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Review article

GENETIC AND EPIGENETIC MECHANISMS OF AGING

GENETIČKI I EPIGENETIČKI MEHANIZMI STARENJA

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Abstract

Aging is inevitable and the representation of old people in the population grows. Accordingly, the understanding of genetic factors and physiological mechanisms involved in the process of normal aging is of increasing importance for maintaining the quality of life in old age. Preserving the physiological functions or "health" of old people will reduce pressure on health systems and costs. In this review, in the light of the latest scientific data and hypotheses, some key questions regarding the genetics, biology and physiology of aging are briefly discussed: what is aging, why it occurs and what are the possibilities of delaying and slowing down of aging.

Keywords:
aging,
genetics,
characteristics,
causes,
delay

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Sažetak

Starenje je neizbežan proces i u populaciji raste zastupljenost starih ljudi. Shodno tome, razumevanje genetskih faktora i fizioloških mehanizama uključenih u proces normalnog starenja od sve je većeg značaja za održavanje kvaliteta života u starosti. Očuvanje fizioloških funkcija ili „zdravlja" starih ljudi smanjiće pritisak na zdravstvene sisteme i troškove. U ovom revijalnom radu, u svetlu najnovijih naučnih podataka i hipoteza, ukratko se razmatraju neka ključna pitanja koja se tiču genetike, biologije i fiziologije starenja: šta je starenje, zašto nastaje i koje su mogućnosti njegovog odlaganja i usporavanja.

Ključne reči:
starenje,
genetika,
karakteristike,
uzroci, usporenje

Introduction

The increase in standards and the progress of medicine in the twentieth century caused a significant increase in life expectancy, from 50 years at the beginning of the 20th century to over 80 years at the end of the century. According to World Health Organization (WHO) data, the number of people over 80 will quadruple to 395 million by 2050 (1). Over the next 5 years, the number of people aged 65 and over will exceed the number of people under 5 years of age. By 2050, the number of people over the age of 65 will exceed the total number of children under the age of 14. The majority of elderly people will live in poorer to middle-developed countries, and by 2050, that number will be up to 80%, according to official statistics (1). Such data unequivocally impose the fact of the need for long-term plans and the development of strategies for the treatment and care of the elderly.

By all means, a significant increase in the frequency of diseases characteristic of postmenopausal and later age is associated with the extension of life and is of multifactorial etiology.

According to the WHO definition, biological aging implies a gradual and continuous involutional physiological process, which no living being can avoid and which begins in early adulthood (1). The period after the age of 65 is commonly referred to as the "third age" (WHO) (1), although the Italian Society of Gerontology and Geriatrics (SIGG) has raised the threshold to 75 years (2). The maximum age that can be reached has not undergone much change, because, biologically speaking, taking into account all the progress of science, the cases of over a hundred years are still limited (3). Genetics plays an important role in this, because the tendency to develop diseases, as well as the possibility of living to a very advanced age (over 100 years), are hereditary characteristics (4).

Genetics of Aging Overview

The genetics of aging deals with changes in genetic material as a cause of aging of humans and other biological species. All previous studies point to the fact that these changes are a significant factor in the aging process (4, 5).

Literature data proved that the wear and tear of the genetic code with age is the main cause of aging. It is a process that represents a genetically programmed failure of the mechanisms that maintain homeostasis (constancy of the internal environment of the organism) (4-6). A number of theories, which fall into two main categories, have been proposed in an attempt to explain the process of aging. The first category is comprised of concepts holding that aging is programmed and those positing that aging is caused by the accumulation of damage. While programmed theories include programmed longevity, endocrine and immunological theory, damage of error theories endeavor with the following: the Free Radical Theory, Error theory, Damage or Error Theories, The Cross-Linking Theory, The Neuroendocrine Theory, The Membrane Theory of Aging and The Decline Theory. The current theories differ in the extent to which the buildup of waste is encoded in the genome and whether it is programmed death or this accumulation that is deemed to bear the costs of evolutionary benefits. In addition to damage itself, the rate of accumulation is also of concern, which results from overall metabolic activity. The most significant changes in the longevity of model organisms prove to be mutations in metabolic pathways (7). According to the abovementioned theories, the aging process is associated with the accumulation of deoxyribonucleic acid (DNA) errors in somatic cells, which are designated as genetic mutations (6). In addition to gene mutations of somatic cells, it was found that the frequency of chromosomal aberrations, both structural and numerical, increases with age.

