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MITOCHONDRIAL DYSFUNCTION AS A KEY DRIVER OF THE AGING PROCESS

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Abstract: This article analyzes the theoretical foundations and modern molecular mechanisms of the aging process. Numerous hypotheses explaining aging exist in gerontology, and the work scientifically presents the classical views of I.I. Mechnikov, I.P. Pavlov, A.A. Bogomolts, A.V. Nagorniy, and V.N. Nikitin, as well as somatic mutation, free radical, telomere, immunological, and genetic (programmed) theories. Furthermore, the role of mitochondrial dysfunction in the aging process is examined, along with associated changes related to oxidative stress, energy deficiency, and disruption of cellular signaling mechanisms. Analyses indicate that aging is not driven by a single factor but is a multi-stage biological process resulting from the interaction of genetic, molecular, immune, and neuroendocrine mechanisms.

Keywords: aging, gerontology, free radicals, telomeres, mitochondrial dysfunction, somatic mutation, immunosenescence, genetic theory

Introduction

Aging is a natural biological process of the organism, characterized by morphological and functional changes at the cellular, tissue, and system levels. The increasing human lifespan has made the study of aging mechanisms a pressing scientific issue, as aging is closely associated with the development of cardiovascular, neurodegenerative, metabolic, and oncological diseases.

Numerous theories exist in gerontology to explain aging, encompassing both historical and modern perspectives. Classical views are based on internal intoxication, nervous system regulation, and tissue alterations, whereas contemporary studies highlight DNA damage, the effects of free radicals, telomere shortening, and mitochondrial dysfunction as primary factors. This article analyzes these aging theories using an integrated approach.

Main Body

In gerontology, there are over 300–500 hypotheses explaining the aging process, encompassing both historical and contemporary biological perspectives. One of the first scientists to attempt a scientific explanation of aging was I.I. Mechnikov. He distinguished between physiological and pathological forms of aging, identifying internal intoxication of the organism as the main cause of pathological aging. According to Mechnikov, the breakdown of proteins by intestinal microflora and the toxic by-products generated during nitrogen metabolism gradually lead to systemic intoxication. The primary targets of these toxic substances are liver and brain cells, whose functional impairment accelerates the aging process. To reduce intestinal putrefaction, Mechnikov recommended the consumption of lactic acid bacteria and described a healthy lifestyle with the concept of “orthobiosis.”

I.P. Pavlov also played an important role in explaining the mechanisms of aging. He emphasized that the functional state of the central nervous system is critical during aging. Chronic stress, constant nervous strain, and emotional overload disrupt regulatory mechanisms,

disturbing the balance between excitation and inhibition. Consequently, the activity of endocrine glands changes, the organism's adaptive capacity decreases, and the aging process accelerates.

A.A. Bogomolts linked aging to changes in connective tissue structure. According to him, the organism's age is determined by the state of connective tissue, as it supports the trophic supply and structural integrity of cells. With advancing age, the elasticity and functional capacity of connective tissue decrease, leading to increased degenerative changes in organs. A.V. Nagorniy and V.N. Nikitin explained aging as a decline in protein synthesis and renewal processes. According to their theory, reduced enzyme activity and slowed protein metabolism limit the functional capacity of cells.

Cellular and Molecular Mechanisms of Aging: Senescence and Telomerase Studies

The study of aging is one of the central directions in gerontology. Scientific analysis of aging began in the 19th–20th centuries with the works of scientists such as Ilya Ilyich Mechnikov and Ivan Petrovich Pavlov. Mechnikov associated aging with the immune system and intestinal autointoxication, while Pavlov linked it to the decline in central nervous system regulatory activity. Later researchers critically re-evaluated these theories, beginning to analyze aging at molecular and genetic levels.

Mechnikov and Contemporary Evaluations

Mechnikov viewed aging as autointoxication caused by toxins produced by putrefactive bacteria in the organism. He emphasized that a decline in the immune system, particularly in phagocytic activity, accelerates the aging process. However, August Weismann criticized this perspective from an evolutionary standpoint, suggesting that aging is an evolutionary constraint occurring after the reproductive period.

