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Review Article

CURRENT ASPECTS OF AGEING THEORIES AND CLASSIFICATION ACCORDING TO MECHANISMS

Abstract

Attempts to define ageing, explain theories and classify them have always been an important issue for biogerontologists. Oxidative stress, telomeres, genetics, hormonal changes, immunity and damage accumulation over threshold values are all common theories that have been studied and modified over a long period of time. Verifications of these theories may lead to enlightenment about molecular mechanisms, and these can give rise to new research to reverse or slow age related pathological changes and increase average life span. Nowadays, an increased ratio of "successful ageing" or "healthier ageing" is a big aim for the whole society. Achieving this purpose also depends on research which studies molecular mechanisms and routine laboratory markers of ageing.

Key Words: Aging; Free Radicals; Inflammation; Longevity; Telomere.

Derleme

YAŞLANMA TEORİLERİNE GÜNCEL BİR BAKIŞ VE MEKANİZMALARINA GÖRE SINIFLANDIRMA

Öz

Biyogerontologlar için yaşlanmayı tanımlamak, teoriler ortaya atmak ve bunları sınıflandırmak her zaman önemli bir sorun olmuştur. Oksidatif stres, telomerler, genetik, hormonal değişiklikler, bağışıklık sistemi ve eşik üstü zarar birikim teorileri, üzerinde uzun süre birçok çalışmalar ve modifikasyonlar yapılmış teoriler olmuşlardır. Yaşlanma teorilerinin geçerliliğinin kanıtlanması bu süreçte etkili olan moleküler mekanizmaların aydınlanmasına, sonrasında da beklenen ömrü uzatmaya ve yaşlanmayla ilgili patolojileri geri döndürmeye ya da yavaşlatmaya yönelik yeni araştırmalara neden olacaktır. Son zamanlarda yüksek "başarılı" ya da "daha sağlıklı yaşlanma" oranları, tüm toplum için büyük bir hedef haline gelmiştir. Bu amaca ulaşmak, yaşlanmanın moleküler mekanizmaları ve laboratuar belirteçleri üzerine yapılacak çalışmalara bağlıdır.

Anahtar Sözcükler: Yaşlanma; Serbest Radikaller; İnflamasyon; Uzun Ömürlülük; Telomerler.

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Introduction

Ageing is a complex biological phenomenon that is hard to define completely. It is not surprising to observe that a search for publications on "ageing" in the United States National

Library of Medicine National Institutes of Health, as updated on February 2013, yielded over 267,000 items.

For centuries, ageing has often been referred to as a mysterious or an unsolved biomedical problem. Indeed, the famous zoologist Peter Medawar, who was to become a Nobel prizewinner in 1960, delivered an important lecture titled "An Unsolved Problem in Biology" in 1951. The unsolved problem was ageing, and when it was published the following year it had a strong influence on the scientific study of ageing (1). This inevitable physiologic process can be simplified as the sum of any progressive, deleterious, endogenous and/or exogenous oriented changes taking place in living cells over time. Many scientific observations, insights, and new or combined theories that explain ageing have concluded that ageing is no longer an unsolved problem in medical sciences.

Today almost every society, including the less developed countries, contains senior citizens. The modern world population in developed countries is constantly getting older and older. Unfortunately most of these elderly people use polypharmacy, and are limited by chronic conditions from performing daily major routine activities (2). Life expectancy is defined as the average total number of years that a human expects to live. In contradiction to life expectancy, life span is the maximum number of years that a human being can live. While the human life span has remained substantially unchanged for the past 100,000 years at ~125 years, life expectancy has substantially increased (from ~27 years during the last century), especially in Western Countries (3,4). Nevertheless, in many developing countries only a small group of people can reach their expected life span due to preventable infectious diseases, poor nutritional status and/or a distorted health system.

The ageing of the organism is characterized by minute, gradual and progressive functional declines of all vital organ systems (5). As organisms age, a large number of behavioral, reproductive, morphological, and biochemical changes occur together with increased incidence of cardiovascular diseases, Alzheimer's disease, Parkinson's disease, cognitive impairment, cataracts, presbyacusia, type 2 diabetes mellitus, osteoporosis, osteoarthritis, sarcopenia, and many types of cancer (6,7). For this reason a thorough vitality-status and risk analysis for each type of these frequent diseases of humans are recommended.

How and why do we get old? What are the fundamental causes of ageing and how can we carry ageing into a longer future? What are the changes at both cellular and molecular levels? Convincing answers to these bewildering inquiries first of all need theories that should explain irreversible advancing characteristics of ageing that are harmful for both physical and mental health (8). Many existing theories are interrelated, just like a network where the elements work independently or depend on each other from time to time. Throughout medical history, more than 300 theories have been proposed to explain the ageing process and a very large collection of information about these theories is present today (9). Many propose novel theories of ageing, as if their theory will by itself explain everything about ageing. In fact, of the various theories of ageing that have been proposed over the years, several undoubtedly have a degree of truth. The focus of this review is the refinement of existing theories. We propose following classification system for existing ageing theories that can mainly be classified as developmental, immune, neuro-endocrine and damage accumulative (Table 1).