It has been shown that DNA damage repair mechanisms lose their ability during aging, so these errors accumulate during life (6). It is still not clear whether it is an accumulation of errors during the development of the individual or whether errors in the genetic material are more frequent during aging. In the course of aging, the activity and number of enzymes that participate in the repair mechanisms decrease, which accumulates disorders in the genetic material. The idea about the important role of disruption of the reporter mechanisms in the aging process is explained by a model that describes that repair can only be done in parts of DNA that are active in transcription. Much of the human genome is transcriptionally inactive and can accumulate errors, as it is exposed to repair enzymes only during replication (8). If in some cells there is a long period between replications and cell division, then DNA damage accumulates and remains until the next replication. Accumulation of errors in DNA leads to replication disorders, which causes disruption of cell division and prolongation of the cell cycle, as well as the appearance of chromosomal aberrations. Genetic instability as a result of impaired repair of DNA errors is one of the causes of

aging (6,8). Accordingly, the consequences are a series of degenerative diseases, increased frequency of malignant diseases and autoimmune diseases, where immune system functions decrease.

Statistically, 6 out of 10 people over the age of 65 suffer from some disease during their lifetime, including arthritis, kidney failure, chronic bronchitis, respiratory failure, bronchial asthma, stroke, diabetes, myocardial infarction, coronary artery disease and other heart diseases (1). In addition, many people after the age of 65 suffer from several diseases at the same time, for example cardiopathies and chronic respiratory diseases, neurological diseases of the degenerative type (atherosclerosis, senile dementia, Parkinson's disease) and almost inevitable degenerative and metabolic diseases of the musculoskeletal system, such as arthritis and osteoporosis, which greatly affects both the quantity and the quality of an individual's life (1).

Epigenetics and aging

In addition to genetics, epigenetic mechanisms also play a significant role in aging processes. Epigenetics is defined as the branch of science that studies all potentially stable heritable changes in gene expression or cellular phenotype that occur without changes in the arrangement of DNA bases. Epigenetic processes link environmental factors to our genetic code and allow external influences to leave a biochemical imprint on our genome (4,9). Such an epigenetic code is defined by chromatin modifications by processes such as DNA methylation and histone post-translational modification (HPTM). In eukaryotic cells, histone and DNA modification processes are coordinated, as important regulators of gene expression in tissue- or development-specific patterns. The DNA methylation, which is performed by adding a CH_3 group to the 5'C atom of cytosine, is a universal mechanism leading to eukaryotic gene inactivation. Human genome contains numerous CpG islands, regions rich in CpG sequences, which are generally located near genes. Epigenetic regulation of gene expression and protein synthesis is achieved by methylation and demethylation of CpG islands. It has been found that during aging there is a change in epigenetic patterns. In general, global hypomethylation of the genome occurs, but also hypermethylation of certain, specific loci (10). It turned out that the dynamics of these processes are predictable, so based on these findings the "DNA methylation clocks" were created. Simply put, the chronological age of an individual can be determined based on DNA methylation analysis, and the two most reliable tools of this type created by Hannum et al. (11) and Horvath (12) have a correlation coefficient greater than 0.9, with an average error of less than 5 years. In aging, an increase in the degree of histone modifications is observed, which can be associated with the aforementioned global hypomethylation of the genome. It is certain that epigenetic changes and aging are closely related and intertwined, so these changes can be seen not only as a consequence but also one of the causes of aging (10).

Research has shown that transient and chronic environmental influences can permanently change the epigenetic code. They accumulate during their lifetime and carry important information about the interactions of that organism with the environment (13,14). In some cases, this information can be of great importance to the offspring and can provide them with certain advantages in adaptation. But also, the accumulation of epigenetic changes can lead to an increase in the risk of various diseases (many epigenetic changes are associated with an increase in the risk of cancer or are a predisposition to psychological disorders) (14). Interesting enough, in identical twins epigenome is initially similar, but begins to differ significantly over time.