Modern researchers have partially confirmed Mechnikov's theory. Roy Walford demonstrated that immune system decline can play a significant role in aging, while Claudio Franceschi, through the concept of "inflammaging," highlighted that low-grade chronic inflammation is a key factor in the aging process. 21st-century microbiome studies by Jeffrey Gordon identified the connection between gut microbiota and the immune system, providing contemporary support for Mechnikov's ideas.

Pavlov and the Neuroendocrine Concept

Pavlov linked aging to a decline in the regulatory activity of the central nervous system. He emphasized that when the balance between excitation and inhibition is disrupted, the reduction of neurotrophic influence leads to the development of atrophic changes. In the neuroendocrine direction, Vladimir Dilman scientifically substantiated that impaired hypothalamic regulation constitutes a central mechanism of aging.

Cellular Mechanisms: The Hayflick Limit

In 1961, Leonard Hayflick discovered that human somatic cells have a limited replication potential. His research, known as the "Hayflick limit," demonstrated that aging is a programmed cellular process. Each somatic cell, after a certain number of divisions, enters a senescent state and ceases to divide further.

Telomeres and Telomerase

Hayflick's research raised the question: why do cells stop dividing after a limited number of replications? The answer was found through telomeres.

Elizabeth Blackburn and Jack Szostak identified special DNA sequences located at the ends of chromosomes, known as telomeres. Telomeres shorten with each cell division, and when they become critically short, the cell enters a senescent state.

Carol Greider discovered the enzyme telomerase, which maintains telomere length. Telomerase:

is active in embryonic and stem cells,

allows cells to divide for a longer period,

shows high activity in many cancer cells.

In 2009, Blackburn, Greider, and Szostak were awarded the Nobel Prize for their discoveries.

The biological bases of aging occur at several levels:

Immune system decline and autointoxication (Mechnikov)

Neuroendocrine regulation (Pavlov, Dilman)

Cellular senescence (Hayflick)

Telomeres and telomerase (Blackburn, Greider, Szostak)

Microbiome and low-grade chronic inflammation (Franceschi, Gordon)

Thus, modern gerontology considers aging as a complex biological process resulting from the combined action of genetic, molecular, immunological, neuroendocrine, and cellular mechanisms. Classical theories (Mechnikov and Pavlov) are integrated with contemporary research, serving as a foundation for a deeper understanding of the biology of aging.

In modern gerontology, particular attention is given to the molecular bases of aging. According to the somatic mutation theory, genetic errors accumulate in DNA with age, repair mechanisms become less efficient, and this leads to cellular dysfunction. The free radical theory posits that reactive oxygen species generated during metabolic processes damage cell membranes, proteins, and DNA, with the resulting harm accumulating due to weakening of the antioxidant defense system. According to the telomere theory, cells have a limited number of divisions, and telomere shortening during each division triggers cellular senescence. The immunological theory emphasizes that aging is associated with a decline in immune system function, resulting in increased susceptibility to infections and tumors. Additionally, the genetic

or programmed theory suggests that aging occurs, to some extent, under biologically programmed genetic control.

In recent years, the concept of mitochondrial dysfunction in gerontology has expanded significantly. While mitochondria were previously viewed primarily as energy-producing organelles, they are now recognized as central regulators of cellular signaling, metabolic adaptation, and stress responses. During aging, mitochondrial respiratory activity declines, and their ability to coordinate cellular responses is also impaired. Muscle biopsies from individuals over 65 years of age have shown a 30–40% reduction in oxidative phosphorylation efficiency compared to younger age groups, indicating that energy deficiency is a significant hallmark of aging.

Experimental models demonstrate that aging is associated with disruption of mitochondrial quality control systems, particularly mitophagy and mitochondrial dynamics. As a result, dysfunctional mitochondria accumulate, oxidative stress increases, and tissue regeneration slows. In animal models, mitophagy activity has been shown to decrease by 35–50%, and respiratory function in skeletal muscles declines. Clinically, these processes are linked to sarcopenia and physical frailty; after the age of 70, 25–30% of the population exhibit significant loss of muscle mass.