Damage Mechanisms

In the fifties, Denham Harman proposed the concept of free radicals having a pivotal role in the ageing process, which results from deleterious damage to tissues by free radicals at the molecular level, modifiable by genetic and environmental factors (10). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are highly reactive molecules or molecular fragments containing one or more unpaired electrons in the outermost atomic or molecular orbitals. They are usually unstable and highly reactive toward losing or picking up an extra electron, so that all electrons in the atom or molecule will be paired (11). The free radical often pulls an electron off a neighboring molecule, causing the affected molecule to become a free radical itself. The new free radical can then pull an electron off the next molecule, and a chemical chain reaction of radical production occurs (12). They react with several biomolecules like proteins, lipids, and nucleic acids, which are constituents of membranes or DNA and RNA, and wreak havoc in the living system.

The damage promoted by ROS and RNS is termed oxidative and nitrosative stress, respectively, seen in a broad spectrum of organisms from invertebrates to humans. Efficient regulation of ROS/RNS production and neutralization is

Table 1— Types of Main Mechanisms and Common Ageing Theories

		I. Damage Mechanisms	II. Immune Mechanisms	III. Developmental Mechanisms	IV. Neuro-Endocrine Mechanisms
Main Ageing Theories	Genetic Longevity Determination			+++	+
	Telomere Shortening			+++	
	Oxidative Stress	+++	++	+++	+
	Mitochondrial Lysosomal Axis	+++		+	
	Immune Theory	++	+++	+	+
	Somatic Mutation	++		+	
	Antagonistic Pleitrophy		+++	++	+++
	Reproductive Cell Cycle	+	+		+++
	Error Catastrophe	+++		+	

essential for avoiding their detrimental effects, and different molecular mechanisms co-operate to preserve this equilibrium, termed 'redox homeostasis' (13). Progressive ageing is associated with higher levels of oxidized biomolecules that have reacted with free radicals (14,15). This theory has been very popular and also has been continuously studied and modified over time. The discovery of superoxide dismutase, which detoxifies the superoxide anion (16), and detection of hydrogen peroxide (H_2O_2) further gave credibility to the free-radical theory of ageing. Harman refined his theory to highlight the role of mitochondria in ageing, since mitochondria are considered to be the main source of ROS (17-19). It has been proposed that 0.2–2% of the total oxygen consumption is converted into free radicals in mitochondria. During energy transduction, a small number of electrons 'leak' out from oxygen prematurely, thereby forming ROS, which is mainly the oxygen free radical superoxide (13,20). The Free Radical Theory of Ageing has been modified to the Oxidative Stress Theory of Aging because of oxygen species such as peroxides and aldehydes, which are not technically defined as free radicals (15).

Several lines of scientific evidence support the oxidative stress theory of ageing. The levels of oxidative damage to lipid, DNA, and protein have been reported to increase with age in a wide variety of tissues and animal models (21,22). Findings in accordance with the oxidative stress hypothesis of ageing can be an increase in protein carbonyl groups, advanced oxidation protein products (AOPP) and malondialdehydes (MDA) as lipid peroxidation products (23-28). Protein carbonyl content is actually the most general indicator and by far the most commonly used marker of protein oxidation in ageing (29). Protein carbonyls are accepted as chemically stable markers of oxidative protein damage in biological samples. AOPP are novel oxidative stress biomarkers, first detected in the plasma of chronic uremic patients in the middle nineties (30). ROS degrade polyunsaturated lipids, forming reactive aldehydes such as MDA. Besides the aforementioned parameters, antioxidant enzymes Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPX), which are significant antioxidant defenses in many types of mammalian cells exposed to oxygen, have been found to be lower among aged subjects (31). SOD catalyzes the dismutation of O_{2-} into O_2 and H_2O_2, which can subsequently be converted to water by catalase. It is reported that ablation of mitochondrial SOD in an otherwise normal animal causes increased endogenous oxidative stress, brought to an end as loss of essential enzymatic components of the mitochondrial respiratory chain and the tricarboxylic acid cycle; enhances sensitivity to applied oxidative stress; and causes early-onset mortality in young adults (32). GPX is viewed as one of the most significant cellular scavengers of hydrogen peroxide and alkyl hydroperoxides in the eukaryotic cell (33). Mice null for GPX1 develop a high incidence of cataract at a young age, suggesting accelerated ageing (34).

