

Cell Biology of Aging - A Review

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Introduction:

Human aging has been a mystery from the dawn of civilization because of its biological complexity -genetic composition, inheritance, epigenetics – along with a constantly changing living environment. Age is different from aging. Age can be identified as a unit of time, such as years (e.g., chronological age). Aging is multifaceted. For example, lifespan/lifecycle is viewed as the duration between the biological conception (gestation) of an individual to the termination of life or death. However, individual genetic inheritance, generational changes, and living environment in different age cohorts (and their bio-psycho-social characteristics) complicate the understanding of aging. Nevertheless, the aging process demonstrates a constant change in molecular composition in human cells with or without external environmental stimuli.

There is a significant amount of research identifying several hallmarks of the aging process. There are twelve hallmarks identified in relation to aging. All of them are specific changes at the molecular level. Genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macro autophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis are the twelve hallmarks of aging^{1,2}

Genomic instability describes the change in a gene's function due to an internal or external cause. Internal mechanisms such as oxidation and hydrolysis, external components such as chemicals, physical, biological agents disrupt the stability and integrity of genomic components³. Genomic instability is identified when one or more molecular structures such as nuclear deoxyribose nucleic acid (DNA), mitochondrial DNA and nuclear architecture are disrupted, altered, or damaged^{1,2,3}. Several molecular mechanisms are identified in disruption, alteration, and genomic damage. Point mutation in a specific location of the DNA, deletion of a DNA sequence, translocation, telomere shortening, one or both DNA strand breakdown, chromosomal rearrangement, and abnormality in the nuclear structure, along with infection by virus and other pathogens, are responsible for breach of integrity and genomic instability^{1,2,3,4}

Heritability is measured as a proportion of genetic inheritance and the sum of genetic inheritance and exposure to environmental factors⁵. Famous twin studies claim that genetic inheritance contributes 20% to 30%, and a study of families with one or more centenarians showed that heritability contributes 48% in male and 33% in female longevity.

However, in a recent genealogy study of several million families, heritability contributed only 10% to 16% to longevity, and previous findings were identified as overstated. It is important to cite that genetic inheritance accounts for 45-69% in cardiovascular disease and heritability contributes 61% in Alzheimer's disease and 78% in diabetes⁵. It is believed that gene expression is regulated by the integrity and stability of the genome, which subsequently contributes to longevity or long lifespan². A better understanding of integrity, stability

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and genomic regulation are critical for a healthy lifespan and aging process^{3,4,6}

Telomere Attrition: In 1961, Leonard Hayflick and Paul Moorhead discovered that cell division has a limit, which is widely known as the Hayflick limit, or cellular senescence⁵ Telomeres are DNA sequences that are located at the end of each DNA sequence of a chromosome. Elizabeth H. Blackburn, Carol W. Greider and Jack W. Szostak jointly won the Nobel prize in 2009 for discovering the telomerase enzyme. Telomerase enzymes protect telomeres and are responsible for important functions such as DNA transcription and translation⁷. Greider and Blackburn¹⁴ found that the telomerase enzyme is required for telomeric DNA repeat synthesis, such as transcription and translation of a DNA sequence, e.g., TTGGGG to AACCCC, where adenine pairs with thymine and cytosine pairs with guanine. The adenine-thymine and cytosine-guanine base pair is designed in a way that they are complementary and antiparallel in DNA structure. Adenine, thymine, cytosine, and guanine are the fundamental structural elements of DNA. There are 2.91-billion base pairs of protein found in the human genome⁸. Each daughter cell divides in the cell cycle; this process is known cell division. Approximately 50-200 base pairs of telomeric DNA are deleted in each cell division⁹. Deletion of DNA base pairs can produce abnormal and/or ineffective protein, which could prevent required intracellular or extracellular functions and trigger disease. The progressive deletion of DNA base pairs of telomere ends is a significant characteristic feature in the aging process and mortality risk^{1,5,6}.

Understanding telomere length regulation is by far the most important mechanism in the aging process. Shortening of telomeres leads to gradual shortening of the lifespan. It could be either normal shortening (due to age or year of life) or disease related shortening (through internal or external stimuli). Telomerase enzymes play a vital role regulating and maintaining the telomeres' length. Therefore, telomerase enzymes are the target of major research/intervention to understand their exact function, regulation, and contribution to longevity. Future collaborative research may involve cell molecular biology along with psycho-social and environmental risk factors that are responsible for telomere length shortening and its cumulative impact on the aging process, longevity, and disease trajectory.

