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Review

Genetic Aspects of Aging and Anti-Aging Strategies

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ABSTRACT

Numerous theories exist concerning aging and its causes. Understanding the factors contributing to aging allows for the implementation of necessary precautions, and while complete prevention of aging may not be achievable, significant strides can be made. Recent advancements in genetic science have brought aging research to a prominent position. Studies on aging will play a crucial role in the future discourse on longevity, emphasizing the importance of the current state of genetic research in this field. The collective findings in this review contribute to a comprehensive understanding of aging, laying the groundwork for future discussions on longevity and the intricate interplay of genetics in the aging process.

Keywords: Aging, anti-aging, cellular aging, DNA damage, oxidative stress, protein modifications

Aging and longevity are determined by a complex interplay of genetic, non-genetic, and environmental factors.[1] Throughout history, humankind has perennially questioned, 'Why do we age?' or 'Why am I aging?' and has endeavored to find answers. Presently, research is underway to investigate the causes of aging, with various theories proposed to explain the underlying reasons for the aging process.[2] Aging is highly variable, dependent on the rates at which changes occur throughout an organism's lifespan.[3] It is recognized that aging is a biological condition arising from stress, manifesting in both physiological and pathological processes.[4] Studies elucidating the pace and overall impact of cellular aging define it as a state of cellular quiescence, irreversibility, and reduced replicative capacity relative to aging.[5]

BIOGERONTOLOGY

Biogerontology is referred to as the science of biological aging, examining the effects of aging on living organisms. The field dealing with the treatment of diseases related to old age is known as 'Geriatrics.' It is assumed that aging arises from the Gerontogenic effect. Biological aging is not controlled by a specific mechanism or regulator. Longevity-correlation analyses conducted on the lifespan of monozygotic and dizygotic twins have indicated that genes have approximately a 25% effect on lifespan. Non-genetic factors, such as environmental factors, healthy nutrition, physical activity, etc., have been observed to contribute to lifespan by more than 75%.[6,7]

The field of 'Gerontology' studies the biochemical processes and alterations in gene activity that affect genes influencing longevity. The emergence of aging is assumed to involve two types of gerontogenic interactions: the discovery of late-acting mutations that manifest their effects later during fertilization and birth, and the period of growth, development, and maturation.[8] In economically developed countries, the average lifespan is between 80 and 85 years. The recorded maximum human lifespan to date is 122 years, five months, and 14 days.[9]

Genes involved in repair and maintenance pathways, crucial for longevity, can have gerontological conditions affecting the aging phenotype. These genetic pathways are classified as general and specific pathways.[10]

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GENETIC FACTORS CONTRIBUTING TO AGING

Telomere Shortening

Genes responsible for telomere extension do not interact during cell division, resulting in telomere shortening after each division. Once telomeres reach a certain length, cell division ceases, and cellular aging begins. While telomeres are active in germ cells, they remain passive in somatic cells. Germ cells, being passed on to the next generation, maintain their active state.[11]

Olovnikov[12] first discovered in 1973 that telomere shortening could control lifespan. In 1990, insights into telomere structure were elucidated through the work of scientists Harley et al.[13]

Aging in human cells occurs in two stages:

M1 Phase: Cell division halts, and aging initiates once telomeres reach a specific length. The cell cannot progress from the G0 or G1 phase to the S phase, leading to a halt in division. If the cell becomes unable to divide, it begins to age. Active expression of oncogenes, including Werner syndrome and various genetic diseases, occurs due to changes in telomere length and function.

