Current View on Biology of Aging

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Abstract

This review article is based on a systematic literature search using Pubmed and keywords aging and senescence, interchangeably. Aging (senescence) is the progressive deterioration of many bodily functions. It may or may not be linked to disease, disability and loss of independence. Populations worldwide are aging. Theories of aging biology are interactive and interdependent. They fall into programmed theories and error or damage theories. Longevity genes are under scientific scrutiny, via utilising microarray technology, founder populations and centenarians' family history. Telomere shortening is another programmed theory to explain healthy senescence. Biochemistry of the endocrine theory includes hormonal deficiencies, growth factors and heat shock proteins. Immuno-senescence furthermore elaborates the programmable aging. Among many of error/damage theories are free radical theory, mitochondrial dysfunction, membrane hypothesis of aging, protein cross-linking and DNA repair and maintenance. Biomarkers of aging, as in senescence marker protein-30 and klotho protein, offer the feasibility for exploring aging biology and physiology, advancing our understanding of genetic and lifestyle contributions to aging, and, at best, developing effective age-defying interventions.

Keywords: Aging, Senescence, Theories of Aging, Longevity, Biochemistry of Aging.

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Introduction

In its broadest sense, aging (senescence) is the progressive universal decline first in functional reserve and then in function that occurs in organism overtime. This loss of function is accompanied by decreased fertility and increased risk of mortality. Aging is heterogeneous. It varies widely in different individuals and in different organs within a particular individual. Aging is not a disease. However, the risk of developing disease is increased often dramatically, as a function of age. [1, 2]

Demography of Aging: A Global Perspective

Populations worldwide are aging. Improvements in environmental factors (sanitation and clean water), behavioral factors (nutrition and reduced risk factors), vaccination (prevention of infections), and disease treatments are largely responsible for the 30-year increase in life expectancy since 1900. [3]

Between 2000 and 2030, the number of older adults worldwide is expected to increase from 420 to 974 million.

At present, 59% of older adults live in the developing countries of Africa, Asia, Latin America, the Caribbean and Oceania. The developing world has the largest absolute number of older adults and is experiencing the largest percentage increase.

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Only 13% of those ≥ 80 years live in the US; over 40% of those ≥ 80years live in Asia. [4] Embedded within these figures are additional critically important factors. Women outlive men; only 15% of centenarians are men. Women also spend a greater portion of their surviving years being disabled than do men. Despite the decrease in disability rates between 1980s and 1990s, epidemics of obesity and physical inactivity may reverse these trends. [4]

Why do we age?

Biological aging is no more an unresolved problem, as changes occurring in biomolecules that lead to the manifestations of aging at higher orders of complexity and then increase vulnerability to all age-associated pathology are under ultramicroscopic scrutiny. [5]

Theories of Aging Biology

Gerontology -studies of aging- is aimed at understanding the cellular and molecular basis of age-related changes and have two ultimate therapeutic goals: preserving function, health and independence, as long as possible, and extending life span. These two goals may not be linked. [6]

Aging today is viewed as many interactive and interdependent processes that determine life span and health with a multitude of factors involved. Theories of aging fall into two groups. The programmed theories hold that aging follows a biological timetable, perhaps a continuation of the one that regulates childhood growth and development.

The damage or error theories emphasize environmental assaults to our systems that gradually cause things to go wrong. Many of the theories of aging are not mutually exclusive. Here is a simplified and briefed rundown of the major theories. [7- 12]

Programmed Theories

1- Programmed Longevity-genetic Hypothesis: Aging is the result of the programmed sequential switching on and off of certain genes with senescence being defined as the time when age-associated deficits are manifested.

Longevity Genes in Connection to Senescence

Investigators are finding clues to aging and longevity in yeast that has intriguing genetic similarities to human cells. Over the course of 21-divisions (generations) certain genes are differentially expressed in the yeast lifespan. Selective over-expression of LAG-1 (longevity assurance gene) for a membrane protein influences the number of divisions in yeast or its longevity (increased by 30%). [13, 14]

A mutation of a gene named ''I'm Not Dead Yet'' or INDT can double the lifespan of fruit flies. By the time that 80 to 90% of normal flies were dead, many of INDY flies were still vigorous, thriving and capable of reproduction. At least two other life-extending genetic mutations have been detected in the fruit fly genome. [15]