At the molecular level, the mitochondrial sirtuin system plays a critical role. Sirtuins stabilize the mitochondrial environment, enhance antioxidant defense, and support metabolic adaptation. With age, their activity declines, reducing cellular stress resistance. Clinical observations indicate that mitochondrial sirtuin-dependent metabolic pathways in elderly individuals may be 20–35% less active compared to middle-aged individuals.

Mitochondrial sirtuins (SIRT3, SIRT4, and SIRT5) are NAD^+-dependent deacetylase enzymes that regulate mitochondrial energetics, oxidative stress, and cellular metabolism. In recent years, these enzymes have been recognized as key molecular regulators of aging and cellular senescence.

SIRT3 and Oxidative Stress

David Sinclair emphasizes that SIRT3 activity during aging is crucial for maintaining mitochondrial function and reducing reactive oxygen species (ROS) levels. Eric Verdin demonstrated that SIRT3 activates mitochondrial enzymes through its deacetylase activity, thereby reducing oxidative damage in cells and slowing the aging process. Through this activity, SIRT3 enhances mitochondrial energy efficiency, preserves cellular metabolic health, and slows degenerative changes associated with oxidative stress.

SIRT4 and Metabolic Energy Regulation

Leonard Guarente demonstrated that SIRT4 regulates amino acid metabolism, lipid oxidation, and energy balance in mitochondria. Reduced SIRT4 activity impairs the cell's ability to produce ATP and increases metabolic stress, which is considered a significant factor accelerating the aging process. Additionally, SIRT4 influences insulin signaling and energy adaptation, making it critical for understanding metabolic syndrome and age-related diseases.

SIRT5 and Mitochondrial Detoxification

David Sinclair and colleagues identified that SIRT5 participates in mitochondrial detoxification through lysine desuccinylation. This enzyme plays a key role in decarboxylating mitochondrial metabolites and regulating ammonia metabolism. As a result, SIRT5 slows aging-associated metabolic disturbances and contributes to the maintenance of cellular viability.

Mitochondrial Sirtuins and Cellular Aging

Mitochondrial sirtuins serve as key molecular regulators of aging through three main functions:

Reducing oxidative stress (SIRT3) – controls ROS levels in cells and prevents DNA, lipid, and protein damage.

Maintaining metabolic energy balance (SIRT4) – stabilizes cellular energetic potential and protects against metabolic stress.

Detoxifying metabolic by-products (SIRT5) – reduces mitochondrial metabolic damage and slows age-related changes.

Moreover, mitochondrial sirtuin activity is directly linked to NAD^+ levels. With aging, the decline in NAD^+ reduces sirtuin activity, thereby accelerating the aging process.

Overall Conclusions from Researchers

David Sinclair: Aging and mitochondrial dysfunction can be slowed through SIRT3, SIRT5, and NAD^+.

Eric Verdin: SIRT3 deacetylase activity reduces oxidative stress and delays the aging process.

Leonard Guarente: SIRT4 regulates metabolic energy balance, and its decline accelerates aging.

Carol Greider, Elizabeth Blackburn, and Jack Szostak: Together with sirtuins, they are central components of mechanisms that extend cellular longevity.

Thus, mitochondrial sirtuins provide a crucial scientific basis for understanding the molecular mechanisms of aging, being directly linked to cellular senescence, energy metabolism, and oxidative stress.

The decline in mitochondrial energetic potential is closely associated with neurodegenerative diseases, cardiovascular pathologies, and metabolic disorders. In brain tissues, ATP production may decrease by up to 40%, while oxidative phosphorylation efficiency in cardiac muscle declines, and mitochondrial oxidative capacity in type 2 diabetes may be reduced by 25–35%, confirming this strong association.

Molecular and Cellular Mechanisms of Aging: Mitochondrial Sirtuins, Telomeres, and Disease-Related Aspects

Aging is a complex biological process that occurs at the cellular level through a variety of molecular mechanisms. In the 19th–20th centuries, scientists such as Ilya Ilyich Mechnikov and Ivan Petrovich Pavlov studied aspects of aging related to immunity, autointoxication, and the central nervous system. Mechnikov associated aging with immune system decline and toxins from the gut microbiota, whereas Pavlov linked it to reduced regulatory activity of the central nervous system. Modern researchers have expanded these theories to the molecular and cellular levels.

