA repair response inducers (Darzynkiewicz et al. 2014), resveratrol and its analogues as inducers of sirtuin stress response, inducers of Nrf2-mediated oxidative stress response (Kumar et al. 2014) and NF-kB-mediated anti-inflammatory response (Haas 2009; Martucci et al. 2017). Diet-microbiota interactions may also involve stress response-mediated hormesis for their health beneficial effects (Sonnenburg and Backhed 2016). A detailed database for aging-related drugs has also been developed (Barardo et al. 2017).

1.5.4 Gene Therapy and Intelligent Redesigning

Biogerontologists have identified hundreds of putative gerontogenes as potential targets for gene therapy against aging (for the latest information on such genes, refer to various online databases, such as http://genomics.senescence.info/genes/) (de Magalhaes 2014b). However, it is important to realize that in almost all such studies, the extension of lifespan by gene therapy was observed when a significant reduction or total inhibition of the activity of one or more genes was achieved. For example, one of the earliest experimental studies performed on the nematode *C. elegans* demonstrated that a chemically induced mutation in a single gene *age-1* resulted in a significant increase in the lifespan of the mutated worms (Friedman and Johnson 1988a, b). Other examples of such "loss of function" gene therapies associated with extended period of survival are (1) nutrition and hormonal sensing and signalling including insulin/insulin-like growth factor-1 and its target forkhead transcription factor (FOXO), (2) energy generation and utilization in mitochondrial respiratory chain and (3) translational interference through target of rapamycin (TOR) (North and Sinclair 2007; Chen et al. 2005; Kenyon 2001, 2005; Hipkiss 2007, 2008; Vellai et al. 2003). Similarly, several mutant mice strains with defects in growth hormone (GH) pathways in terms of deficiencies of GH levels and GH

receptor have extended lifespans (Napoli et al. 2003; Purdom and Chen 2003; Longo and Finch 2003). Application of RNAi technology, together with the role of circulating RNAs, and small noncoding RNAs, has also identified numerous genes whose normal levels of activities are lifespan restricting and can be a target for gene therapy (de Magalhaes 2014b).

In contrast to the above studies on the longevity-promoting effects of the lost or reduced activities of various genes, studies have also been performed on testing the effects of adding one or multiple copies of some genes on aging and longevity of model systems. These include the addition of gene(s) for one of the protein elongation factors (Shepherd et al. 1989), antioxidant genes superoxide dismutase and catalase (Orr and Sohal 1994; Sun et al. 2004; Parkes et al. 1998; Schriner and Linford 2006), sirtuin (Rogina and Helfand 2004), FOXO (Giannakou et al. 2004), heat shock proteins (Yokohama et al. 2002; Morrow et al. 2004; Walker and Lithgow 2003), heat shock factor, (Hsu et al. 2003; Morley and Morimoto 2004), protein repair methyltransferase (Chavous et al. 2001) and klotho, which is an inhibitor of insulin and IGF-1 signalling (Kurosu et al. 2005).

One of the challenges for these gene therapy-oriented aging interventions is that very little is known about the physiological price paid for inactivating or overstimulating genes whose normal function is a part of the general metabolism and signalling (Rincon et al. 2004; Van Voorhies et al. 2006). For example, laboratory-protected longevity mutants in *C. elegans* have reduced Darwinian fitness when competing with the wild-type worms under nutritionally challenging conditions (Walker et al. 2000; Chen et al. 2007; Van Voorhies 2003). Similarly, extension of murine lifespan by the addition of *klotho* gene induces insulin resistance and disruption of insulin/IGF-1 signalling pathway (Rincon et al. 2004; Van Voorhies et al. 2006; UNGER 2006; Wang and Sun 2009).