In *Caenorhabditis elegans* (a nematode, the roundworm), altering *daf*-2 gene to reduce its activity, can double lifespan of adult worms. The *daf*-2 gene in *C.elegans* is similar to a gene found in humans that functions in hormone control. [16]

The emerging technology of microarrays can help clarify what changes are occurring simultaneously in diverse cells as they age. For now, gene products are thought to influence **replicative senescence**. Hayflick limit describes a certain number of cell divisions after which cells enter a state in which they no longer proliferate and DNA synthesis is blocked. [17] At least, four genes involved in replicative senescence have been identified. Senescent cells are resistant to dying, and continue to respond to hormones and other outside stimuli though they cannot proliferate. [18]

Cellular senescence triggers also important changes in gene expression. So it can be critical early in life because it limits cell proliferation and helps suppress cancer. However, upon getting older, senescent cells might be harmful because changes in genes they express might actually promote unregulated growth and tumour formation. This concept that genes, which have beneficial effects early in life, can also have detrimental effects later is known as **antagonistic pleiotropy.** [19] An example of antagonistic pleiotropy in humans is p53, a gene that directs damaged cells to stop reproducing or die. The gene helps prevent cancer in younger people, but may be partly responsible for aging by impairing the body's ability to renew deteriorating tissues. Because of antagonistic pleiotropy, it is likely that tinkering with genes to improve late-life fitness could have a detrimental effect on health at younger ages. [19]

Proliferative genes, like *c-fos*, trigger cell proliferation. *C-fos* gene encodes a short-lived protein that is thought to regulate the expression of other genes important in cell division. Proliferative genes are countered by antiproliferative (tumour suppressor) genes as *RB* (retinoblastoma) gene and *p53* gene. Mutations in these silencing genes have been shown to affect the lifespan of *C.elegans* and yeast. [20] The delicate balance between the two kinds of genes establishes the limited proliferation and replicative (cellular) senescence. In some cases, however, a cell somehow escapes this control mechanism and goes on dividing, becoming immortal, eventually forming tumours. This is one area in which aging and cancer research intersect. So replicative senescence is apparently retained as a defence against cancer. [21]

Genetics and Exceptional Longevity

Family studies may also identify features of delayed or successful aging. Twin studies suggest that ≈30% of the variation in longevity can be attributed to genetic factors, with the remainder being attributable to environmental and behavioural factors. Long life span runs in families, and studies of centenarians and their offspring may define particularly adaptive phenotypes. For example, centenarians are less likely to be carriers of the apolipoprotein E ε4 allele, which is associated both with risk for heart disease and Alzheimer disease. Ashkenazi Jewish centenarians and their offspring have been found to have larger High-Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL) particle sizes, a lower prevalence of hypertension, cardiovascular disease, and the metabolic syndrome and a greater likelihood of carrying an athero-protective variant of the cholesteryl ester transfer protein gene. As studies of genetically more homogeneous populations (founder populations) such as those in Iceland and Sardinia progress, additional genetic contributions to healthy aging may be identified). [22, 23]

Telomere Shortening and Accumulation of Senescent Cells Hypothesis

Natural chromosome ends, unlike random DNA breaks, had special properties that protect them from end-to-end fusion. The highly conserved telomere structures at the ends of linear chromosomes consist of tandem repeat DNA sequences and associated proteins. [24] Telomere protects chromosomes from recombination and recognition as damaged DNA, moreover, provides a mean for complete replication of chromosomes, contributes to the functional organization of chromosomes within nucleus and participates in the regulation of gene expression. Most importantly, it serves as a molecular clock that controls the replicative capacity of human cells and their entry into senescence. Telomere shortening was observed with progressive cell division *in vitro* and increased age *in vivo.* [25]

Normal mammalian somatic cell proliferates a maximum number of times *in vitro*, being referred to as the Hayflick limit (see above). [26] The shortening in normal human cells acts as a molecular clock that could monitor the replicative history of cells. [27] At the Hayflick limit, one or more critically shortened telomeres trigger permanent growth arrest known as replicative senescence. [28] Telomerase is an RNA dependent DNA polymerase that synthesises telomeric DNA sequences and almost universally provides molecular basis for unlimited proliferative potential. Telomerase activity was found to be absent in most normal human somatic cells (egg, sperm cells, bone marrow and gastrointestinal cells are among the exceptions) but present in over 90% of cancerous cells and *in vitro* immortalised cells, enabling cells to replace lost telomeric sequences and divide indefinitely. [29] It is another territory where cancer and aging research merge.