Genetics cannot be influenced, nor can the environment that affects us, but we can adapt our life and our behavior to the conditions in order to live as long as possible. Moderate and regular physical activity (minimum 150 min per week of aerobic training, in strength exercises for larger muscle groups of upper and lower extremities), avoiding long stays in one position (lying, sitting, crouching, standing) enable uniform and slower aging of muscles and bones (15). Avoiding harmful habits such as drugs, tobacco and alcohol, stress and great psychophysical efforts significantly contribute to slowing down the development and occurrence of many diseases and prolonging working and life expectancy (1). Mechanistically, it is well accepted that the mentioned habits induced oxidative stress and accumulation of intracellular damage, determined by reactive oxygen species (ROS), that might orchestrate the progressive loss of control over biological homeostasis and the functional impairment typical of aged tissues. Oxidative stress contributes to the pathogenesis of several cardiovascular, pulmonary and neuronal disorders common among elderly people, such as myocardial infarction, diabetes, atherosclerosis, chronic obstructive pulmonary disease (COPD) or Alzheimer's disease. Alteration of epigenetic enzyme activity, histone modifications and DNA methylation is, in fact, typically associated with the aging process. Specifically, aging presents peculiar epigenetic markers that, taken altogether, form the still ill-defined "aging epigenome" (14). On the contrary, healthy diet with several small meals during the day, with lots of fruits and vegetables, has a positive effect on metabolism and health, and thus slows down aging (16). Memory and brain work retain their vitality if a person eats properly and constantly engages (even in the old days) in various spiritual and intellectual activities (17).

Telomeres and aging

One of the theories of aging that has recently been given importance, and which is also the most probable, is the theory about telomeres, their length and degree of biological age (18). While chronological age is determined by the number of years we live, biological age is determined by other markers such as skin elasticity, bone density,

quality of vision and body weight (18). If everything were ideal, they would match, but under the influence of not-so-ideal everyday life, the biological age is almost always above the chronological one.

With a well-balanced diet, lifestyle (15,17) and adequate use of supplements, it is possible to have a more than favorable effect on the extension of biological age (16). This is where the already mentioned telomeres and the function of the telomerase enzyme come into play (18).

Telomeres are short repeating sequences of nucleotides located at the ends of DNA molecules. They consist of TTAGGG sequences of bases repeated up to several thousand times (14). The basic function of telomeres is to protect the DNA molecule from damage and maintain its stability during the process of cell division. During cell division and DNA replication, due to the impossibility of the replication enzyme (RNA polymerase) acting on the end of the telomere, the new, replicated DNA that is created is significantly shorter than the initial molecule (14). As a result, the genome of each newly formed cell is shorter by several tens of base pairs from the telomere area, and after a series of successive divisions, the DNA ceases to be protected. The cell recognizes such a molecule as damaged, stops dividing, gradually slows down metabolism and enters a state of rest. Cells that are in the resting phase are characterized as old cells and are more common in organisms of older chronological age. This basic principle does not apply to cells in which the function of the telomerase enzyme, whose function is to restore telomere strings, has been retained (14).

Untidy lifestyle, irregularity and improper diet, and excessive exposure to physical and psychological stress burden the organism. Such conditions entail changes in cell metabolism and accelerate the aging process. This is precisely the basis of differences in biological and chronological age. Numerous studies have proven a positive correlation between shortened telomere length and various conditions such as inflammatory diseases, hormonal disorders, but also cancerous conditions, which are often shown as a consequence of the aging of the organism (18).

Scientists can estimate biological age by measuring the length of telomeres, which shorten each time cells divide. Studies looking at telomeres have shown that stress affects young doctors or multiple pregnant women, causing cells to age beyond calendar years (19). Earlier longevity research typically explored the possibilities of telomere lengthening as a means of extending the lifespan of animals. However, the discovery of ways to rewind epigenetic clocks has only recently come into the focus of scientists.