In 1961, Leonard Hayflick discovered that human somatic cells have a limited replication potential. This phenomenon, known as the "Hayflick limit," demonstrated that cells enter a senescent state and cease to divide, providing scientific evidence for a programmed cellular mechanism of aging.

Telomeres and the telomerase mechanism explain the molecular basis of aging. Elizabeth Blackburn and Jack Szostak identified telomeres as DNA structures that protect chromosomes from degeneration. Carol Greider discovered the enzyme telomerase, which elongates telomeres and extends cellular division, acting as a molecular factor that slows the aging process.

Mitochondrial sirtuins (SIRT3, SIRT4, SIRT5) are NAD^+-dependent deacetylase enzymes that regulate mitochondrial energetics, oxidative stress, and metabolism. SIRT3 reduces ROS levels in cells, protects against oxidative damage, and enhances mitochondrial energy efficiency, thereby slowing the aging process (Verdin, Sinclair). SIRT4 regulates lipid and amino acid metabolism, maintaining cellular energy balance and reducing metabolic stress (Guarente). SIRT5 participates in mitochondrial detoxification through lysine desuccinylation, slowing aging-associated metabolic disturbances (Sinclair). Furthermore, mitochondrial sirtuin activity is directly linked to NAD^+ levels, which decline with age, resulting in reduced enzyme activity and accelerated aging.

Cellular Senescence, Telomeres, Telomerase Mechanisms, and Mitochondrial Sirtuins in Aging

Cellular senescence, telomeres and telomerase mechanisms, and mitochondrial sirtuins collectively form the molecular and cellular mechanisms of aging. These mechanisms play a critical role in slowing neurodegenerative and cardiovascular diseases, extending cellular longevity, and regulating the molecular aging process. Modern gerontology, therefore, enables a comprehensive understanding of the biology of aging, integrating classical theories (Mechnikov and Pavlov) with molecular, cellular, and disease-related contexts.

At the same time, contemporary perspectives indicate that mitochondrial dysfunction should not be interpreted as the sole cause of aging. Aging is a multi-system process, wherein mitochondrial impairments develop in conjunction with loss of genetic stability, enhanced chronic inflammation, disrupted neuroendocrine regulation, and alterations in cellular signaling pathways. Moreover, reactive oxygen species (ROS) are not solely harmful; at low concentrations, they function as signaling molecules that support cellular adaptation. Consequently, antioxidant therapies do not always produce the expected clinical benefits.

Current scientific evidence suggests that aging is not driven by a single mechanism, but rather emerges as a complex, multi-step biological process resulting from the interaction of

genetic predisposition, molecular damage, mitochondrial dysfunction, immune and neuroendocrine changes, and lifestyle factors.

Cellular and Molecular Mechanisms of Aging: Senescence, Genetic Basis, and Disease Associations

Aging is a complex biological process that occurs at the cellular level through molecular, genetic, and metabolic mechanisms. In the 19th–20th centuries, scientists such as Ilya Ilyich Mechnikov and Ivan Petrovich Pavlov studied aspects of aging related to immunity, autointoxication, and the central nervous system. Mechnikov associated aging with a decline in immune function and toxins from the gut microbiota, whereas Pavlov linked it to decreased regulatory activity of the central nervous system. Modern researchers have expanded these theories to investigate aging at the molecular and cellular levels.

Cellular Aging and Senescence

In 1961, Leonard Hayflick discovered that human somatic cells have a limited replication potential. This phenomenon, known as the "Hayflick limit," demonstrated that cells enter a senescent state and cease to divide. Senescence is characterized by the loss of a cell's ability to proliferate while maintaining metabolic activity. Senescent cells typically produce inflammatory mediators, cytokines, and proteases, which contribute to chronic inflammation and degenerative changes in tissues.

