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MODERN BIOTECHNOLOGICAL APPROACHES TO LIFESPAN EXTENSION OF ANIMALS AND HUMANS

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The purpose of the research was to analyze current data concerning the problem of extending the life of multicellular animals and humans. The modern views about the processes of aging and prolongation of life are presented. The analysis focused on the genetic mechanisms of aging and mainly biotechnological approaches (genetic engineering, gene therapy, the use of stem cells, and the reprogramming of the genome) to prolong the life of multicellular organisms. For comparison, some traditional methods of prolonging life are described (drug therapy, exercise training, calorically restricted nutrition). This analysis allows to postulate the perspectives and advantages of using biotechnological methods for prolonging life in comparison with traditional ones.

Key words: aging, lifespan extension, stem cells, genome reprogramming.

The phenomenon of aging and the problem of lifespan extension of multicellular animals and humans

At the present time, aging is defined as a intrinsic to multicellular organisms process of degeneration and damaging of biomolecules, tissues, organs, and ultimately, the whole organism, resulting in death [1]. Aging can be interpreted as an adaptive mechanism for eliminating senescent individuals from population, who outlive their usefulness and are no longer able to quickly adapt to variable environment due to arising harmful mutations, and for replacing aged individuals with young ones, whose genome contains beneficial mutations facilitating such adaptation. Thus, there is a succession of generation, that is, the individuals, who have maximum number of beneficial mutations inherited (passed down) from parents and fixed in genome, as well as novel mutations accumulated after the birth and, which are not associated with parents, have the greatest selective advantages.

Unicellular organisms do not need such an elimination of the individual from the population, since their life span is limited by the intervals between cell divisions resulting in formation of two new organisms. Individuals carrying harmful mutations are rejected during the selection process and are removed from the population. If multicellular organisms had been deprived of such mechanism, their populations would have doomed to extinct due to the accumulation of harmful mutations and the inability to adapt to ever-environmental changes.

The study of the aging phenomenon is closely related to search ways and approaches to the problem of prolonging life of species. Today, such terms as “anti-aging”, “anti-aging medicine,” etc. are used in the field of research on mechanisms for extending of life span. V. V. Frolkis, in his time, proposed the term “vitauct” (from “vita”— life, “aucto”— increase) [2].

The problem of human aging and extension of lifespan through prolongation of its active creative period have been vital for many centuries [3]. However, all attempts to solve this problem had practically no results. The main reason for this was ignorance of the

basic molecular mechanisms of aging, which become gradually appear only in the most recent time.

The evolution of multicellular organisms, since their emergence, is inextricably linked to succession of generations and inevitable death of certain individuals. The limitation of life cycle of these organisms is determined by sexual reproduction with the subsequent elimination of the individual from the population. When the processes of pubertal growth and reproduction, resulted in the appearance of new individuals (offspring), are completed, the aging processes rapidly develop, leading to the end of life cycle and death. The goal of this process is to remove an individual from the population, replacing it with new one, more viable (robust) individuals (offspring).

As mentioned above the essence of these processes is to renew the gene pool engaging new genome sequences arisen from mutations, among which, the beneficial ones will be selected (via selection process) ensuring better adaptability to variable environment. Individuals with negative/harmful mutations will be eliminated.

Considering all these facts, a desire to prolong life of certain individuals will encounter the obstacles determined by the above-mentioned evolutionary molecular mechanisms for eliminating of senescent individuals from population of species.

There are several possible strategies with aid of which researchers hope to slow aging and extend life span of an individual. For example, the calorie restricted (though balanced) diet increases life span. Researchers have also some expectations for drugs and other biologically active substances (based on medicinal plants, antioxidants, hormones) that would affect the body cell repair [3]. The same is true for prolonging life through physical activity.

Other approaches, based on the achievements of modern biotechnology, focus on use of such methods of the tissue rejuvenation as genetic engineering, gene therapy, stem cells, and reprogramming of genome. Nevertheless, significant progress in these areas has not been made currently, and how soon (in years or decades) this progress will be made is unclear.

