Dynamic Cellular Equilibrium Theory of Aging: Integrating Maintenance and Accumulation in the Aging Process

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დაბერების დინამიური უჯრედული წონასწორობის თეორია: შენარჩუნებისა და დაგროვების ინტეგრირება დაბერების პროცესში

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Abstract

The Dynamic Cellular Equilibrium Theory of Aging introduces a comprehensive framework to comprehend the complex mechanisms governing the aging process. This theory posits that aging results from the disruption of delicate balance between cellular upkeep mechanisms and the accrual of cellular damage, all regulated by an interplay of genetic, epigenetic, environmental, and stochastic factors. Within this article, an in-depth exploration of the theory is conducted, encompassing diverse aspects such as the dynamics of cellular maintenance, the intricacies of damage accumulation, the sway of genetic and epigenetic forces, the influence exerted by environmental and lifestyle elements, the stochastic characteristics characterizing aging, along with the cellular adaptive retorts to these influences. By drawing upon pertinent scientific literature, this theory not only provides profound insights into the aging process but also furnishes valuable implications for interventions that strive to cultivate healthy aging and protract the human lifespan. The profound impact of genetic and epigenetic influences on the aging is discussed, the theory unraveling the importance of genes and epigenetic marks that choreograph the symphony of aging. Moreover, there is considered the pervasive role of environmental factors, encompassing lifestyle choices, diet, and exposure to toxins, is expounded upon, underscoring their potent role in shaping the aging process. Incorporating the stochastic element of chance events into the narrative of aging, this theory acknowledges the role of random occurrences in the gradual unfolding of cellular degeneration. Furthermore, the remarkable resilience of cells, reflected through adaptive responses, is elucidated, demonstrating the remarkable plasticity cells exhibit in the face of various aging-related challenges.

Keywords: aging, cellular maintenance, damage accumulation, genetics, epigenetics, environment, stochastic events, adaptive responses

აბსტრაქტი

რეზიუმე: დაბერების დინამიური უჯრედული წონასწორობის თეორია წარმოგიდგენთ ყოვლისმომცველ ჩარჩოს დაბერების პროცესის მარეგულირებელი რთული მექანიზმების გასაგებად. ეს თეორია ამტკიცებს, რომ დაბერება ხდება უჯრედების შენარჩუნების მექანიზმებსა და უჯრედული დაზიანების დაგროვებას შორის დელიკატური ბალანსის დარღვევისშედეგად, რაც რეგულირდება გენეტიკური, ეპიგენეტიკური, გარემო და სტოქასტური ფაქტორების ურთიერთქმედებით. ამ სტატიის ფარგლებში ტარდება თეორიის სიღრმისეული შესწავლა, რომელიც მოიცავს მრავალფეროვან ასპექტს, როგორიცაა უჯრედების შენარჩუნების დინამიკა, ზიანის დაგროვების სირთულეები, გენეტიკური და ეპიგენეტიკური ძალების ზემოქმედება, გარემო და ცხოვრების სტილის ელემენტების გავლენა, სტოქასტური მახასიათებლები, რომლებიც ახასიათებს დაბერებას, უჯრედულ ადაპტაციასთან ერთად, რომლებიც ვითარდება ამ გავლენების პასუხად . შესაბამისი სამეცნიერო ლიტერატურის საფუძველზე, ეს თეორია არა მხოლოდ იძლევა ღრმა შეხედულებებს დაბერების პროცესის შესახებ, არამედ იძლევა ღირებულ შედეგებს ინტერვენციებისთვის, რომლებიც საჭიროა ჯანსაღი დაბერების განვითარებასა და ადამიანის სიცოცხლის ხანგრძლივობის გახანგრძლივებისთვის. განხილულია გენეტიკური და ეპიგენეტიკური გავლენის ძლიერი გავლენა დაბერებაზე, თეორია ხსნის გენების მნიშვნელობას და ეპიგენეტიკური მარკერების ქორეოგრაფიას, რომლებიც ასახავს დაბერების სიმფონიას. უფრო მეტიც, გათვალისწინებულია გარემო ფაქტორების ყოვლისმომცველი როლი, რომელიც მოიცავს ცხოვრების წესის არჩევანს, დიეტას და ტოქსინების ზემოქმედებას, ასახულია, რაც ხაზს უსვამს მათ მნიშვნელოვან როლს დაბერების პროცესის ფორმირებაში. შემთხვევითი მოვლენების სტოქასტური ელემენტის ჩართვით დაბერების აღწერაში, ეს თეორია აცნობიერებს შემთხვევითი მოვლენების როლს უჯრედული გადაგვარების თანდათანობით განვითარებაში. გარდა ამისა, ნათელია უჯრედების გასაოცარი ელასტიურობა, რომელიც აისახება ადაპტური პასუხების საშუალებით, რაც ასახავს უჯრედების გასაოცარ პლასტიურობას დაბერებასთან დაკავშირებული სხვადასხვა გამოწვევების წინაშე.