"Despite the generally accepted thesis that biological age is, in a certain way, changeable, the extent to which biological age undergoes reversible changes during life and the events that cause such changes remain unknown," explains Vadim Gladishev, a molecular biologist from Harvard Medical School and co-author of the new study (19).

Research shows that despite the consequences of pregnancy on the mother's body, the mother's cells look "younger" during pregnancy than they should be according to chronological age (20,21).

A clear pattern that has emerged across some trials is that exposure to stress increases biological age, the researchers write in their published paper. When the stress was alleviated, the biological age could be completely or partially recovered (20). This is clearly demonstrated by analysis of changes in biological age in response to major surgery (19,22).

Blood samples from elderly patients who underwent emergency surgery showed an increase in markers of biological age that returned to baseline one week after the procedure (22). However, the patients who decided to undergo the surgery did not show signs of accelerated aging. Finding signals among millions of hyperactive cells is a difficult task, so the researchers compared multiple epigenetic clocks. Their findings suggest that the body is capable of reversing the processes of biological aging (22). Notably, it is one thing to observe fluctuations in the body's processes, and quite another to try to use them therapeutically to reverse the effects of aging. The body is capable of many remarkable things that modern medicine can barely imitate, and we do not yet know whether these transient changes in cellular aging have noticeable or lasting health effects.

Certain cells such as germ cells, embryonic stem cells and bone marrow cells naturally contain the active enzyme telomerase, which after DNA duplication lengthens telomeres and prevents cell aging. Numerous studies have proven a positive tissue reaction to the reactivation of telomerase (23). During this process, telomeres are lengthened and, consequently, the life span of the cell is extended (23). Improvements in glucose tolerance and insulin sensitivity, reduced loss of bone and subcutaneous fat, and improvement in liver health were observed (24).

Science has progressed, but how can we? Nobel Prize Winner Elizabeth Blackburn (25), but also many other researchers (19-21) point out that we have more control over our telomeres than we think. Proper nutrition, quality sleep and regular physical activity, while avoiding stress and certain chemicals to which we can be exposed on a daily basis, leave a mark on our telomeres, with special

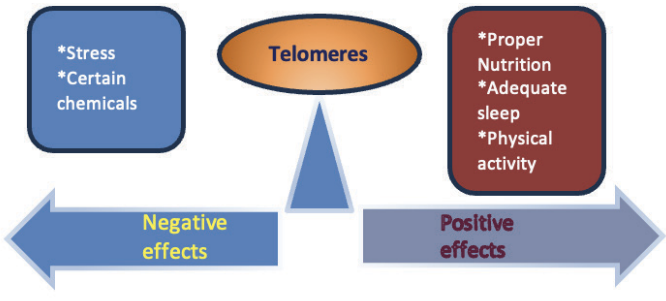

Figure 1. Negative and positive factors affecting telomeres length.

reference to certain exercise programs for both physical and mental functioning (**figure 1**). These are aspects that can be influenced. Better standardization of exercise protocols and their implementation in primary and secondary health care systems would enable more efficient application of them and raise the population's awareness of the imperative of their regular application. Spreading knowledge and good rehabilitation programs in the future should be key goals in defining a global strategy for slowing down aging, thus the promotion of healthy aging.

Genetic mechanisms of aging identified in model organisms

For several decades, the nematode *Caenorhabditis elegans* (*C. elegans*) has been used as a prominent animal model for studying the genetics of aging. The main advantages of this model organism in experiments are its short life span, simple manipulation in experimental work, completely sequenced and well-annotated genome as well as availability of both forward and reverse genetic analyses (26).

In *C. elegans*, two main classes of mutants have been identified. The first class consists of individuals with mutations in genes involved in the electron transport chain in mitochondria, such as *clk-1* and *isp-1*. Mutations in these genes lead to a moderate reduction in the capacity of oxidative phosphorylation and are associated with extended life span in *C. elegans*. These experimental results marked the first direct link between energy metabolism and longevity (27).