The term "maximum lifespan" was elucidated in the works [3, 4], and it was noted that certain interventions, such as calorie restriction diet, can increase the maximum lifespan, while others may increase the mean or median, but not the maximum, lifespan. To date it is cogently proved that human lifespan, in particular, the maximum lifespan, is mainly determined by genetic factors (see below). The maximum human lifespan (under the optimal conditions for the functioning of the organisms) is suggested to be around 120–125 years [3–6].

It is impossible to cover in one article such huge topic as the aging process, its mechanisms and possibility to prolong life of multicellular organisms (moreover, for humans, the point is to prolong active, creative period of life). Therefore, given the determining role of genetic mechanisms in the aging process, this overview will focus on molecular genetic theories and mechanisms of aging, which enable us to understand the essence of the relevant modern biotechnological approaches to extension of lifespan.

The main theories and mechanisms of aging

The analysis of all existing theories of aging is beyond the scope of this review; therefore, the emphasis will be placed on "genetic" theories based on age-related damages to the genome and the possibility of their elimination in order to increase life span.

Evolutionary theories of aging are based on the assumption that there are certain genes, which provide a selective benefits in early life and have negative effects in later life (antagonistic pleiotropy theory), or longevity "insurance" genes (disposable soma theory). Research in human and animal genetics resulted in the identification of new genes, so-called gerontogenes, whose overexpression or mutations increase life span. Furthermore, genetic and epigenetic (environmental) mechanisms, positively affecting lifespan, have also been identified. Gerontogenes are classified as lifespan regulators, mediators, effectors, housekeeping genes, involved in the mitochondria function, as well as in regulation of cellular aging and apoptosis. Most of these genes, as well as genetic and epigenetic mechanisms, involved in the regulation of lifespan, are closely linked to each other, and to a response to stress. These concepts were analyzed, in particular, in [7–9] (Fig. 1, 2), where the interconnection between genetic and epigenetic (environmental) factors of aging and life span was demonstrated.

Genetic mechanisms of aging

An analytical overview of the achievements in genetics of aging and life span was presented in [7, 9]. Evolutionary, cellular and molecular-genetic views on the nature of aging were summarized. Classifications (evolutionary

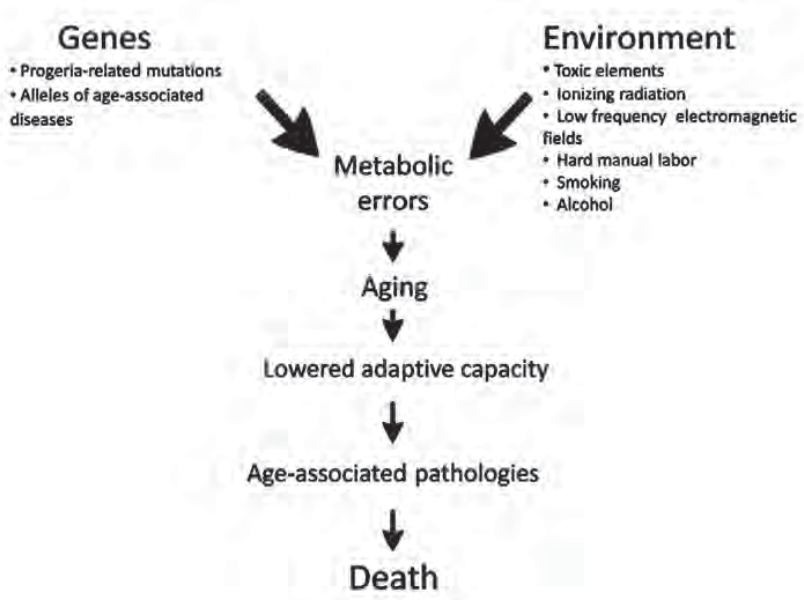

Fig. 1. **The effect of environmental and genetic factors on aging and the formation of age-dependent diseases [7]**