2- Endocrine Theory: Biological clocks act through hormones to control the pace of aging. The decline and loss of circadian rhythm in secretion of some hormones produces a functional hormone deficiency state.

Antiaging hormone replacement therapies include oestrogen, progesterone, testosterone, thyroid hormones, melatonin and human Growth Hormone (hGH). [30- 35] Mechanistically, the relevance of these hormones to human longevity remains to be established. [36] On one instance, hormonal mechanisms have proved effective in activation of longevity genes and cancer resistance, via activating chaperones (the cancer antagonists and genetic buffers) and immune response genes. [37]

The corner stone of hormone replacement therapy is to *only* replace hormones for which there is a demonstrable deficiency. Hormonal supplements appear to increase risk and provide few clear-cut benefits for the healthy individuals and do not seem to slow the aging process.

Growth Factors

Growth or trophic factors are some type of hormones. Insulin-like Growth Factor-1 (IGF-1) is one example. It mediates many of hGH actions. Growth hormone releasing factor is another example. This trophic factor stimulates the release of hGH. Growth factors might have an important role in longevity determination. In nematodes, for instance, mutations in at least two genes in the IGF-I pathway result in extended life span. [38- 40]

Heat Shock Proteins (HSPs)

Despite their names, HSPs are produced when cells are exposed to various stressors, not only heat. Their expression can be triggered by exposure to toxic substances such as heavy metals and chemicals, and even behavioural and psychological stresses, helping cells to dismantle and dispose of damaged proteins and facilitating the making and transport of new proteins.

HSPs levels depend on age. Thus, stress response genes, particularly HSP70, are now the major candidates in the gene-longevity association studies. [41] Old animals placed under stress have lower levels of HSP-70 than young animals under similar stress. In addition, a striking decline in HSP-70 production is found to *in vitro* cells approaching senescence. In the adrenal cortex as well as in blood vessels, HSP-70 expression appears closely related to responsive stress hormones as glucocorticoids and catecholamines. This, therefore, casts new light on HSPs-neuroendocrine puzzle in the aging process. [42]

3- Immunological Theory and Defective Host Defences: A programmed decline in immune system functions leads to an increased vulnerability to infectious disease and thus aging and death. [43, 44]

In any aging immune system**,** while the total number of T-cells remains about the same, the proportion of functioning population of T-cells and their lymphokine products decline with age. Studies have also shown that in older people and unlike younger people, T-cells destroyed by cancer chemotherapy or irradiations take longer to renew. [45] One group of T-cell products, interleukins, is found at different levels as people age. Some, like interleukin-6, rise with age, and it is speculated that they interfere in some way with the immune response. Others, like interleukin-2, which stimulates T-cell proliferation, tend to fall with age. [46, 47] In a recent Italian study, a strong axial linkage involved the polymorphism of immunogenetics, longevity, and the control of cardiovascular disease. It could show that people genetically predisposed to weak inflammatory activity may be at reduced chance of developing Coronary Heart Disease (CHD) and, therefore, may achieve longer lifespan if they avoid serious life-threatening infectious disease. Such a linkage had significant gender dependence. [48]

Error Theories

1- Free Radical (FRs) and Oxidative Stress Hypothesis of Aging: Oxygen sustains us. Yet, oxygen maybe a primary catalyst for much of the damage associated with aging. Like all furnaces, mitochondria generate potentially harmful by-products, oxygen Free Radicals (FRs), also known as reactive oxygen species, during ATP metabolism. FRs steal mates for their lone electrons (more stable when paired) from other molecules, sparking a chain reaction of oxidations. Mitochondria are particularly prone to FRs damage, the major source and the prime target. As damage mounts, mitochondria become less efficient, progressively generating less ATP and more FRs. [49]

The free radical theory of aging emerged from the views of Gerscham [50] who postulated that oxygen free radicals were the common molecular mechanism of oxygen and radiation toxicity and of Harman [51] who considered that free radicals generated as by-products of biological oxidations produce random and cumulative cellular damage leading to tissue and organ aging.