Studies with animal models showing increased longevity are consistent with the Oxidative Stress Theory of Aging; the longer-lived animals show reduced oxidative damage and/or increased resistance to oxidative stress. Early studies on caloric restriction, which is the first and most studied experimental manipulation shown to increase life span and retard ageing, showed that oxidative damage to lipid, DNA, and protein was reduced in caloric restricted rodents compared to rodents fed *ad libitum*. Subsequently, caloric restricted mice were also shown to be more resistant to oxidative stress (21,35-37).

Immune Mechanisms

Claudio Franceschi proposed the immune theory of ageing in 1989, suggesting that the ageing process is indirectly controlled by a network of cellular and molecular defense mechanisms (38,39). Franceschi identified mononuclear phagocytes as the chief modulator of innate immunity, inflammation and stress factors. Both endogenous and exogenous stress activators can lead to a chronic inflammation state. These potentially harmful pro-inflammatory signals at a later stage of life may lead to a possible advancing step in ageing through progressive depletion of the immune system and other systems. On the other hand, they may act antagonistically, having developmental roles in the early stages of life (40). They eventually called this process "inflamm-ageing", which is characterized by the complex set of conditions that can be described as low-grade, controlled, asymptomatic, chronic and systemic (39,41). Guinta proposed that inflamm-aging may constitute the subclinical paradigm of autoimmunity syndromes (41). The human body essentially begins to produce auto-antibodies targeting its own tissues, and the production of time-acquired deficits primarily in T cell function predisposes the elderly to the development of infections and autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (42,43). Functional capacity of the immune cells has been proposed as a marker of health. Studies with mice having premature senescence, long-lived mice and human centenarians have ascertained that several immune functions are good markers of biological age and predictors of longevity (44).

Interestingly, reactive oxygen and nitrogen species are heavily implicated in the inflammatory processes (4,45). It can be concluded that the oxidative stress theory of ageing overlaps others, suggesting direct and indirect interactions across different mechanisms.

Developmental Mechanisms

It is very well known that genes influence both ageing and age-related diseases. Premature ageing syndromes can establish very prominent evidence that genes have major effects during senescence. Hutchinson Gilford Syndrome (HGS), segmental precocious ageing syndrome, is a very rare inherited disease represented as growth retardation and early cardiovascular events resulting in death during the second decade of life (46). HGS, progeria of the child, is caused by mutations in the gene *LMNA* (1q21.2), encoding a nuclear envelope protein, lamin A (47). On the other hand, Werner's syndrome (WS), progeria of the adult, is caused by a mutation in a gene coding for *WRN*, which is a member of the RecQ helicase family. WS is characterized by features resembling precocious ageing, appearing as a variety of visible features associated with ageing, such as graying of the hair and skeletal changes, which occur much earlier than expected (48-50). However, progeroid syndromes do not fully represent accelerated ageing. The most striking age related diseases have not been observed in HGS patients (51). But for WS patients, diabetes, cataract and cancers of mesodermal origin are common, although death usually results from an event of vascular origin at a median age of 47 (52).

Besides information from the aforementioned 'caricature of ageing' diseases, many researchers have always looked for genes that affect life span. The discovery that the single gene mutations *age-1* and *daf-2* could extend life span one to two fold in the nematode *C.elegans* revealed that longevity is under genetic control (53,54). Extended life span was shown to depend on another locus as well, *daf-16*, defining a non-linear interaction between genes for this process (55). Molecular identifications lead to understanding all three of these genes as components of the insulin/IGF-I signaling pathway (56,57). Gene *age-1* encodes a phosphatidylinositol-3-kinase (PI3K) that functions in this pathway (58). DAF- 2 protein resembles mammalian receptors that allow cells to respond to insulin or insulin like growth factors. As a result of mutations in age-1 or daf-2, DAF-16 protein enters the nucleus and causes transcription of genes that promote longevity (46). So it can be concluded that genetic longevity determinants are highly correlated to the nutritional status of the organism. As a matter of fact, these mechanisms can be an establishing connection between neuro-endocrine and genetic regulations, working together over the ageing process.

All these genetic findings suggest a strong basis for the genetic longevity program of ageing. What about direction of senescence? Telomeres are multiple DNA base repeat sequences located at the ends of eukaryotic chromosomes (43). It is hypothesized that telomeres function as a mitotic clock by getting progressively shorter with every cell cycle, leading to erosion and dysfunction at the cellular level, and are associated with cell cycle delay, triggering of the DNA damage response, and apoptosis (59). The telomere theory of ageing is based on the idea of normal somatic cells having a definite life span and losing telomeric DNA every time they divide, as a function of ageing (43). The length of telomeres, and in particular the abundance of short telomeres, has been proposed as

a possible biomarker of ageing and of general health status (60). Telomerase is the enzyme responsible for maintaining the stable length of telomeres by the addition of guanine-rich repetitive sequences, so this enzyme conserves the capacity for essential replication (61). Senescent human cells lose about half of their telomeric length and show the accumulation of oxidized and ubiquitinated proteins together with decreased proteosome activity (62). This finding makes a significant bridge between telomere theory and damage accumulation theory. Ageing researchers Elizabeth Blackburn, Carol Greider and Jack Szostak, the 2009 Nobel laureates, were very conscious of the influence their research on telomerase has on biogerontology (63).