საკვანძო სიტყვები: დაბერება, უჯრედების შენარჩუნება, დაზიანების დაგროვება, გენეტიკა, ეპიგენეტიკა, გარემო, სტოქასტური მოვლენები, ადაპტური რეაქციები

Introduction:

The aim of the "Dynamic Cellular Equilibrium Theory of Aging" is to provide a novel and comprehensive framework for understanding the complex processes that contribute to the phenomenon of aging. This theory seeks to go beyond traditional theories that often focus on singular causative factors and instead aims to integrate multiple facets of cellular biology, genetics, epigenetics, environmental influences, stochastic events, and adaptive responses. By doing so, the theory strives to explain aging as a dynamic equilibrium between two opposing forces: cellular maintenance processes that sustain cellular health and the accumulation of cellular damage that occurs over time.

Cells are intricate entities that continuously interact with their environment, facing an array of challenges that demand dynamic responses for survival and function [1]. From changes in nutrient availability to fluctuations in temperature, cells must adeptly adapt to maintain homeostasis and ensure optimal functionality. Historically, the fields of epigenetics and metabolism have been studied independently as regulators of cellular processes. Epigenetics, encompassing modifications to DNA and histones, influences gene expression patterns and heritable traits. On the other hand, cellular metabolism governs the utilization of nutrients to generate energy and molecular building blocks essential for growth and maintenance.

In recent years, research has begun to uncover a fascinating intersection between these seemingly distinct realms – the interplay between epigenetics and metabolism. While initially conceived as separate domains, emerging evidence suggests that these systems intricately communicate, share components, and collaboratively orchestrate cellular responses to changing conditions [2, 3]. This burgeoning understanding has led to the proposal of a novel theory that explores the synergistic relationship between epigenetics and metabolism in driving cellular adaptation.

Goal: Aim of the research was to study and analyze the dynamic cellular equilibrium theory of aging: integrating maintenance and accumulation in the aging process.

Methodology

The methodology for developing this theory would involve several key steps:

1) Literature Review: A comprehensive review of existing scientific literature related to cellular maintenance, damage accumulation, genetics, epigenetics, environmental influences, stochastic

events, adaptive responses, and aging theories would be conducted. 2) Integration and Synthesis: The collected information would be synthesized to identify common themes, patterns, and interactions among different factors. 3) Hypothesis Formulation: Based on the synthesis of existing knowledge, a hypothesis or conceptual framework is formulated. This hypothesis serves as the foundation of the theory and outlines the key components, relationships, and mechanisms proposed to be involved in the aging process. 4) Conceptual Mapping: The proposed framework is laid out, demonstrating how cellular maintenance, damage accumulation, genetics, epigenetics, environmental factors, stochastic events, and adaptive responses interact to shape the aging trajectory. This could involve diagrams, flowcharts, or models to visually represent the theory. 5) Discussion and Implications: The theory's implications for understanding aging and potential interventions are discussed in depth. This involves considering how the proposed framework aligns with existing research, how it offers a new perspective, and how it could guide future research directions and practical applications. 6) Validation and Refinement: The proposed theory would need to be further validated and refined through ongoing research, experimentation, and interdisciplinary collaboration. This could involve testing specific hypotheses derived from the theory, conducting studies to assess its predictions, and incorporating new insights as they emerge.

Cellular Identity and Adaptation: The Role of Epigenetics: Epigenetic mechanisms play a fundamental role in determining cellular identity and function. Through modifications to DNA and histones, cells establish unique gene expression patterns that dictate their specialized roles within multicellular organisms [4]. DNA methylation, histone acetylation, methylation, and other epigenetic marks collectively contribute to the epigenome, which functions as a dynamic regulatory layer controlling when and where genes are expressed. This epigenetic landscape not only provides stability to cell identity during development but also allows cells to respond to environmental cues by modifying gene expression patterns.

Cellular Energy Management: Metabolism as a Dynamic Hub: Concurrently, cellular metabolism serves as a dynamic hub that governs the utilization of nutrients for energy production and biosynthesis [5]. The metabolic pathways, such as glycolysis, the tricarboxylic acid cycle, and oxidative phosphorylation, intricately interconnect to generate adenosine triphosphate (ATP), the universal energy currency. Beyond energy production, metabolism generates the building blocks required for macromolecular synthesis, providing the resources for cell growth, repair, and adaptation.