M2 Phase: To transition from M1 to M2 phase, the p53 and Rb-like proteins of the cell are disrupted by viral oncogenes during M1. These proteins, not found in the G1 phase, skip to the G2 phase and proceed to the S phase, allowing cell division to continue. In somatic cells, telomerase enzyme activity decreases, leading to telomere shortening. Cells die at M2 if telomeres become excessively short. If telomere length remains at a certain level at M2, cells surpass M2 and continue dividing, a phenomenon regulated or reactivated by telomerase enzyme regulation.[14]

Deoxyribonucleic acid (DNA) tumor viruses such as simian virus 40, human papillomavirus, and Adenovirus, along with chemical carcinogens and radiation, can prevent cellular aging through the transformation process. Tumor viruses bind to tumor cells and deactivate the cell suppressor tumors, p53, and p110Rb proteins. Evidence suggests that the viral transformation of p53 and p110Rb molecules leads to an extension of lifespan by inhibiting cellular inactivation. Immortal cells lacking p53 and p100Rb molecules are observed in cases of mutations and chromosomal abnormalities.[15]

Telomeres are structures containing non-coding DNA with the sequence 5′-TTAGGG-3′.[16] Transcription occurring in the telomerase reverse transcriptase (TERT) promoter ensures the maintenance of telomerase levels in various cell types. Lack of TERT expression in human fibroblasts results in telomere shortening, leading to aging after cell division and replication.[17] Telomerase's primary function is to confer immortality to cells by preserving the integration of chromosome ends. DNA polymerase synthesizes telomeres through reverse transcription, preventing the fusion of chromosomes. Telomerase has significant implications in diseases such as cancer metabolism and aging.[18]

The initial evidence suggesting that telomere length contributes to aging was observed in primary fibroblasts, where telomeres shortened with increasing donor age, leading to replicative senescence when telomeres reached a critically short length.[19]

Telomerase was first discovered in the ciliated protozoan *Tetrahymena thermophila*, which divides its macronuclear genome into 20,000 small chromosomes.[20] Telomeres, formed by the assembly of double-stranded TTAGGG repeats through specific proteins, protect the genomic structure by preventing chromosomal fusion. Telomere length varies within each cell, and human leukocytes typically have an average of 92 telomeres of varying lengths.[21] Humans are born with telomeres ranging from 5 to 15 kb, influenced by environmental factors. Telomere shortening, varying between 20-50 bp, occurs due to oxidative stress and various factors damaging DNA.[22]

DNA Damage

DNA damage occurs spontaneously in cells that make up the human body every day, alongside changes in DNA methylation and histone modifications. These damages lead to cell cycle arrest due to the halting of DNA and ribonucleic acid (RNA) polymerases, initiating a response indicating the need for DNA repair. Conditions such as apoptosis and senescence contribute to aging. DNA repair induces epigenomic changes that assist in the repair process.[23]

While DNA damage was initially thought to cause genetic instability, recent *in vivo* and *in vitro* studies suggest that DNA inflammation induces type 1 interferons and other inflammatory mechanisms within the cell. Accumulation of DNA damage in cells due to prolonged stimuli leads to chronic inflammation, tissue degeneration, and functional impairment with aging, and indirectly activates pro-inflammatory signals of DNA damage response.[24,25]

An example linking persistent DNA damage to premature aging is observed in Fanconi anemia, an autosomal genetic disorder causing advanced bone marrow failure through hematopoietic stem and progenitor cells.[26]

Mammalian cells contain two genomes: nuclear and mitochondrial. Nuclear DNA includes approximately 20,000-25,000 intergenic genomes, while mitochondrial DNA has a circular plasmid containing 37 genes that code for 16,569 bases. Inherited mtDNA mutations have been implicated in various human diseases.[27,28]

Various factors influencing stress can trigger cellular stress. Nuclear DNA damage, often occurring with double-strand breaks, is fundamental to senescence. Senescence, discovered through telomere loss in human fibroblasts, limits cell numbers and induces cell cycle arrest through DNA damage.[29]

Oxidative stress facilitates DNA damage, contributing to aging. Factors inducing DNA damage, including oxidative stress, lead to damage to DNA bases or single-strand breaks. Increased oxidative stress accelerates telomere shortening at the ends of chromosomes.[30,31]

Although limited information is available on the transmembrane protein PLA2R1's role in cancer and aging, studies have shown that it induces cellular aging by increasing reactive oxygen species (ROS) production and the amount of DNA damage, ultimately leading to cell death.[32]

Studies indicate that Rapamycin extends the lifespan of various organisms, including mice, *Caenorhabditis elegans*, *Drosophila*, and *Hydra*.[33] The translation of p53 results in an increase in DNA damage.[34]