Neuro-Endocrine Mechanisms

It has been hypothesized that the role of neuro-endocrine axes in ageing is perceptible by the disruption of physiologic patterns of hormone release. The neuro-endocrine theory proposes that ageing is due to changes in neural and endocrine functions that are crucial for: 1) coordination and responsiveness of different systems to external stimuli; 2) programming physiological responses; and 3) the maintenance of an optimal functional status for reproduction and survival (4). There are many examples to support the neuro-endocrine theory.

One of the neuro-endocrine theory proposals is cortisol surge or elevations related to chronic stress over the years that may result in normal ageing in the elderly (43). The master gland, the anterior pituitary, itself undergoes changes while ageing, such as fibrosis and vascular alterations. These changes, including hypogonadism in older men and women, can be seen either as a part of normal ageing or as a dysfunction that needs treatment (64). The Reproductive-Cell Cycle Theory proposes that the hormones which regulate reproduction act in an antagonistic pleiotrophic manner to control ageing via cell cycle signaling; promoting growth and development early in life in order to achieve reproduction, but later in life, in a futile attempt to maintain reproduction, becoming dysregulated and driving senescence (65). The natural age-related decline in plasma GH levels and the concomitant decrease in IGF-1 that occurs in mammals is likely a protective mechanism to decrease metabolic activity and cellular division. Elevated levels of either GH or IGF-1 throughout life contribute to the pathological changes associated with ageing such as increased collagen cross-linking, osteoarthritis, immune system dysfunction, insulin resistance, oxidative damage, sensitivity to stress and cancer (66). In addition to this, mice lacking GH or GH receptor outlive their normal siblings and exhibit symptoms of delayed ageing associated with improved insulin signaling and increased stress resistance (67).

Whilst the neuro-endocrine theories mentioned above are the standard theories in this field, information on the *klotho* gene has provided a special and new outlook for biogerontologists. There are two parts of the klotho protein: 1.Membrane klotho functions as a receptor for regulation of phosphate and vitamin D; 2. Secreted klotho functions as a humoral factor with pleiotropic activities, including suppression of growth factor signaling (68-70). A defect in klotho expression in mice leads to a syndrome resembling ageing, whereas overexpression of klotho in mice extends the life span (71,72). Further studies on the klotho gene are expected to provide new and challenging insights into endocrine regulation of various metabolic and ageing processes (70).

Conclusion Remarks and Future Directions

Even though slowing, stopping or even reversing the process of ageing is mentioned every day in scientific communities, an excellent theory unifying all clinical and physiological features of ageing is hard to see on the horizon of the near future. In spite of all the efforts by scientists, it is still quite arduous to differentiate so called "physiologic or successful ageing" from asymptomatic diseases, individually. The ageing process of humans runs differently for each individual, is complex, and even shows diversity in various body compartments within each individual, leading to differences between chronological and biological age. A clear cut distinction between chronological ageing and biological ageing would contribute a lot to clinicians' perspectives on the treatment and evaluation of individual patients. Oxidative stress parameters on main macromolecules, length of telomeres, endocrine status of patients, subclinical inflammation indicators and investigation of gene expression are all candidates to be biomarkers of ageing.

The determination of biological age- and vitality-parameters is an important and essential tool for any physician in preventive or anti-ageing medicine. On the basis of exactly defined vitality values, any medical preventive method can be exactly monitored, instead of relying only on superficial control of symptoms. For the patient, a precise test value is a better motivator for long term adherence and compliance. For this reason, biological markers of ageing and vitality are necessary modern instruments for preventive medicine to

increase health and vitality and to reduce age related diseases and disability. But it is still an open and controversial question whether to use biological markers in routine practice after sufficient evidence based medicine research. To understand the precise and stochastic mechanism of ageing and age related diseases, there is a rising need for accurate, well planned and time-consuming in vivo research studies.

Abbreviations

Advanced Oxidation Protein Products (AOPP), Glutathione Peroxidase (GPX), Hutchinson Gilford Syndrome (HGS), Hydrogen Peroxide (H_2O_2), Phosphatidylinositol-3-kinase (PI3K), Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS), Superoxide Dismutase (SOD), Werner Syndrome (WS)

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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