Another experimental model system used for testing potential gene-based aging interventions is the Hayflick system of limited proliferative lifespan of normal diploid differentiated cells in culture (Rattan and Hayflick 2016). Most of these interventions are mediated by transient or permanent transfection and ectopic expression of different genes and have focused on extending the replicative lifespan of cells by bypassing the cell cycle checkpoints (Campisi and D'Adda Di Fagagna 2007; Itahana et al. 2004; Collado et al. 2007). The ectopic expression of telomerase is one such widely used genetic intervention (Simonsen et al. 2002; Davis and Kipling 2005). However, these studies have raised an important point of caution that continuous proliferation of such genetically modified non-aging cells often leads to their genomic instability, transformation and carcinogenic activity (Wang et al. 2000; Serakinci et al. 2004). Similarly, in the case of animals, although telomerase-negative mice had reduced lifespan and several other abnormalities, overexpression of telomerase in their skin increased myc-induced hyperplasia (Lansdorp 1997; Flores et al. 2006).

In the case of humans, although several single gene mutations are known which lead to accelerated aging and significantly reduced lifespan (Martin 2005; Martin et al. 2007), no gene mutations have yet been identified which increase the human lifespan. A strategy that has been used extensively to identify potential longevity

genes is by gene association analysis of genetic polymorphisms with human longevity (Singh et al. 2007). The full list of genes associated with human longevity, generally identified by both single nucleotide polymorphism (SNP) analysis or by genome-wide association studies (GWAS), can be retrieved from http://genomics.senescence.info/genes/. To what extent this information can be used to develop gene-based aging interventions in humans is not yet clear.

Some future scenarios for aging interventions include intelligent redesigning either by the so-called strategies for engineered negligible senescence (SENS) (De Grey 2006) or by post-humanistic or trans-humanistic enhancements through robots and cyborgs combining both organic and biomechatronic body parts (Palese 2012). Such interventions, if successful, raise several ethical issues such as the social and environmental consequences of extreme longevity and the basic understanding of what it means to be human (Chan 2008; Seppet et al. 2011).

1.6 Recapitulation

The principles of aging and longevity, as described in Table 1.1, indicate that the occurrence of aging in the period beyond ELS of the species is inevitable owing to the imperfections of the survival mechanisms. Aging in itself is not a disease but is the universal cause of age-related diseases. Therefore, whereas optimal treatment of each and every disease, irrespective of age, is a social and moral necessity, maintaining health and improving the quality of human life in old age require a shift in approach from aging as a disease to aging as a life condition that can be modulated.

Although "aging is a disease" label may have some role to play in attracting the attention of big business and investors (de Magalhaes et al. 2017), it totally disregards the scientific history and understanding of the biological basis of aging. If aging is a disease, then it is our own fault – we breathe, we eat food, and we have complex but imperfect biochemistry (Rattan 2016a). The so-called war against aging and any other similar rhetoric are totally misplaced, because there is no enemy within or without. Aging must be approached as a stage in life history of an individual, which is served best by biomedical, technological and social interventions, which could diminish the severity of age-related frailty, along with a possible extension of healthspan and lifespan.

Biogerontologists are beginning to narrow down the potential aging pathways, including insulin/IGF-1 growth axis, mTOR activity and stress resistance, which could be amenable to manipulation (de Magalhaes 2014a, b). There is evidence that those and other metabolic pathways can be effectively modulated by lifestyle alterations, such as intermittent food restriction, exercise and nutritional and pharmacological interventions (Vaiserman et al. 2016). However, one major challenge still is to translate the information gathered from studies performed on experimental model systems of insects, nematodes, rodents and others to human beings. After all, human are perhaps our ultimate target for such interventions!

Another challenge for biogerontologists trying to develop effective means of aging intervention is to come out of the reductionistic mode of doing experiments. The three pillars of health – food, physical activity, and mental and social engagement – require a change in the way the experiments are designed and performed. The history of aging intervention research has shown that taking this or that single compound of natural or synthetic origin, force-feeding it to some experimental model system and analysing one or few molecular targets have, so far, not led to any really useful practical interventions for human beings – whatever the hype by the media or the cosmetic industry.

Furthermore, if we want to curtail the mushroomic growth of self-proclaimed specialists and longevity gurus making false promises, muddling the thinking and promoting impractical and even harmful interventions, then cross-disciplinary collaborations among biologists, engineers, sociologists, philosophers and other scholars from humanities and sciences must be developed (Le Bourg 2013). We also need to ask ourselves as to what is the ultimate aim of aging research: is it to eliminate aging and death forever? And even more importantly, could we, would we and should we do that?

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