The association between aging and mitochondria is based upon the role of these organelles in providing cell energy and the physiological decline of organ energy expenditure on aging. [52- 54] Hence, the mitochondrial hypothesis of aging considers mitochondria selectively as the pacemaker of tissue aging due to continuous mitochondrial production of reactive oxygen and nitrogen species, capable of membrane lipo-peroxidation, protein oxidation and glycoxidation, in addition to DNA damaging-oxidation, leading to cumulative oxidative damage. [55]

The greater an organism's rate of oxygen basal metabolism, the shorter its lifespan. For example, age-related oxidative stress may promote vascular inflammation via multiple pathways converging on NF (Nuclear Factor)-kappaB and endothelial activation in aged arteries. [56]

But FRs do not go unchecked. Cells utilise antioxidants to counteract them. These include vitamins C and E as well as enzymes such as superoxide dismutase, catalase and glutathione peroxidase. Nonetheless, some FRs manage to circumvent these defences, cellular repair mechanisms eventually falter and some internal breakdowns are inevitable, leading to cellular senescence and apoptosis. [57]

Studies have demonstrated that inserting extra copies of superoxide dismutase gene into fruit flies extend their average life span by 30 percent. [58, 59] Further experimental evidence lends support to the FRs hypothesis, where higher levels of superoxide dismutase and catalase have been found in long-lived nematodes. In one compelling study, giving nematodes synthetic forms of these antioxidants significantly extended their normal lifespan. [60] For now, the effectiveness of dietary antioxidant supplementation remains controversial in helping people to live longer. [61- 64]

2- Mitochondrial Dysfunction: A common deletion in mitochondrial DNA with age compromises function and alters cell metabolic processes and adaptability to environmental change. More to it, age-related alterations in the supramolecular architecture of oxidative phosphorylation proteomic complexes might explain alterations in ROS production during aging. [65] That might be coupled with accumulating high levels of mitochondrial DNA (mtDNA) mutations in polymerase gamma deficient mice showing a premature aging phenotype. Thus, a more causative role has been proposed for mtDNA mutations and aging of mitotic as well as postmitotic tissues. [66]

3- Membrane Hypothesis of Aging: Aging cell membrane becomes less fluid. This impedes its efficiency to conduct normal function and in particular there is a toxic lipofuscin accumulation, which results in membrane dysfunction and degenerative disease. It is known that Alzheimer disease patients have much higher levels of lipofuscin deposits than their healthy controls. The essential and regular transfer of sodium and potassium is impaired in the cells declining efficiency, thus reducing communication. It is also believed that electrical and heat transfer is also impaired. [67, 68]

4- Protein Cross-linking: Accumulation of cross-linked proteins damages cells and tissues slowing down bodily processes. In a non-enzymatic glycosylation or glycation, glucose attaches to proteins, setting in motion a chain of complex and slow chemical reactions that yield cross-linking of proteins, thereby altering their biological and structural roles, disrupting, as a result, cellular function eventually. [69]

Glycation and oxidation are interdependent processes since FRs and cross-links (also known as Advanced Glycation End products; AGEs for short) seem to accelerate the formation of one another. Cross-linking, interestingly, may play a role in damage to DNA. AGEs have been linked to cataract, atherosclerosis, nephropathy and Alzheimer disease. Thus, not only do the complications of diabetes mimic the physiological changes that accompany old age, but also diabetics have shorter than average life expectancies. In effect, much research on cross-linking has focused on diabetes as an accelerated model of aging. [70, 71]

5- Somatic DNA Damage and Repair- Genome Maintenance: Genetic mutations occur and accumulate with increasing age, causing cells to deteriorate and malfunction**.** Additional insights about aging may be derived from understanding the clinical syndromes that produce premature aging phenotypes, the so-called segmental progerias. These syndromes are rare inherited disorders that mimic normal aging imperfectly. They include Werner syndrome, Bloom syndrome, Cockayne syndrome, Hutchinson-Gilford progeria and Rothmund-Thompson syndrome. [72]

Hutchinson-Gilford progeria involves a mutation in lamin A, a component of the nuclear envelope. [73] The symptoms have an onset in early childhood, and median survival is only about 13 years. All the other well-studied progeria syndromes involve mutations in DNA RecQ-helicases that are involved in DNA repair and recombination. [74] These syndromes have features of accelerated aging and are associated with an increased risk of cancers. Werner syndrome has accelerated atherosclerosis as a prominent feature. Whether these conditions can reveal secrets of normal aging is questionable. However, they suggest that the maintenance of the genome integrity is a vulnerable function that can lead to premature aging if it is performed sub-optimally. [72,75]

