The Science of Healthy Aging

Genes, Milieu, and Chance

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ABSTRACT: Healthy aging and longevity depend on successful and dynamic interactions among biological, psychological, and environmental factors. Biological aging occurs mainly during the period of survival beyond the evolutionarily required *essential lifespan* (ELS). Natural selection processes for survival and successful reproduction have selected for a range of genetically determined ELS-assuring maintenance and repair systems (MRSs). The progressive failure of MRSs, and the consequent accumulation of molecular heterogeneity and damage, underlie the biological basis of aging, age-related diseases, and eventual death. However, the genetic processes of MRSs operate in a complex hierarchy of factors which range from intracellular molecular factors to physiological, psychological, environmental, and other stochastic factors, including chance. This view also facilitates setting up a framework for understanding, researching, and developing effective and realistic strategies for aging intervention, prevention, and therapies. Manipulating genes and the milieu in which genes and gene products operate opens up novel possibilities of aging intervention and prevention. Gene therapy, stem cells, and modulation through functional foods, nutriceuticals, cosmeceuticals and lifestyle alterations, including mild stress-induced hormesis, are examples of such strategies at various levels of development and practice.

KEYWORDS: lifespan; survival; longevity; stress; hormesis; homeostasis; homeodynamics

INTRODUCTION

The doubling of human life expectancy during the last 100 years has occurred primarily because of a reduction in birth-related maternal and infant deaths. Some further improvements in the chances of survival of the elderly after the age of 80 years and living beyond 100 years are also noted, which

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TABLE 1. Three principles of aging and longevity

1. ***Evolutionary life history principle:*** Aging is an emergent phenomenon seen primarily in protected environments which allow survival beyond the natural lifespan of a species, termed *essential lifespan* (ELS).
2. ***Non-genetic principle:*** Although genes are involved in determining the ELS of a species, aging and longevity of an individual is not programmed in specific gerontogenes.
3. ***Mechanistic principle:*** Accumulation of molecular damage and increased molecular heterogeneity is the cause of age-related failure of homeodynamics.

are also due to improved biomedical and nutritional conditions. However, this extension in lifespan has not been matched so far by equivalent improvements in the health-span in old age. The main reason for this failure lies in the basic biology of our bodies, which has been shaped through millions of years of evolution, and which may not be amenable to simple interventions. Healthy aging and longevity depend on successful and dynamic interactions among biological, psychological, and environmental factors, and a combination of genes, environment, and chance determine the course and consequences of aging. This view also facilitates setting up a framework for understanding, researching, and developing effective and realistic strategies for aging intervention, prevention, and therapies. Gene therapy, stem cells, and modulation through functional foods, nutriceuticals, cosmeceuticals, and lifestyle alterations are examples of such strategies at various levels of development and practice. The aim of this article is to provide a brief overview of the biological basis of aging, which can provide the bases for the evaluation and development of potential interventions and therapeutic approaches for achieving healthy aging and longevity.

AGING: FROM DESCRIPTION TO PRINCIPLES

Biogerontology, the study of the biological basis of aging, has so far gathered a large body of descriptive data about the age-related changes in organisms, organs, tissues, cells, and macromolecules. These data clearly show that the progression and rate of aging are highly variable in different species, in organisms within a species, in organs and tissues within an organism, in cell types within a tissue, in subcellular compartments within a cell type, and in macromolecules within a cell. Although these data imply that there are no universally applicable markers of aging, three general principles of biological aging can be derived (TABLE 1).

First, the evolutionary *life history principle* describes aging as an emergent phenomenon that takes place primarily in protected environments which allow survival beyond the natural lifespan in the wild. The natural lifespan of a species, termed *essential lifespan* (ELS),[1,2] or the *warranty period*,[3] is the

time required to fulfill the Darwinian purpose of life in terms of successful reproduction for the continuation of generations. Species that undergo fast maturation and have an early onset of reproduction with large reproductive potential generally have a short ELS, whereas slow maturation, late onset of reproduction, and small reproductive potential of a species is concurrent with its long ELS. For example, the ELS of *Drosophila* is less than a week as compared with that of about 50 years of *Homo sapiens*, even though in protected environments (laboratories and modern societies, respectively), a large proportion of populations of both species can and do live for much longer than that. Therefore, from an evolutionary point of view, ELS is the canvas against which the genetic selection and functional optimization unfold. Detailed arguments about evolutionary explanations for the origin and occurrence of aging can be accessed in extensive writings of several authors.[4,5]

Second, the *non-genetic principle of aging* specifies that aging and longevity of an individual are not programmed in specific gerontogenes. Unlike development, which is a highly programmed and well-coordinated genetic process in the evolutionary life history of an organism, there is no genetic program that determines the exact duration of survival of an organism. Furthermore, studies on establishing an association between genes and longevity have reported that the genetic heritability of variance in lifespan is less than 35%.[6,7] 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. There is ample evidence from studies performed on yeast and other fungi, nematodes, insects, rodents, and humans that mutations in various genes can affect the lifespan, and some of these mutations are also the cause of premature aging syndromes in human beings.[8,9] Several studies have reported an association between human longevity and single nucleotide polymorphisms in a variety of genes in various biological pathways, including heat-shock response, mitochondrial functions, immune response, cholesterol metabolism, and others.[7,10–13]