CELLULAR DEATH AND OXIDATIVE STRESS IN AGING

Aging leads to a decrease in cell numbers due to programmed cell death occurring in various cell types.[35]

The oxidative stress theory of aging is based on the accumulation of oxidative damage in macromolecules through ROS, leading to functional losses associated with aging.[36] This theory has gained acceptance in long-lived species, including *Saccharomyces cerevisiae*, transgenic mice, C. elegans, birds, and the naked mole-rat (*Heterocephalus glaber*). Malondialdehyde and 4-hydroxynonenal are used to determine oxidative stress, both being toxic and mutagenic aldehydes.[37] Proposed by Harman[38] in 1956, the theory suggests that elevated ROS levels facilitate oxidative stress, causing structural damage to DNA macromolecules and resulting in damage at the cellular and tissue levels.[39,40]

Oxidative stress increases mitochondrial membrane permeability, leading to the release of factors that restrict cell survival, causing tissue damage through apoptosis and necrosis due to ROS.[41]

Reactive oxygen species serve as radicals to generate molecular oxygen, arising from enzymatic and non-enzymatic mechanisms. Various antioxidants remove ROS from within the cell.[42] Reactive oxygen species have short lifespans and rapidly react with biomolecules to alter their activities. Low levels of ROS within the cell allow for normal cellular function through redox signaling.[43] An increase in ROS formation with a decrease in neutralization leads to an elevation in oxidative stress at the cellular and tissue levels.[44,45]

Oxidative stress induces damage by causing lipid peroxidation in mitochondrial membranes and other membranes, as well as irreversible modifications in nucleic acids.[44] Activation of nicotinamide adenine dinucleotide phosphate oxidase leads to oxidative stress, increasing the levels of ROS.[46] Studies have shown that caffeine, an alkaloid, has effects on aging and oxidative stress. For instance, in human vascular endothelial cells, caffeine has been observed to prevent aging induced by oxidative stress. The effects of low concentrations of caffeine on cellular and tissue-level changes associated with aging caused by oxidative stress remain uncertain.[47]

The rise in oxidative stress with a decrease in mitochondrial antioxidant levels disrupts cell signaling, leading to the loss of cell and tissue homeostasis and promoting aging.[48] The continuous accumulation of oxidative damage in proteins, cellular lipids, or DNA accelerates the rate of aging.[49] Oxidative damage and chronic inflammation, linked to aging at the cellular and tissue levels, form a foundation that encourages functional decline in cardiovascular and skeletal muscle systems.[50] Oxidative stress increases significantly with intense exercise and ischemia, compounding the effects of aging.[51]

As mitochondrial oxidative damage increases with age, it alters mitochondrial dynamics by balancing fission, fusion, and autophagy processes.[52] Oxidative stress not only affects cell

survival, apoptosis, and cancer migration but also possesses bactericidal properties.[53] Studies indicate that dysfunctional mitochondria affected by an increased level of oxidative stress play a role in the pathogenesis of neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases.[54] Cumulative oxidative stress emerges as a primary factor contributing to aging and age-related neurodegenerative disorders in cellular, molecular, and behavioral studies.[55]

Given the high oxygen consumption in the retina, it exhibits resistance to oxidative stress.[56] Mitochondrial and motor impairments specific to Parkinson's disease arise in the midbrain's substantia nigra region due to the death of dopaminergic neurons triggered by oxidative stress.[57]

During aging, mitochondria without any function produce more ROS, leading to increased damage to telomeres due to oxidative breakdown. Telomeric DNA damage caused by oxidative stress has been strongly evidenced in human and animal models to accelerate rapid telomere shortening.[58] Intestinal aging induces structural changes and increases oxidative stress, significantly impacting the health of the elderly.[59] As endogenous antioxidant systems become less effective with age, elderly individuals become more sensitive to oxidative stress.[60] Nitro-oxidative stress plays a crucial role in endothelial cell dysfunction and inflammation.[61]