In the normal wear and tear of cellular life, DNA undergoes continual damage as in deletions and mutations, further suggesting that DNA damage and repair are parts of the aging puzzle. It is known that an animal's ability to repair certain types of DNA damage is directly related to the lifespan of its species. Humans repair DNA more quickly and efficiently than mice or other animals with shorter life spans. Furthermore, defects in DNA repair is found in people with a genetic or familial susceptibility to cancer. Therefore, if DNA repair processes decline with age while damage accumulates, it could explain why cancer is more common among older people. [76, 77]

Especially intriguing is repair to mitochondrial DNA injured at a much greater rate than nuclear DNA. Mitochondrial stream of damaging oxygen radicals during metabolism coupled with vulnerability of unshielded (unlike the nuclear envelop) mitochondrial DNA are among the underlying causes. [78]

It has been shown that mitochondrial DNA damage exponentially increases with age, and as a consequence, energy production diminishes overtime in cells, paralleled by physiological performance decline. [78] Most lately, there has been emerging links between the Biological Clock (BC)/circadian rhythm and the DNA damage response and aging processes. [79] Establishing molecular link between specific BC proteins and factors that control the mammalian cell cycle/DNA damage checkpoints was further highlighted in tumorogenesis and cancer progression. [79] Genetic determinants of longevity assuring Maintenance and Repair Systems (MRS) are also tailored to senescence. Progressively accumulative damages in the MRS lead to age-related failure of MRS, molecular heterogeneity, cellular dysfunctioning, reduced stress tolerance, diseases and ultimate death. [80] In addition, the interplay of *MORF/MRG* family of genes was also traced and implicated in cell growth, differentiation, DNA repair, and thereby aging (81). Among many, *MRG15* is found unique in that it associates with both histone deacetylases and histone acetyl transferase complexes, thus potentially plays a role in both transcriptional silencing and activation, and in effect, chromatin remodeling. [81]

Biomarkers Related to Aging

Biomarkers are increasingly employed in understanding physiological processes that change with age, diseases linked to age, and the aging process itself.

Senescence Marker Protein-30

Feng et al. [82] report a Senescence Marker Protein-30 (SMP30) as a novel antiaging molecule localised in nuclear and cytoplasmic extracts of hepatocytes. Because the SMP30 expression is reduced by carbon tetrachloride, it is speculated that SMP30 expression is modulated by oxidative stress aggravated with advancing age. The amino-acid alignment from various animal species revealed a highly conserved structure with an organophosphatase activity hydrolysing sarin, soman and butan known as lethal toxic nerve chemicals. [82] More to it, SMP30 rescues cell death by enhancing plasma membrane Ca^{2+} pumping activity in HepG2 cells, [83] thus maintaining intracellular Ca^{2+} -homeostasis.

Klotho the Novel Antiaging Protein

Antiaging *klotho* (after the Greek goddess who spins the thread of life), protein over-expressed by mice show an extended existence and a slow aging process through a mechanism that may involve the induction of a state of insulin and oxidant stress resistance. [84]. Conversely, *klotho* gene mutation leads to a syndrome strangely resembling chronic kidney disease in patients undergoing dialysis with multiple accelerated premature aging-related disorders, including hypo-activity, sterility, skin thinning, muscle atrophy, osteoporosis, vascular calcifications, soft tissue calcifications, defective hearing, thymus atrophy, pulmonary emphysema, ataxia and abnormalities of the pituitary gland as well as hypoglycaemia, hyperphosphatemia and paradoxically high plasma calcitriol levels. [85]

As a consequence, vast observations link *klotho* to an important role in Ca^{2+} homeostasis via novel regulatory mechanisms of active calcium re-absorption from renal tubular lumen TRPV5 (Transient Receptor Potential channel Vanilloid subtype 5). [85] *Klotho* can function also as a cofactor essential for the stimulation of Fibroblast Growth Factor (FGF) receptor by FGF-23. In fgf-23 deficient mice, ablation of vitamin D signalling rescues bone, mineral and glucose homeostasis. It further inhibits the intracellular insulin/insulin-like growth factor-1 signalling cascade, thus, taken together, advocating *klotho* as a regulator of oxidative stress and senescence. [84] Moreover, PPAR-gamma, a transcription factor involved in adipogenesis, glucose homeostasis, bone turnover, and inflammation, has now been shown to up-regulate *klotho* expression. This prompts, therefore, further exploration of the role and mechanism of action of PPAR-gamma in *klotho*-aging-bone diseases axis. [86]