Epigenetic Alterations describes the change in genes due to living environment and behavior. Epigenetic alterations are reversible. Epigenetic alteration involves methylation or acetylation to the DNA, post-translational histones modification, transcriptional alterations, chromatin remodeling and changes in gene expression^{1,9}. Methylation and/or Acetylation is a biochemical process of adding or removing biochemical structures such as methyl and/or acetyl groups to a specific DNA. Histones are known as a supporting protein structure to DNA. Histone modification (mainly through acetylation) can be beneficial or detrimental depending on the binding site and structural modification of DNA (López et al., 2023). Cellular homeostasis, age-associated metabolic decline, and over expression of DNA protein are major examples because of histone modification¹ A better understanding of the epigenetic alteration in the aging process can improve our understanding of serious disease (e.g., cancer), and it can also be an important target for anti-aging treatment¹⁰.

Antagonistic pleiotropy (AP) is a well-accepted evolutionary theory of aging proposed in 1957 by George Williams. However, it is not proven yet whether AP represents the same features in epigenetic alteration. AP explains when a single gene controls more than one trait or characteristic features. These characteristics (or traits) are specific and special features of a gene that can be transferred from parent to child, which represent specific physical appearance or behavioral expressions. This is known as phenotypic expression. The theory of AP claims that with the same gene, one trait is beneficial in early life and the other trait is harmful to later life due to the natural selection process¹¹

Testosterone could be a good example of this. Testosterone is hormone beneficial in early life, as it is related to growth maturation, but excess testosterone could produce prostatic hyperplasia in later life¹¹. Another good example is insulin-like growth factor-1 (IGF-1). Abdellatif et al. (2023) claim that cardiac IGF-1 is essential in early age but harmful for older adults. Their study showed that overexpression of the IGF-1 receptor is beneficial at early age because it accelerates cardiac activities, but it is detrimental in old age because overproduction of IGF-1 results in premature heart failure¹².

Loss of Proteostasis: The human cell maintains coordinated activities during new protein production, such as RNA translation, folding, synthesis, repair, and degradation^{1,13}. These activities are known as proteostasis or protein homeostasis. Proteostasis demonstrates the regulatory mechanism of protein production that protects protein integrity and prevents damages. Intracellular components such as proteasome and lysosome are involved in such activities and regulation. The loss of protein regulation is characterized by the failure of protein production due to misfolding, oxidation, glycation, and ubiquitination. Misfolding, oxidation, glycation, and ubiquitination are different bio-chemical or structural processes inside the cell, but the end results are the same, such as producing dysfunctional or ineffective proteins¹¹. There are several age-related diseases, e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, and cataracts, which occur due to loss of protein regulation¹.

Disable Autophagy: Phagocytosis is an important mechanism that removes waste material from the cell. For example, phospholipid phosphatidylserine is one of the mechanisms that protect cell death, maintain cellular homeostasis, and prevent infection¹³. Change in phospholipid phosphatidyl serine mediated phagocytosis is considered an important therapeutic target for atherosclerosis, neurodegenerative disease, and cancer. There are several active intracellular mechanisms which are responsible for digestion, reuse, recycling, and elimination of damaged intracellular elements. Lysosomes execute such digestion and elimination functions¹⁴. López et al. claim that there are several autophagy genes that decrease with age, such as ATG5, ATG7, and BECN1. Several phagocytosis mechanisms are observed inside the cell such as micro-autophagy, macro-autophagy, and chaperone-mediated autophagy¹. Phagocytosis mechanisms decrease with the advanced age, while phagocytosis executes important cellular functions such as digestion, homeostasis, metabolism, and elimination and prevents intracellular damage^{1,14}.

Deregulated Nutrient-Sensing: Each cell has its own cellular metabolic activities and regulator for nutrients. Deregulated nutrient-sensing is characterized by an inability to regulate anabolism and storage of intracellular nutrients due to lack of nutrient regulators^{1,15}. Deregulation of nutrient sensing pathways are commonly found in metabolic

diseases. Glucose, amino acids, and lipids are basic cellular components that synthesize and break down to produce adenosine triphosphate (ATP), which is the energy unit of our body¹⁶. ATP is required for growth development, reproduction, and survival. Limitation in nutrient intake, or caloric restriction, is an important theory of aging. Intracellular and extracellular glucose, amino acid, and lipid sensing mechanisms and signaling events are deregulated in several important diseases¹⁵. For example, IGF regulates growth, development, and tissue homeostasis through neuronal signals and neuronal circuits. The United Kingdom biobank study shows that higher production of IGF-1 is associated with dementia, diabetes, vascular disease, and osteoporosis in older adults^{1,2,16}.