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 checkpoint 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. Most of these genes have well-defined roles in normal metabolism, in intra- and intercellular 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 that result in their altered biological role with age. Therefore, such genes have been termed *virtual gerontogenes*.[14,15] 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.[16]

Third, the *mechanistic principle* characterizes aging as a progressive increase in molecular heterogeneity and functional impairment, which is mainly due to the accumulation of molecular damage in nucleic acids, proteins, and lipids. Since homeostasis or homeodynamic ability of a living system is primarily due to its maintenance and repair systems (MRSs), it is the progressive failure of the MRSs that is the biochemical basis of aging and age-related diseases. The evidence that MRSs are crucial determinants of natural survival and longevity comes from experiments performed to retard aging and to increase the lifespan of organisms. For example, anti-aging and life-prolonging effects of caloric restriction (CR) are seen to be accompanied by the stimulation of various maintenance mechanisms. These include increased efficiency of DNA repair, increased fidelity of genetic information transfer, more efficient protein synthesis, more efficient protein degradation, more effective cell replacement and regeneration, improved cellular responsiveness, fortification of the immune system, and enhanced protection from free-radical- and oxidation-induced damage. Genetic selection of various organisms for longer lifespan also appears to work mainly through an increase in the efficiency of maintenance mechanisms, such as antioxidation potential. The identification of long-lived mutants of the nematode *Caenorhabditis elegans*, involving various genes, provides other examples that increased lifespan is accompanied by an increased resistance to oxidative damage, an increase in the activities of antioxidant enzymes, and an increase in thermotolerance. A comparative analysis of the ability of cells isolated from a variety of animals to resist oxidative stress also showed that species lifespan was directly related to the MRSs.

AGING INTERVENTIONS: THERAPY OR PREVENTION?

As a biomedical issue, the biological process of aging underlies all major human diseases, such as atherosclerosis, cancer, cardiovascular defects, cataracts, diabetes, dementia, macular degeneration, neurodegeneration, osteoporosis, and sarcopenia. 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.

Unlike some other fields of research, it is central to biogerontology that effective means of intervention are found, developed, and applied to modulating human aging in order to prevent the onset of age-related diseases and improving the quality of 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 different from the treatment of one or more specific diseases.[17] In the case of a disease, such as a cancer of any specific kind, its therapy will, ideally, mean the removal and elimination of the cancer cells and restoration of the affected organ/tissue to its original disease-free state. What will be the "treatment" of aging and to what original "age-free" stage one would hope to be restored—to day 1?, year 1, 10, 30, 50? or what? Similarly, although piecemeal replacement of nonfunctional or half-functional body parts with natural or synthetic parts made of more durable material may provide a temporary solution to the problems of age-related impairments, it does not modulate the underlying aging process as such.

Scientific and rational anti-aging strategies aim to slow down aging, to prevent and/or delay physiological decline, and to regain lost functional abilities. However, the history of anti-aging research and therapy is replete with fraud, pseudoscience, and charlatanism, which has often given a bad name to the whole field. Claims for miraculous remedies and promises for an extremely long lifespan are prevalent even today. However, while not giving serious consideration to the claims made by charlatans, it cannot be ignored that several researchers are making genuine attempts to test and develop various means of intervention for the prevention and treatment of age-related diseases, for regaining functional abilities, and for prolonging the lifespan of experimental organisms.

$E = GMC^2$: A FORMULA FOR ETERNAL LIFE

A wide range of molecular, cellular, and physiological MRSs 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 response 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. A progressive shrinking of the homeodynamic space is the hallmark of aging and the cause of origin of age-related diseases. Therefore, in order to modulate aging and to achieve healthy old age and/or to extend lifespan indefinitely, three main conditions need to be fulfilled, as represented by the equation $E = GMC^2$, discussed below.

The first parameter G represents genes, which are the basis of survival, growth, development, and MRSs. If all the genes involved in MRSs, especially in the pathways of damage removal and repair, can be manipulated in such a way that their interactive accuracy and efficiency remains functional indefinitely, then the first requirement for eternal life is fulfilled. However, at

present our knowledge about the numbers, variations, interactions, and means of manipulating genetic networks is too meager to even conceptualize what may be possible to do in this respect.

The second parameter *M* represent 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 orders of organization including the 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, or by increasing the levels of such biochemicals through nutritional supplemenation. Some of the main anti-aging approaches include supplementation with hormones including growth hormone, dehydroepiandrosterone, melatonin, and estrogen, and nutritional supplementation with synthetic and natural antioxidants in purified form or in extracts prepared from plant and animal sources, 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. Furthermore, claims for the benefits of intake of high doses of vitamins and various antioxidants and their supposed anti-aging and life-prolonging effects have very little scientific evidence to back them. In contrast to this, nutritional modulation through CR has been shown to be an effective anti-aging and longevity-extending approach in rodents and monkeys. But this is a highly debatable issue at present both in terms of the practicalities of defining CR and of applying CR in human beings in physiological and evolutionary contexts.[18]

Another promising area of milieu improvement for achieiving healthy aging and longevity is through mild stress-induced hormesis. As discussed above, a critical component of the homeodynamic property of living systems is their capacity to respond to stress. In this context, the term "stress" is defined as a signal generated by any physical, chemical, or biological factor (stressor) that, in a living system, initiates a series of events in order to counteract, adapt, and survive. While a successful and overcompensatory response to low doses of stressors improves the overall homeodynamics of cells and organisms, an incomplete or failed homeodynamic response leads to the damaging and harmful effects of stress, including death.