Cellular aging is regulated through molecular mechanisms such as telomere shortening, DNA damage, oxidative stress, and sirtuin enzyme activity. In addition, aging-related genes play a critical role. Notably, the 9p21 locus on human chromosome 9 is associated with cardiovascular diseases and cellular senescence. This locus encodes cell cycle regulators such as CDKN2A and CDKN2B, which are crucial for the formation of senescent cells. Mutations and polymorphisms at the 9p21 locus increase the risk of chronic diseases, particularly atherosclerosis and myocardial infarction.

Mitochondrial Sirtuins and Aging

Mitochondrial sirtuins (SIRT3, SIRT4, SIRT5) are NAD^+-dependent deacetylase enzymes that regulate mitochondrial energetics, oxidative stress, and metabolism. SIRT3 reduces ROS levels, protects against oxidative damage, and enhances mitochondrial energy efficiency, thereby slowing the aging process (Verdin, Sinclair). SIRT4 regulates lipid and amino acid metabolism, maintaining cellular energy balance and reducing metabolic stress (Guarente). SIRT5 participates in mitochondrial detoxification through lysine desuccinylation, slowing aging-related metabolic disturbances (Sinclair).

The activity of mitochondrial sirtuins is directly linked to NAD^+ levels. With advancing age, NAD^+ levels decline, reducing the activity of these enzymes and accelerating the aging process.

Telomeres, Parental Genes, and Aging

Telomeres are DNA sequences located at the ends of chromosomes that shorten during cell division. Elizabeth Blackburn and Jack Szostak identified telomeres as structures that protect

chromosomes from degeneration. Carol Greider discovered the enzyme telomerase, which maintains telomere length and extends cellular division.

Recent research indicates that parental DNA can influence the telomere length of offspring. Scientists from the University of Pennsylvania reported in *Current Biology* that parental telomere length actively modulates telomere length during the early days of embryonic development. Experiments in mice demonstrated that if the father possesses long telomeres and the mother short ones, embryonic telomeres become significantly longer; conversely, if the father has short and the mother long telomeres, embryonic telomeres shorten. This process involves the ALT (alternative lengthening of telomeres) mechanism—typically observed in cancer cells—which extends telomeres via DNA recombination as an alternative to telomerase.

Thus, the telomere theory provides a framework for understanding the inheritance of aging and lifespan through parental genes.

Conclusion

Aging is a complex, multi-stage, and multifactorial biological process that cannot be fully explained by a single theory. Hypotheses proposed by classical scientists—such as Ilya Ilyich Mechnikov's theory of internal intoxication, Ivan Petrovich Pavlov's nervous system regulation, and A.A. Bogomolts' connective tissue alterations—laid the foundation for understanding the mechanisms of aging. Modern research highlights the critical roles of molecular and genetic factors, including DNA damage, free radicals, telomere shortening, immune system decline, and mitochondrial dysfunction.

Cellular aging (senescence) is characterized by the loss of proliferative capacity while maintaining metabolic activity. Genes such as p16 (CDKN2A), p19 (ARF/CDKN2A), and the 9p21 locus play crucial roles in halting the cell cycle and increasing the risk of chronic diseases.

Telomeres and telomerase regulate cellular division, directly influencing senescence and aging. Recent studies indicate that parental DNA actively modulates offspring telomere length during the early days of embryonic development. The ALT (Alternative Lengthening of Telomeres) mechanism is activated in this process, altering telomere length and thereby affecting the aging and lifespan of the next generation.

Mitochondrial sirtuins (SIRT3, SIRT4, SIRT5) regulate energy metabolism, oxidative stress, and toxin clearance, protecting cells and slowing the aging process. At the same time, cellular senescence and mitochondrial dysfunction contribute to the development of neurodegenerative diseases (Alzheimer's, Parkinson's) and cardiovascular disorders.

Therefore, understanding aging requires a complex, systemic, and integrative approach. Based on research findings, optimizing lifestyle, increasing physical activity, implementing caloric restriction, and supporting mitochondrial function are recommended. Furthermore, molecular and genetic insights are essential for preventing aging-related diseases, preserving cellular viability, and developing strategies for healthy longevity.

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