Mechanism of Biological Aging-A Review

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Abstract

Aging is a universal, inherent, natural phenomenon that occurs in all organism. Aging involves morphological and functional changes in cellular and extracellular components leading to progressive decline in most biological functions. It causes reduction in strength, basal metabolism, sexual activity and the body's defenses.

Aging is the progressive decline in the maintenance of homeostasis, which leads to decreased response of the body against internal and external stress. It involves imbalance between free radicals and the antioxidant mechanism lead to damaged cells, tissues, and organs resulting in age related changes.

With age there is modifications in energy metabolism, insulin sensitivity, neuroendocrine function and induction of hormesis response. Telomere shortening, mitochondrial dysfunction, increase of oxidative stress, alteration of insulin-like growth factor and growth hormone signaling are considered to be important contributors of aging process.

Recently many genes and changes in gene expression have been found associated with aging which affects many biological processes and are associated with senescence and oxidative stress.

This review focuses on the underlying mechanism of biological aging. With an increase in the number of elderly population and the patients of age-related diseases, it is becoming increasingly important to consider these in the field of research. We have attempted to discuss the different aging mechanism along with the newer concepts, which can give a direction for the future research studies.

Keywords: *Hormesis, Senescence, Epigenetic, Endocrine dysfunction, IGF1 regulation.*

Introduction

Aging is a time-sequential deterioration of body function that occurs in most animals and considered as an inevitable fact of life. It is a complex multifactorial process characterized by progressive functional decline at the molecular, cellular, tissue, and organismal levels.

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Adaptations with evolutionary changes occurs in most complex organisms that involves biological mechanisms that purposely limit their internally determined lifespans beyond a certain species-specific age. Senescence results in programmed aging and it is an unavoidable side effect of a beneficial property. Evolutionary theories of aging explain why mortality rises with age as health and function decline. According to this as individuals age, mutation and natural selection causes mortality because less of lifetime fertility remains.[1]

Different natural aging mechanisms together result in progressive deterioration of body function and failure of metabolic processes. This review discusses different

mechanism responsible for biological aging mechanisms.

For this review, we conducted a literature search on PubMed and google scholar ranging from February 1, 1993 to May 30, 2020, querying the following terms and related synonyms: "senescence and aging", "telomerase activity and lifespan", "epigenetic regulation of aging", "metabolic changes with aging", "endocrine and metabolic changes in stress", "oxidative stress in aging", "inflammatory changes with aging". Search also included individual key terms like "Hormesis", "IGF regulation", "Klotho gene", "Nrf/CNC protein". We restricted our search to articles published in English.

Hormesis and Aging

Breakdown of self-organizing systems, homeostasis and reduced ability to adapt to the environment results in aging. According to the concept of evolution aging occurs due to the absence of natural selection after reproductive stage of life. Fitness can be defined as the ability of an individual to leave copies of its genes to future generations.[2]

Hormesis is viewed as an evolutionary-based adaptive responses. Hormesis is the adaptive responses to stress and environmental challenges with beneficial effects of biological systems. It helps in improving cellular functions and its tolerance to more severe stress. Hormesis can be explained as an evolutionary adaptation that acts to maintain fitness in a changing external environment. [2,3]

Cells and organisms evolved to survive exposures to toxic agents and further to use those toxic agents to their advantage. Low concentrations of toxic metals activate stress defense mechanisms and through this induce hormetic effects. Spinoso-Castillo et.al. through their study proved that low concentrations of toxic metal silver nanoparticles induce hormetic effects through activating plant stress defense mechanisms.[4]

Hormesis is characterized by stimulation of many independent cellular functions such as enhancements of DNA repair, antioxidant defenses and autophagy. Recent findings have demonstrated that hormesis can occur when a challenge is imposed after acute injury. Preconditioning and the adaptive response causes postinjury metabolic challenges and faster recovery.[5] One of the ways dietary restriction improves cellular functioning is by enhancing endogenous cellular stress responses and energy metabolism. Prophylactic intermittent fasting (e.g., every-other-day fasting [EODF]) can protect neurons against injury by dampening oxygen free radical formation and inflammation, and activating cell survival pathways. It causes increase in the growth factor expression and axonal plasticity. Jeong M et.al. studied the effect of dietary restriction, in the form of every-other-day fasting (EODF), prior to (pre-EODF) and after (post-EODF) an incomplete cervical SCI in rats. Both the prophylactic pre-EODF and therapeutic post-injury-initiated EODF resulted in improved functional recovery.[6]