Several meta-analyses performed on innumerable research papers published in the fields of toxicology, pharmacology, 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 was termed as *hormesis* in 1940s (for the historical development of the term, see Calabrese[19]). The key conceptual features of hormesis are the disruption of homeodynamics, the modest overcompensation, the re-establishment of homeodynamics, and the adaptive nature of the process. A wide variety of physical,

chemical, and biological agents exhibit hormetic dose–response, and these include heavy metals, pesticides, antibiotics, chemotherapeutic agents, ethanol, aldehyde, chloroform, pro-oxidants, vitamins, trace elements, and ionizing radiation.

The paradigm for considering the applicability of hormesis in aging intervention is the well-documented beneficial effect of exercise, which, at a biochemical level, results in the production of potentially harmful substances, such as free radicals, acids, and aldehydes.[20] Thus it is hypothesized that if biological systems are deliberately exposed to mild stress, so that their homeodynamic pathways of maintenance and repair are challenged and activated, this should lead to achieving beneficial hormetic effects, including health- and longevity-promoting effects. Hormesis in aging is, therefore, defined as the life-supporting beneficial effect resulting from the cellular responses to single or multiple rounds of mild stress.[20] Since the harmful effects of severe stress have long overshadowed the beneficial hormetic effects of low-level stress, applying hormesis in aging research and therapy is a relatively recent development.

Mild stresses that have been reported to delay aging and prolong longevity in various systems include temperature shock, irradiation (UV-, gamma- and X-rays), heavy metals, pro-oxidants, acetaldehyde, alcohols, hypergravity, exercise, and food restriction.[17,20–22] Hormesis-like beneficial effects of chronic but mild undernutrition have been reported for human beings. Intermittent fasting has been reported to have beneficial effects on glucose metabolism and neuronal resistance to injury. Although at present there are only a few studies performed that utilize mild stress as a modulator of aging and longevity, hormesis is a useful experimental approach in biogerontology.

Several dietary components, such as vitamins, antioxidants, trace elements, minerals, ethanol, and even herbicides and pesticides, have been shown to have typical hormetic dose–response. All such compounds (natural or synthetic), which bring about biologically beneficial effects by acting through one or more pathways of maintenance and repair and stress response, are termed *hormetins*.[20,23] The hormetic effects of various vitamins and macro- and micro-minerals, including iron, iodine, fluorine, selenium, and copper, have also been reported.[24] Additionally, the effects of zinc also show a typical hormetic dose–response, and its beneficial effects are considered to be achieved through stress response–induced alterations in gene expression of various maintenance and repair pathways.[25,26]

Dietary intake of moderate amounts of ethanol has been shown to have memory-enhancing beneficial effects in mice.[27] The cardioprotective, antioxidative, and other beneficial effects of wine are considered to be due to flavonoid and non-flavonoid components, such as resveratrol,[28] which also have hormetic dose–response. Since resveratrol's mode of action involves regulating various pathways of maintenance, repair, and metabolic rate, it qualifies to be called a hormetin.

Other potential hormetins are various antioxidants, including components of spices and other medicinal plants. Almost all antioxidants show hormetic dose–response and become pro-oxidants above certain doses. Furthermore, in some cases, such as alpha-lipoic acid and coenzyme Q10, it is their pro-oxidant activity in producing hydrogen peroxide, which induces defensive responses, which is the basis of their ultimately beneficial effects.[29] Components of various medicinal plants used frequently in the traditional Chinese medicine (TCM) and in the Indian Ayurvedic system of medicine are claimed to have anti-aging effects, which appear to be achieved through hormetic pathways. For example, celasterols and paeoniflorin, present in some medicinal herbs used in TCM, have cytoprotective effects and induce heat-shock proteins in human cells.[30,31] Similarly, curcumin, which is the active component in the commonly used yellow food spice *Haldi* and is derived from the roots of *Curcuma longa*, is a co-inducer of stress proteins and has wide-ranging biological effects, depending on its dosage.[23,32]

Hormesis may also be an explanation for the health-beneficial effects of numerous other foods and food components, such as garlic, gingko, and other fruits and vegetables.[24,33,34] 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. For example, it may be possible to develop multi-hormetin formulations as anti-aging drugs and nutriceuticals whose mode of action is through hormetic pathways by mild stress-induced stimulation of homeodynamic processes.

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 has highlighted the vulnerability of all strong and weak links, and has reasserted the significance of chance events, which are not amenable to regulation and manipulation. Therefore, whereas the science of healthy aging and longevity is based in solid footing, the dreams of eternal youth are best left to thrive in the domain of the unscientific.

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