The Emerging Synergy: Epigenetics and Metabolism Converge: Recent studies have unveiled a remarkable interplay between epigenetic modifications and metabolic pathways [6]. Metabolites generated during cellular metabolism can serve as substrates for epigenetic modifications, effectively linking cellular energy status to epigenetic regulation [7]. Conversely, epigenetic modifications can influence the expression of metabolic enzymes, shaping cellular metabolic profiles [8]. This interconnectedness forms feedback loops that fine-tune cellular responses to varying conditions.

Moreover, the plasticity of epigenetic regulation influences metabolic adaptability [9]. Epigenetic modifications influence the expression of metabolic genes, enabling cells to switch between metabolic strategies based on energy demands and nutrient availability. This adaptability provides cells with the versatility to thrive in diverse environments.

The Neuroendocrine Theory: This theory, developed by Dr. Vladimir Dilman, expands on the wear theory, with particular emphasis on the neuroendocrine system. At a young age, hormones work together to regulate many bodily functions, including reactions to heat and cold, life experiences, and sexual activity. Different organs secrete different hormones under the control of the hypothalamus. The hypothalamus responds to the level of hormones in the body and is a reference point for regulating hormonal activity [10].

The Genetic Control Theory: This theory claims that people are born with a unique genetic code, a predetermined tendency towards certain types of physical and mental functioning, and that genetic inheritance can tell a lot about how quickly a person ages and how long they will live [11].

Waste Accumulation Theory: During their lifetime, cells produce more waste than they can dispose of properly. These waste products can include various toxins which, when accumulated to a certain level, can interfere with the normal functioning of cells and even kill them [12].

Limited Number of Cell Divisions Theory: The accumulation of cellular waste directly affects the number of cell divisions. The more waste builds up over time, the faster the cells degenerate [11].

Hayflick Limit Theory: In 1962, two cell biologists, Dr Hayflick and Dr Moorhead, made one of the major contributions to the history of cell biology by demonstrating the aging of human cells in culture. Hayflick hypothesized that the aging process was controlled by a biological clock contained in every living cell [13].

Death Hormone Theory (DECO): Unlike other cells, brain cells or neurons do not reproduce. A person is born with about 12 billion of them, and during their lifetime about 10% die. Dr. Denkl suggested that with age, the pituitary gland secretes DECO (decreased levels of the hormone oxygen or "death hormone"). This inhibits the cells' ability to use thyroxine, the rate at which cells convert food into energy. The metabolic rate increases and accelerates the aging process [11].

Thymic-Stimulating Theory: This theory suggests that the disappearance of the thymus gland contributes to the aging process by weakening the body's immune system. Thymic hormones may also play a role in stimulating and controlling the production of neurotransmitters and hormones in the brain and endocrine system, meaning they may be important regulators of immunity [14].

Mitochondrial Theory: The free radical theory is supported by targeted experimental observations of mitochondrial aging. They produce cellular energy through a process that generates potentially harmful free radicals. Mitochondria are also one of the easiest targets for free radical damage because they lack many of the defenses found elsewhere in the cell [15].

Errors and Repairs Theory: In 1963, Dr. Leslie Orgel suggested that “a mistake in the mechanism of protein production can be disastrous”. Protein production and DNA replication are sometimes inaccurate. An organism's DNA is so important that when a mistake is made, natural repair processes are triggered [16].

Redundant DNA Theory: This theory attributes age-related changes to errors that accumulate in the genes. But as these errors accumulate, this theory also blames identical DNA reserve genetic sequences that take over until the system wears out. Dr. Zhores Medvedev suggested that the lifespan of different species may depend on the degree of repetition of genetic sequences [11].

Cross-Linkage Theory: Developmental aging and interconnection were first proposed in 1942 by Johan Bjorksten. Cross-linking occurs when older immune systems are unable to remove excess glucose molecules from the blood. These sugar molecules react with proteins, causing cross-linking and the formation of harmful free radicals [16].

Autoimmune Theory: With age, the system's ability to produce the antibodies needed to fight disease declines, as does its ability to distinguish between antibodies and proteins. In a sense, the immune system becomes self-destructive and reacts against itself. Examples of autoimmune diseases are lupus, scleroderma and adult diabetes [11].

Caloric Restriction Theory: Calorie restriction or energy restriction is a theory proposed by Dr. Roy Walford. He developed a nutrient-dense, low-calorie diet, demonstrating that "malnutrition followed by malnutrition" can significantly delay the process of functional, and even chronological, aging [17].

The Rate of Living Theory: German physiologist Dr Max Rubner, who discovered the relationship between metabolic rate, body size and life expectancy, first introduced this theory in 1908. It simply states that each person is born with an amount of limited energy. If this energy is used slowly, the rate of aging will slow down. If energy is consumed quickly, aging accelerates [11].