Senescence Association with Aging

Senescence is cellular program that induces a stable growth arrest and limits the proliferation of aged or damaged cells. It is a stress response triggered by insults associated with aging. Mitotic cells divide a finite number of times before they cease replication and senescence starts. Genomic instability and telomere attrition are associated with triggering senescence and are considered primary aging hallmarks. A stable growth arrest ensures that the damaged or transformed cells do not transfer their genomes. [7,8]

Aging is considered to be associated with decline in mitochondrial function contributing to specific aspects of the aging process like cellular senescence, chronic inflammation and the age-dependent decline in stem cell activity. [9]

Telomerase activity and telomere length are found to be associated with stressful conditions. At the cellular level, stress can promote earlier onset of age-related effects. In a study on 58 healthy premenopausal women the perceived stress and chronicity of stress was found significantly correlated with higher oxidative stress, lower telomerase activity, and shorter telomere length. The high-stress group had significantly shorter telomeres (raw mean T/S ratio = 1.13 ± 0.17), than the low-stress group (raw mean T/S ratio = 1.33 ± 0.15). There was 550-bp telomere length shortening in the high-stress group compared with the low-stress group which indicates that their lymphocytes had aged the equivalent of 9–17 additional years.[10]

Recent studies are focusing on methods for improving telomerase activity and telomere length. Tolahunase M. et. al. studied the effect of Yoga and Meditation based lifestyle intervention (YMLI) on cellular aging in healthy individuals. They found significant increase in the telomerase activity, total antioxidant capacity β-endorphin, BDNF, and sirtuin-1 after 12 weeks of YMLI.[11]

TA-65 is a small molecule telomerase activator used as dietary supplement discovered from a traditional Chinese medicine. In a study conducted in Barcelona, Spain subjects taking the low dose of TA-65 (250 U) had significantly increased telomere length over the 12 months period.[12]

Lin P.C. et. Al. did a double-blind placebo-controlled trial to evaluate the antiaging effects of a food supplement containing placental extract. Samples were evaluated for $CD34^+$ cells, insulin-like growth factor 1 (IGF1), and telomerase activity, which are all markers related to aging. Telomerase activity differed significantly between the control and food supplement groups. The average telomerase activity was found to increase by 30%. [13]

Epigenetic Regulation

Gene expression is central to the cellular function and its fate. Maintenance of the fundamental structure of chromatin is key to slowing down the aging process. Transcription factors, histone proteins, DNA methylation, and nucleosome positioning, are related to control of gene expression. Also, non-coding RNAs have been found to play a crucial role in regulating chromatin states and gene expression.[14]

Increased genomic instability and inappropriate transcription are associated with increased aging. The packaging of the eukaryotic genome into nucleosome wrapped around histones plays a critical role in regulating the activities of the genome. Histone post-translational modifications have been shown to affect aging. Sen P. et. al. showed in their study the critical role of H3K36 methylation in restoring chromatin structure and prevents spurious cryptic transcription. The study found that the Loss of H3K36me3 in aged yeast cells results in the production of intragenic short transcripts and a shorter life span.[15]

Oxidative stress contributes to various age-related degenerative diseases and the process of aging. Past studies have found transcription regulators which function in stress responses and functions continuously to maintain homeostasis of these various processes in th body. One of them is the SKN-1 protein in the C. elegans and Nrf/CNC protein in the mammals. They are considered importance in aging and longevity. Nrf/CNC proteins are associated with cellular protective and maintenance function. Nrf2 act as a regulator of antioxidant and xenobiotic defense, proteostasis and metabolic regulator. [16]

p53 is a transcription factors well known to be associated with senescence, thus to the aging process. Long non-coding (lnc)RNA molecules, are a vast class of regulators of gene expression affecting both transcriptional processes and post-transcriptional events. Senescence-associated lnc RNAs (SAL-RNAs) shows lower abundance in senescent cells. Reduced *SAL-RNA1* levels causes enlarged morphology, positive β-galactosidase activity, and heightened p53 levels. By these mechanisms it delays senescence and aging. [17]

