Review Article

Aging Is Not a Disease: Implications for Intervention

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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 demonstrable 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.

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

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	Cytchrome 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 disregulation 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/), 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

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