An individual that is a *clk-1* mutant is characterized by a lack of an enzyme that participates in the synthesis of ubiquinone (coenzyme Q), an electron acceptor in the respiratory electron transport chain. It has also been shown that a mouse with moderately reduced oxidative phosphorylation exhibits an improvement in glucose homeostasis and an increased lifespan. Gene *isl-1* encodes iron-sulfur protein in mitochondrial complex III; when it was shown that mutants live longer, it was the first evidence of the influence of impaired electron transport function on the extension of life span. All this indicates that reduced mitochondrial function can promote aging (27).

The second class of *C. elegans* mutants had alterations in genes that control hormone mechanisms in the insulin/insulin-like growth factor 1(IGF-1) signaling (IIS) pathway. Such examples are mutations in the *daf-2, daf-16* and *age-1* genes, which are associated with increased lifespan not only in worms but also in flies and mice (26). This is of utmost importance because ISS was the first nutrient sensing pathway with a demonstrated direct impact on aging process.

In *C. elegans* the *daf-2* (from "dauer abnormal formation") gene encodes the insulin/IGF-1 receptor, an important component in IIS. *Daf-2* mutant with reduced receptor activity remains young for a long time and shows a longer life span compared to wild-type individuals. The *daf-2* gene is in functional connection with the *daf-16* gene, through negative regulation. The *daf-16* product is the FOXO (forkhead box transcription factors class O) protein homolog, a transcription factor that regulates stress response processes, antimicrobial activities, detoxification from xenobiotics and free radicals, and other types of cell, tissue and organism defense at the gene level. The *daf-16* mutations suppress the positive effect of *daf-2* mutations on lifespan extension (26).

The TOR (target of rapamycin) signaling pathway interacts with IIS, and suppression of TOR has been shown to extend *C. elegans* lifespan. TOR and its mammalian ortholog mTOR are highly evolutionary conserved serine-threonine kinases that react on growth factors, nutrient or oxygen status and promote appropriate changes in cell growth, proliferation, survival, and metabolism. It was found that TOR activation of the ISS pathway down-regulates the expression of proteins from the sirtuin family, and also inhibits autophagy mechanisms important for the preservation of cellular integrity, through the removal of damaged mitochondria. Experiments on *C. elegans* have shown that both of these pathways play a key role in extending life span (27).

Sirtuins are protein deacetylases important in modulating pathways involved in the aging process. In mammals, some sirtuins regulate glucose and fat metabolism by promoting mitochondrial biogenesis in liver and muscle tissue. This effect is achieved through the transcriptional coactivator peroxisome proliferator-activator receptor-gamma coactivator 1 alpha (PGC-1a). They also affect the cell cycle and cell survival by reducing the p53 tumor suppressor activity. The polyphenol of plant origin, resveratrol, affects the extension of life span in different species precisely by acting through sirtuins. Thus, resveratrol increases the activity of some sirtuins and extends the lifespan of yeast by nearly 70%. A similar effect was achieved in the short-lived fish *Nothobranchius fuzeri*, in which, after treatment with resveratrol, the life span was extended by about 60%, while preserving motor and cognitive abilities. In experiments on a mammalian model, middle-aged mice on a high-calorie diet showed a significant increase in lifespan after treatment with resveratrol (27).

Progeria syndromes – single gene disorders associated with premature aging

Progeria syndromes, described in humans, are characterized by premature aging phenotype and are caused by inherited defects, mostly in DNA repair systems (**table 1**). Examples of these disorders are Cockayne syndrome, Fanconi anemia, Werner, Bloom, Rothmund-Thomson and Hutchinson-Gilford syndromes, xeroderma pigmentosum, ataxia-telangiectasia. The main manifestations of progeria syndrome include signs of premature aging, such as gray hair, hair loss, atherosclerosis,

Table 1. Some human progeria syndromes, causative genes and their roles/encoded proteins. Rodríguez-Rodero S. et al (27).