Disruption in the DNA methylation patterns are found associated with aging. Heyn et. al. performed whole-genome bisulfite sequencing (WGBS) of newborn and centenarian genomes. They observed that the centenarian DNA had 494,595 less methylated cytosine—phosphate—guanine dinucleotides (mCpGs) than did the newborn DNA. More hypomethylated CpGs were observed in the centenarian DNA compared with the neonate and it covered all genomic compartments, such as promoters, exonic, intronic, and intergenic regions. [18]

Gentilini et. al. studied human population for the role of epigenetics in the modulation of longevity. Global DNA methylation and Alu elements methylation were higher in centenarian's offspring than in offspring of non-long-lived parents. In all old subjects they identified a pattern of 709 CpG loci, exclusively located within CpG islands, with hypermethylation. They confirmed that genome-wide levels of methylation decrease with age, there is a tendency for DNA methylation to increase mainly in CpG islands localized in the promoter regions.[19]

Another gene related with aging is klotho. It is an aging-suppressor gene., which partially explains why a mutation to the *Klotho* gene causes extensive aging phenotypes. Circulating Klotho also has direct effects on tissues and cells that do not express Klotho. It is positively correlated with the expression of IGF-1 and IGF binding protein-3. Increases resistance to oxidative stress. *β*Klotho contributes to the regulation of energy metabolism and α-Klotho have been associated with ovarian tumors.[20]

Arking et.al. performed DNA sequencing to screen for mutations in *KLOTHO* that could influence human aging and identified an allele, termed KL-VS, containing six sequence variants in complete linkage disequilibrium, two of which result in amino acid substitutions F352V and C370S. They demonstrated that heterozygosity for KL-VS contributed to improved longevity. [21]

Endocrine Dysfunction and Aging

Aging results in subtle changes both in ACTH and cortisol secretion. According to neuroendocrine theory, decreased sensitivity of hypothalamus and peripheral receptors would cause energy misbalance, inadaptability, and weakening of immune and reproductive ability. The loss of hypothalamic sensitivity leads to progressive loss of homeostasis, alterations in hormone concentrations, and reduction of neurotransmitters and signaling molecules. [22]

Glucocorticoid excess is associated with age-related changes, including loss of muscle mass, hypertension, osteopenia, visceral obesity, and diabetes, among others.[23]

High levels of cortisol in humans is observed to have neurodegenerative effects. Reduction of corticosterone level reduces learning and memory deficits and attenuates loss of neuronal viability and plasticity. In a study done on rats the effect of calorie restriction along with adrenalectomy was found to be neuroprotective with an elevated level of levels of brain-derived neurotrophic factor (BDNF), transcriptions factors (pCREB). Both are considered the markers of neurotrophic activity. Hippocampal complex governs the age-related cognitive decline. More protection of the pyramidal neurons in the CA2/3 region of the Hippocampal complex was observed in the group with combination of calorie restriction along with adrenalectomy.[24]

Secretion of growth hormone declines with aging. With age Genetic mutations causes disruption of growth hormone signaling, the production of growth hormone-releasing hormone, and the growth hormone receptor function. In a study intended to explores the effects of caloric restriction and genetic disruption of growth hormone signaling on murine aging, it was found that the mice subjected to both caloric restriction and disruption of growth hormone signaling survived longer.[25]

Banks et.al. studied the effects of treatment with the GH-releasing hormone (GHRH) receptor antagonist MZ-5-156 on SAMP8 mice, a strain that develops with aging cognitive deficits and has a shortened life expectancy. Mice treated for 4 months with MZ-5-156 showed increased telomerase activity, improvement in oxidative stress in brain and muscle strength. IGF-I measured 2 h after single injection of MZ-5-156 showed a significant decrease of about 12%. Also mean life expectancy increased by 8 weeks with no increase in maximal life span, and tumor incidence decreased from 10 to 1.7%. [26]