Exposure to an excessive amount of ROS results in oxidative stress-mediated cellular damage, causing oxidation of biomolecules, including DNA, proteins, and lipids.[62] The generation of oxidative stress and inflammatory agents will lead to increased endoplasmic reticulum stress and mitochondrial dysfunction.[63]

CELLULAR AGING

Cellular aging involves irreversible losses resulting from the loss of the replicative capacity of primary cells initially due to DNA damage occurring in defective telomeres. Telomere dysfunction arises from telomere shortening during DNA replication.[64] Cellular aging represents the state of the cell stress response, characterized by morphological and biochemical changes. It is a complex process where cells remain active, but the cell cycle stops.[65,66] Cellular aging was first defined using non-dividing diploid fibroblast cell lines by Hayflick and Moorhead[67] in 1961. It is a condition where physiological functions, such as cellular differentiation, decrease over time. The number of aging cells increases with age in various tissues and organs. Cellular aging is one of the most significant features of aging.[68,69]

Several conditions contribute to cellular aging, including DNA damage, inflammation, oncogenes, mitogens, reactive metabolites, proteotoxic stress, and damage occurring in molecular patterns.[70] Cellular aging is a state where repeated symmetric cell copies, critically short telomeres, and the permanent cessation of the cell cycle due to the DNA damage response occur. Most aging cells show epigenetic and chromatin structural changes.[71]

Studies have demonstrated that excessive mitochondrial DNA mutations lead to physiological mitochondrial dysfunction and premature aging.[72,73] Cellular aging can facilitate wound healing. For example, inflammation-induced cellular aging reduces the critical role of fibroblast migration and proliferation in the formation of new tissue when new tissue formation occurs.[74] Cellular aging is a controlled process involving both positive and negative conditions such as embryonic development, wound healing, tumor suppression, and aging.[75]

Flow cytometry imaging is a device used to observe *in vivo* aging cells, enabling the evaluation of numerous aging markers at the single-cell level and their detection at the protein level.[76] Aging cells contribute to the prevention of tumor formation by causing cell cycle arrest.[77] Hypotheses suggest that aging cells, accumulating in various tissues over time, age, and space, contribute to impairments associated with many chronic diseases in humans and animals.[78] Cancer cells are susceptible to many stress factors that contribute to aging, such as oncogenic signaling, replicative stress, hypoxia, ROS, and nutrient deprivation. Some anti-cancer treatments also trigger the aging of cancer cells. Different types of leukocytes mediate the removal of aging cells by the immune system. Most of these leukocytes are present in the innate immune system.[79] DNA damage, telomere shortening, oncogene activation, metabolic signals, mechanical stress, and mitochondrial dysfunction trigger the formation of aging cells.[80]

PROTEIN MODIFICATIONS

Amino acids, particularly tyrosine, are found around the protein shell, and these proteins are known to contribute to biological aging and age-related diseases.[81] Cellular changes occur significantly with aging. Caveolin-1 has been suggested as a marker in fibroblasts and endothelial cells.[82] Many cellular and

signaling pathways, including mammalian targets of rapamycin (mTOR), Sirtuin 1, and AMP-activated protein kinase, contribute to aging. The mTOR contributes to the extension of human life and the slowing of the aging process. Autophagy and inflammation have a significant impact during the aging process.[83] The accumulation of damaged proteins has been implicated in age-related diseases such as aging, type 2 diabetes, cancer, neurodegenerative disorders, cardiovascular diseases, and visible impairments.[84]

Accumulation of damage in cellular proteins, lipids, and cell organelles occurs during the aging process, leading to disorders at the cellular, organellar, and organ levels, contributing to age-related diseases and cell and organism death.[85] Amino acid limitation reduces age-related DNA damage and extends lifespan by blocking the Tor1/Sch9 cascade. All amino acids contribute to cellular sensitization.[86,87]

ENVIRONMENTAL FACTORS

The effects of exercise on longevity have been observed in genetically determined long-lived individuals such as centenarians.[88] A significantly less recognized factor is air pollution. Rapid industrialization and urbanization have turned environmental pollution into a public health issue. In 2019, the WHO determined that 99% of the world's population lives in places where air pollution levels exceed WHO limits, identifying air pollution as the single largest environmental health factor for humans. Air pollution has been identified as a cause of degenerative formations in skin aging, pigmentary problems in the skin, and the onset of skin disorders.[89]