Syndrome	Gene	Function
Cockayne Syndrome	*ERCC6 (CSA)* *ERCC8 (CSB)*	DNA repair
Fanconi Anemia	*FANCA, FANCB, FANCC, FANCD1,* *FANCD2, FANCE, FANCF, FANCG,* *FANCI, FANCJ, FANCL, FANCM, FANCN*	DNA repair
Werner Syndrome (WS)	*WRN*	DNA helicase
Bloom Syndrome	*BLM*	DNA helicase
Rothmund-Thomson Syndrome	*RECQL4*	DNA helicase
Hutchinson-Gilford Syndrome	*LMNA*	Structural protein

increased risk of cancer, skin changes, metabolic diseases (diabetes, hyperlipidemia) and senile dementia. These syndromes are also called "segmental progerias" because they usually involve only some of the many features of physiological aging. Most progeria syndromes are based on mutations in genes involved in DNA repair systems. However, in the severe autosomal dominant form of progeria, Hutchinson-Gilford syndrome, there is a mutation in the gene coding for lamin A (LMNA), which is a structural protein of the nuclear membrane. The *LMNA* mutation leads to anomalies in the cell structure, which has also been shown in animal models. Progeria syndromes are an outstanding illustration of the direct influence of genetic factors on the aging process. By studying these disorders, a better understanding of pathological mechanisms will be achieved, and strategies for new molecular therapies could be developed (27, 28).

Polymorphisms in human aging-related genes

Numerous association studies have investigated the possible connection of gene polymorphisms with human aging and longevity. Previously, candidate genes were examined and selected according to data obtained on animal models, or by their importance for aging-related processes and diseases. In the last decades, Genome-Wide Association Studies (GWAS) predominate, in which a huge number of variants in the entire genome are analyzed simultaneously. However, the results of association studies are mostly inconsistent and ambiguous (28, 29). In the candidate genes/pathways approach, the somatotropic axis as the IIS equivalent in mammals was studied. Body growth is mediated by pituitary growth hormone (GH), which activates the GH receptor (GHR) leading to IGF-1 secretion and its binding to the IGF-1 receptor (IGF-1R) on target cells, with the final effect of triggering cell growth and survival. Gene polymorphisms associated with lower plasma IGF-1 levels are detected in Ashkenazi Jewish centenarians (29). In addition, a significant association of polymorphisms in the *FOXO3A* gene, a homolog of the *daf-16* gene in *C. elegans*, has been described in several populations (27). Some variants in the HLA locus as well as in genes involved in free radical detoxification also showed association in aging studies (27). The significance of genes involved in the etiopathogenesis of multifactorial diseases associated with aging and old age, such as cardiovascular diseases or dementia, was also studied extensively. However weak or no consistent association was observed (27, 29). For example, Apolipoprotein E (ApoE) play important role in lipid metabolism and in processes of remodeling and reparation in central nervous system. Three common ApoE isoforms, ApoE2, ApoE3 and ApoE4, show strong genetic determination by e2, e3, and e4 allele. At least, variable distribution of ε4 allele may contribute to the regional risk of cardiovascular and Alzheimer's diseases. Allele-frequency comparisons between younger and older populations suggest an effect of *APOE* on mortality, but these data are not consistently confirmed. In the study conducted on the Serbian population, Maksimovic et al. (30) analyzed the distribution of *APOE* gene polymorphism in a group of University students and retained University professors. They found no statistically significant difference in alleles and genotypes distribution between younger and elder group of participants. Also, there was no significant difference compared to *APOE* data previously obtained in the YUSAD cohort of healthy school children (15 years of age) from different regions of Serbia. In both students' and retained professors' groups, as well as in the YUSAD cohort, the frequency of *APOE* e4 allele was < 10%. These results do not support the important role of *APOE* e4 form in the morbidity and mortality in the Serbian elderly population, but authors emphasized that gene-environmental-social interactions should be considered (30).

Considering the growing amount of data from GWAS and other studies, as well as the need for their complex processing and careful interpretation, special tools of the database dedicated to the genetics of aging were formed (31, 32). Contemporary authorities in the field suggest five main pathways for future studies of human aging and longevity, which include: insulin/insulin-like growth factor 1 signaling, DNA-damage response and repair, immune function, cholesterol metabolism and

telomere maintenance. More specific, they believe that significant discoveries could be expected in the identification and functional analysis of rare variants in genes responsible for these pathways (29).

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