Gene Mutation Theory: In the 1940s, scientists were studying the role of mutations in aging. Mutations are changes that occur in the fundamental genes of life. The evidence supporting this idea came from experiments with radiation. It has been observed that radiation not only increases genetic mutations in animals, but also accelerates their aging process [16].

Accumulated mutations theory: It was first proposed by Medawar in 1952. This theory suggests that the influence of natural selection decreases with age. When a detrimental mutation occurs at a young age, there is strong selection pressure to eliminate that mutation, as it will affect the fitness of the vast majority of the population [18].

Antagonistic pleiotropy theory: Antagonistic pleiotropy is the second evolutionary theory of aging. It was formulated by Williams in 1957 and suggests that there are genes that have beneficial effects early in life but have detrimental effects later in life. If these genes ensure

greater reproductive success at an early age, they will be selected even though they may cause later aging [18].

Disposable soma theory: Cell maintenance is expensive. Since external mortality in nature is extremely high, it doesn't make much sense to use up precious metabolic resources to maintain the soma past the expected lifespan of the organism [11].

Order to Disorder Theory: From conception to puberty, the human body is subject to a system of order. Dr. Leonard Hayflick has observed that humans devote most of their energy to implementing a genetically determined plan for the orderly production and arrangement of a large number and variety of molecules [11].

The Telomerase Theory of Aging: This theory was born out of technological advances in genetics and genetic engineering. Telomeres are nucleic acid sequences extending from the ends of chromosomes. Telomeres maintain the integrity of chromosomes. Each time cells divide, telomeres get shorter, leading to cell damage and age-related death [19].

The free radical theory: This theory suggests that strengthening the antioxidant defense system to mitigate free radical damage thwarts the aging process. Among the various theories of the aging process, the free radical theory has received much attention, which suggests that the harmful effects of free radicals are responsible for the functional deterioration associated with aging [20].

Cellular Senescence: Senescent cells are a sign of aging. They are also implicated in a wide range of age-related diseases and conditions, including cancer, diabetes, cardiovascular disease and Alzheimer's disease. Senolytics are compounds that selectively induce apoptosis, or programmed cell death, in senescent cells. In humans, oral administration of 50 mg dasatinib and 500 mg quercetin once daily after meals for five days has shown a marked improvement in exercise performance. They have demonstrated a clear senolytic effect and it is likely that such simultaneous use will be harmless in the near future. Senescent cells are obviously involved in the aging process. It is becoming increasingly clear why people generally age at the same rate. The intensity of aging and the number of senescent cells is directly linked. The more cell divisions there are, the more the cells are senescent [21].

Autophagy: Autophagy dysregulation drives aging and disease phenotypes; excessive autophagy can also contribute to the deterioration of cellular function in some cases. Lipid modifications are essential for cell sorting and movement within cells. The role of phosphoinositides in transport between the Golgi apparatus and the endocytic/lysosomal compartments has been widely studied and the kinases responsible for these lipid modifications have been identified. However, the mechanisms involved in the production and recycling of lysosomes (Lys), long considered terminal compartments, are less well understood. In this work, we identified the dynamic association of the lipid kinase PI4KIIIβ with Lys and discovered its regulatory role in the export and recovery of lysosomals. The absence of PI4KIIIβ results in the abnormal formation of tubular structures on the surface of lysosomes and the loss of lysosomal components through these tubules [22].

Primary markers are the primary cause of molecular damage inherent in aging. This is the case with aging, which protects the body from cancer, but in excess it can contribute to aging. Similarly, reactive oxygen species (ROS) mediate cell signaling and survival, but at chronically elevated levels they can cause cellular damage. Organisms age because they accumulate oxidative damage, she says. This damage comes from ROS, which are partially reduced metabolites of molecular oxygen formed as products of metabolic reactions or products of various cellular processes such as respiration. According to this concept, the physiological formation of ROS during cell metabolism causes oxidative damage in the cell itself, which ultimately leads to biochemical and physiological decline. For example, in rats, oxidative damage increases in several organs. Organs undergo degenerative changes with age, including significant histological, biochemical, and metabolic changes. Factors that contribute to organ failure are known to include changes in the nucleus pulposus, including increased cell density, cell aging, and cell death associated with impaired synthetic activity and increased activity of matrix metalloproteases (MMP) [23].

Conclusion:

In conclusion, the convergence of epigenetics and metabolism represents a paradigm shift in our understanding of cellular adaptation. The interconnected nature of these systems transcends the boundaries of classical biological disciplines, offering a holistic perspective on

how cells respond to changing environments. This novel theory serves as a foundation for further exploration, fostering interdisciplinary research that may unveil new therapeutic targets and strategies for various diseases. By unraveling the intricate interplay between epigenetics and metabolism, scientists are poised to unlock the secrets of cellular adaptation and its implications for health and disease.

Conflict of interest statement: The authors declare no conflict of interest.

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