PROGERIA SYNDROME

The expression of progerin leads to nuclear morphological abnormalities, misregulated gene expression, chromatin changes, mitochondrial dysfunction, defects in DNA repair, and rapid telomere shortening, promoting cellular decline and causing premature aging. The most characteristic feature in the cytology of fibroblasts of Hutchinson-Gilford progeria syndrome patients is the occurrence of nuclear morphological abnormalities.[90]

Genomic instability occurs due to deficiencies in DNA repair in premature aging syndromes, creating a state of instability that facilitates the early and high occurrence of cancer cases. This instability also contributes to the acceleration of aging and cancer processes.[91] Hutchinson-Gilford progeria syndrome is a condition in children characterized by gradual aging at the cellular and organismal levels. Jonathan Hutchinson discovered this disease in 1886. Progeria occurs due to a mutation in lamin A, encoded by the LMNA gene.[92] Hutchinson-Gilford progeria syndrome is observed in one in 4-8 million newborns, and aging symptoms appear 18-24 months after birth. These symptoms include growth retardation, thin and wrinkled skin, abnormal pigmentation, subcutaneous fat loss, joint stiffening, and weakened bone structure.[93]

LONGEVITY GENES

A significant portion of people wish to live longer, especially when their health is in good condition, and some aspire to extend their lives limitlessly. Two different pathways are identified for yeast Ras2 activation: protein kinase A (PKA) and mitogen-activated protein kinase pathways. There is evidence supporting the role of the PKA pathway in promoting longevity.[94] Naked mole-rats have a longer lifespan, while hypomorphic ribosomal yeast mutants have a shorter lifespan. Accuracy in yeast mitochondrial ribosomes is associated with longevity.[95]

Genes associated with increased lifespan have been discovered in yeast, worms, flies, and mice, resulting in respective enhancements in longevity.[96,97] Numerous theories have been proposed regarding the evolution of aging, including the programmed death theory, the mutation accumulation theory of aging, the antagonistic pleiotropy theory of aging, and the evolutionary maintenance theory.[97] The autophagic decline is observed in many organisms with aging.[98,99]

ANTI-AGING

Various treatments, including medications, exercise programs, and hormone therapies, are spreading worldwide as medical interventions to mitigate the effects of aging. The global market for anti-aging health products is steadily increasing.[100]

Conditions such as telomere loss, genomic instability, epigenetic changes, proteostasis loss, irregular nutrient sensing, and mitochondrial dysfunction are notable molecular and cellular occurrences in the aging process.[101]

Mutations in mitochondrial DNA in elderly individuals lead to genomic instability. Telomeres are located at the ends of chromosomes and facilitate cellular aging once they reach a critical length known

as the Hayflick limit. Aging is a state of decreased bodily functions.[102] The skin is affected by aging, resulting in thinning, loss of elasticity, and dermal-epidermal flattening.[103,104] Harrison found that rapamycin has been observed to increase survival rates by 14% in females and 9% in males.[105]

In conclusion, the intricate nature of aging involves a dynamic interplay between genetic, non-genetic, and environmental factors. Biogerontology explores the effects of aging on living organisms, emphasizing the multifaceted influences that contribute to longevity. Telomere shortening, DNA damage, and oxidative stress emerge as pivotal factors in cellular aging, influencing processes such as apoptosis and senescence. The role of longevity genes, identified in various organisms, sheds light on potential pathways for extending lifespan. Progeria syndrome exemplifies how genetic mutations can accelerate aging, while environmental factors, including air pollution, also play a role in age-related skin disorders. The somatic mutation theory highlights the impact of DNA damage on aging, emphasizing the need for cellular responses and repair mechanisms. Overall, the comprehensive understanding of these molecular and cellular processes contributes to ongoing research in anti-aging interventions and underscores the complex dynamics that govern the aging phenomenon.

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