Metabolism and Aging

Aging is considered as a progressive failure of metabolic processes. Studies have shown that carbohydrate intolerance develops as part of the aging process. The peripheral insulin resistance causes carbohydrate intolerance. It is considered to be caused by a post-receptor defect in target tissue. The development of insulin resistance may be more closely related to abdominal adiposity commonly seen in aged individuals. [27,28]

Skeletal muscle loss is a major unfavorable phenotypic change observed with aging. Sarcopenia is suggested to be due to a reduced basal rate of muscle protein synthesis. Muscle proteins are resistant to the anabolic action of insulin in the elderly. Rasmussen et.al. in their study found that muscle protein synthesis increased only in the young individuals during hyperinsulinemia. Changes in muscle protein synthesis were correlated with changes in leg amino acid delivery and blood flow. [29]

IGF1 pathway plays a key role in regulating longevity and studies indicates that common genetic mechanisms may exist for regulating IGF1 levels and lifespan. Yuan et.al. studied the median lifespans, and circulating IGF1 levels at 6, 12 and 18 months for 32 female and 32 male mice. Plasma IGF1 levels showed a significant inverse correlation with median lifespan at 6 months. Also, for the longer-lived mice strains, the negative correlation of IGF1 and lifespan became stronger and more significant. [30]

Genetic factors attribute to the variation in IGF-1 level and longevity. Leduc et.al. identified a major genetic determinant of IGF-1 level variation on Chr 10 that was associated with longevity. Their analysis confirmed a relationship between a locus regulating IGF-1 level (*Igf1q4* and *Igf1q8*) and longevity. The haplotype associated with lower IGF-1 was also associated with an increase in median lifespan and a lower mortality rate. [31]

Inflammation and Aging

Multiple mediators of cell maintenance are known to decline in aging. Recent evidence suggests that dysregulation of molecular inflammatory process plays a key role in the aging process. Chronic up-regulation of pro-inflammatory mediators occurs during the aging process due to an age-related redox imbalance that activates many pro-inflammatory signaling pathways. NF-κB is considered to be the major culprit responsible for the systemic inflammatory process seen during aging as it regulates the transcription of pro-inflammatory molecules. NF-κB is a transcription factor activated by oxidative stimuli and have shown increased activity with aging in a variety of tissues, including heart, liver, kidney, and brain tissues. [32,33]

Bruunsgaard et. al. explored the effects of TNF-α and IL-6 on survival in healthy 80-year-old people after the adjustment for known risk factors and co-morbidity. In the follow-up period of 6 years TNF-α was found associated with mortality in men, but not in women, whereas low-grade elevations in IL-6 were found associated strongly with mortality in both sexes. [34]

Inflammation observed in aging also relates to increased heat shock proteins, increased ROS and oxidized lipoproteins which activate the Toll-like-receptors (TLRs) pathway, initiating an inflammatory response whose key mediators are IL-1, IL6 and TNFα. [35]

Evidence suggests that antioxidants and anti-inflammatories can reduce the pace of shortening of telomere length during aging.[36] Shin C et. at. suggested that with low-grade inflammation along with moderately elevated serum homocysteine (HCY) levels may influence the attrition of leukocyte telomere length (LTL) in older adults. They found a significant inverse association between HCY levels and LTL in participants with serum hs-CRP levels of ≥ 2 mg/L ($p < 0.05$).[37]

In summary, aging is a gradual accumulation of molecular damage due to failure of maintenance of biological functions and defense against stress. Genes are associated with aging in form of lifespan regulator, effector, involving mitochondrial function, energy metabolism and cellular senescence. Aging is a progressive failure of metabolic processes and it is characterized metabolically by insulin resistance, changes in body composition, and declines in growth hormone (GH), insulin-like growth factor-1 (IGF-1) functioning.

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