Conclusion

A broad interpretation of the different degenerative changes during senescence should be adopted, with the major conclusion that aging is multicausal. This entails as well that aging cannot be reversed, although it may be modulated, as, for example, by calorie restriction. [87] Pharmacological intervention is another avenue. As most genes that affect longevity encode components of the Target of Rapamycin (TOR) pathway, rapamycin is a promising drug for age-related diseases. It seems to have anti-tumor, bone-sparing and calorie-restriction-mimicking 'side-effects'.[88-90] Moreover, Sirtuin genes function as anti-aging genes in yeast, *Caenorhabditis elegans,* and *Drosophila*. The NAD requirement for sirtuin function indicates a link between aging, metabolism and mitochondrial biogenesis.

A boost in sirtuin activity may in part explain how calorie restriction extends life span, hence, providing novel therapeutic leads to combat diseases of aging. [91, 92]

The FoxO family of Forkhead transcription factors plays an important role in longevity and tumour suppression by upregulating target genes involved in stress resistance, metabolism, cell cycle arrest and apoptosis. In *Caenorhabditis elegans*, the daf-16 gene, a mammalian homolog of FoxO genes, was shown to function as a longevity gene. [93] FoxO transcription factors translate a variety of environmental stimuli, including insulin, growth factors, nutrients and oxidative stress, into specific gene-expression programs. The effective control of FoxO activity in response to environmental stimuli is likely to be critical to prevent aging and age-dependent diseases, including cancer, neurodegenerative diseases and diabetes. [94] Furthermore, recent large-scale Genome Wide Association (GWA) studies for type 2 diabetes and myocardial infarction have also found major variants in this locus, confirming the p16/p15 region as a key aging site, providing new potential targets for interventions to slow aging. [95]

Impressively, a wide array of studies has provided evidence for a role of the activation of innate immunity during aging process in mammals in a process called inflamm-aging. The master regulator of innate immunity is the NF-kappaB system. Interactive aging-associated signalling cascades are regulated via the longevity factors of FoxOs and SIRT1 that can inhibit NF-kappaB signalling and simultaneously protect against inflamm-aging process. [93]

As we further pinpoint the interplay of the influences on how we age, new and effective interventions that may prevent disease and promote healthy aging and independence are increasingly attractive, and hence, the biology of aging is a vigorously evolving science.

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نظريات الشيخوخة وطول العمر

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الملخص:

يعتمد هذا البحث على أساس منهجي وعبارات رئيسية باستخدام senescence والشيخوخة بالتبادل. إن الشيخوخة هي التدهور التدريجي للعديد من الوظائف الجسمية وهذا التدهور قد يكون أو لا يكون مرتبطاً بمرض أو إعاقة وفقدان الاستقلال.

سكان العالم يشيخون. إن النظريات المتعلقة بالشيخوخة وبيولوجيتها ترتبط تفاعلاً واعتماداً وتندرج إلى نظريات البرمجة ونظريات الخطأ أو التلف .

جينات المعمرين يجرى عليها تدقيق علمي باستخدام التكنولوجيا microarray والمجموعات السكانية المؤسسة وتاريخ العائلة للذين بلغوا سن المائة .

إن اختصارtelomere نظرية برمجة أخرى لشرح senescence بطريقة صحية. إن الكيمياء الحيوية في نظرية الغدد الصماء تشمل نواحي القصور الهرمونية وبروتينات النمو وعوامل الصدمة الحرارية .

شيخوخة المناعة تفصل الشيخوخة المبرمجة. ومن بين الكثير من نظريات الأخطاء أو التلف، نظرية الراديكالات الحرة، الخلل الوظيفي للمايتوكندريا، وفرضية الأغشية للشيخوخة وترميم وصيانة الربط في البروتين أو الحامض النووي .

إن biomarkers للشيخوخة مثل klotho وprotein-30 بروتينات تعرض لاستكشاف بيولوجيا وفسيولوجيا الشيخوخة ودفع عجلة فهمنا للمساهمات الوراثية المتجهة نحو الشيخوخة وارتباطها بنمط الحياة وفي أحسن الأحوال تطوير فاعلية المداخلات لتحدي التقدم بالعمر.

الكلمات الدالة: الشيخوخة senescence، نظريات الشيخوخة وطول العمر، الكيمياء الحيوية للشيخوخة.