Mitochondrial Dysfunction: Mitochondria are known as a powerhouse; they are a major intracellular component, responsible for energy production. ATP is a unit of energy in our body. Our entire body function is dependent on the total amount and rate of energy generation by mitochondrial internal machines, known as the electron transport chain (ETC)¹⁷. In 1988, Anita Harding and Doug Wallace discovered that a large deletion and a point mutation in mitochondrial DNA produce several diseases, and they are linked to maternal inheritance¹⁹. Mitochondrial dysfunction primarily results from the mutation of mitochondrial DNA¹. However, accumulation of increased amounts of reactive oxygen species (ROS) is an important mechanism of mitochondrial dysfunction where oxygen molecules are unable to enter the mitochondrial ETC where ATP is produced¹⁷. Reactive oxygen species, also known as free radicals, are characterized by the unpaired oxygen which enhances oxidative stress and cellular degeneration¹⁷. With age, the number of increased free radicals decreases energy production and restricts the functional capacity of a cell.

Cellular Senescence is described as irreversible change in the cell or complete loss of function resulting in cell death¹⁸. The mechanism of cell death is known as senescence-associated secretory phenotype^{1,6}. There are several mechanisms that characterize cellular senescence or cell death, such as telomere shortening, genomic mutation, epigenic alteration, dysregulation of autophagy, drugs/chemicals, radiation, and oncogenic and metabolic insults^{1,6}. Huang et al²⁰ have reported that senescent cells

demonstrate cell cycle arrests or morphological alterations of cells. Several biomarkers of cellular senescence have been identified, including SA- β gal, p16 and p21²⁰. However, senescence-associated secretory phenotype (e.g., irreversible cell-cycle and pro-inflammatory characteristics) due to mitochondrial dysfunction is considered the most important driver of cellular senescence and the aging process^{18,21}.

Stem Cell Exhaustion: Stem cells are characterized by reproducing either the same type of cell or different types of cells, and their ability to tissue-specific differentiation is critical for survival and regeneration²². Stem cell exhaustion describes the loss of renewal capacity that is required for repair of tissue injury; however, it is not clear whether aging causes a reduced number of stem cells or decreases the number of stem cells is associated with aging. However, accumulation of toxic metabolites such as reactive oxygen species, epigenetic alteration of DNA damage, accumulation of damaged protein, and mitochondrial dysfunction can reduce the number of stem cells^{1,2,22}

Altered Intercellular Communication describes the change or loss of communication between cells. For example, neuro-hormonal systems, renin-angiotensin systems, and insulin-IGF-1 systems are responsible for producing specific signals for specific intracellular or intercellular functions¹. The loss of internal signal-response capacity or maintaining homeostasis to execute normal functions is characterized as altered intercellular communication^{1,2}. For example, Wang et al.¹⁰ have reported that intercellular communication in hepatic tumors involves tumor proliferation, invasion, apoptosis, angiogenesis, metastasis, inflammatory response, gene mutation, immune escape, metabolic reprogramming, and therapeutic resistance.

Chronic inflammation describes an increased level of inflammatory cytokines and biomarkers, such as CRP (C-reactive protein), TNF- α , and IL-6, which prevents growth and repair, increases intracellular damage, and destabilizes cellular homeostasis^{1,2}.

Dysbiosis is described as a rate of change in the number of gastrointestinal microorganisms which regulate the distribution, absorption, metabolism, and elimination of nutrients^{1,2}.

Conclusion

Intracellular mechanisms and hallmarks of aging demonstrate either a change in function, or a loss of

function. Regardless of the change or loss of functions, the ultimate result presented either as disease, or systemic abnormality or death. The consequence of aging is better supported as gradual decline in cellular digestion, decreased elimination, maldistribution, and the inability to reproduce and maintain homeostasis. Nevertheless, cell molecular biology alone does not explain aging. Bio-psycho-social collaboration is essential for a better understanding of aging.

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