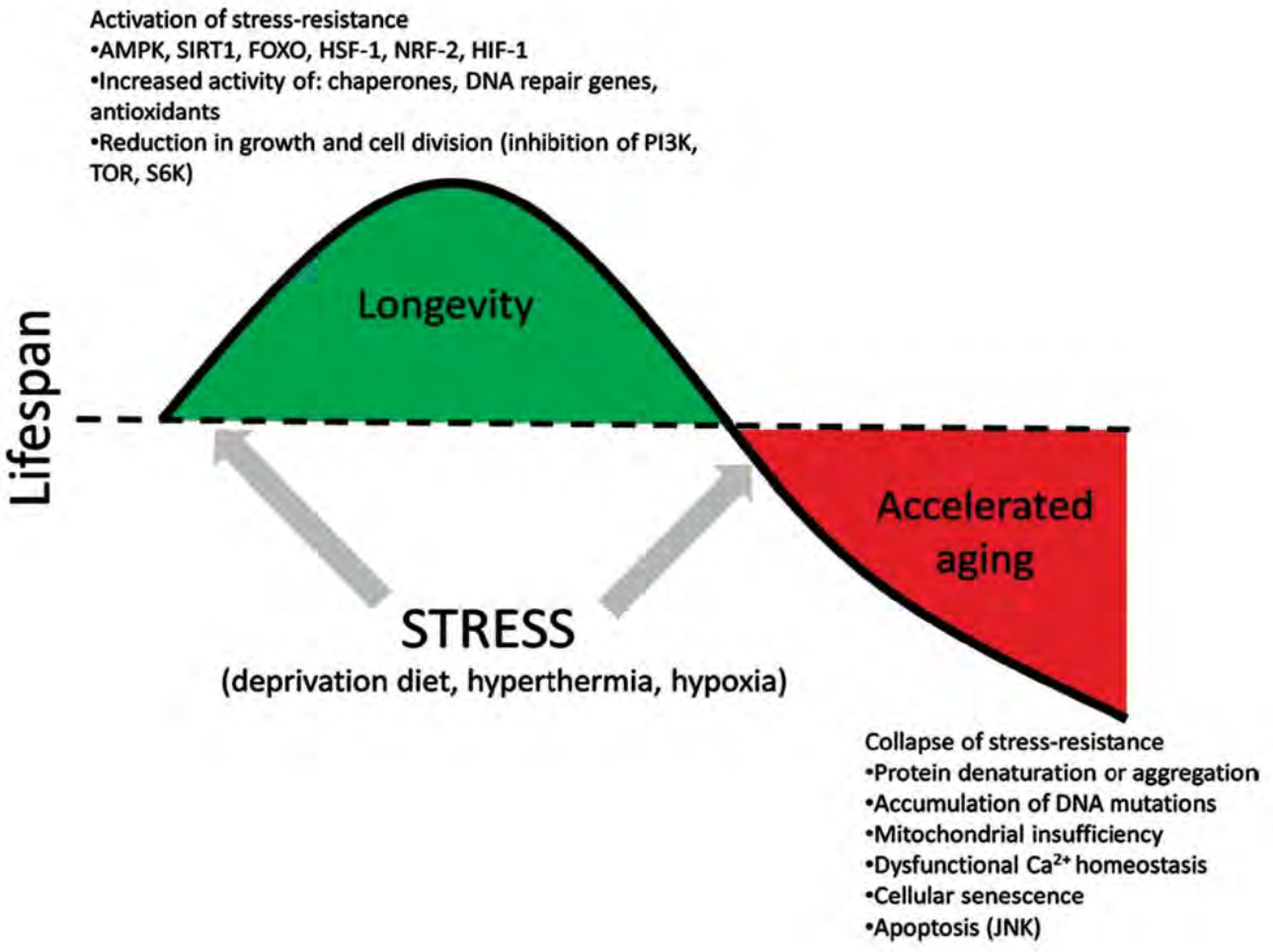

Fig. 2. **Stresses of various magnitudes affect aging rate and lifespan through different mechanisms [9]**

and phenomenological) of lifespan genes were analyzed, and new functional classification was proposed. The main pleiotropic mechanisms of aging namely, replicative and stress-induced cell senescence, maintenance of genome stability and apoptosis were described. In the authors' view, extreme environmental conditions (starvation, temperature stress, disorder of light rhythm, exposure to radiation, oxidative stress) cause a switch from reproduction program to the stress-resistance one. The main regulatory and effector pathways underlying this stability were considered. A comprehensive overview of the interaction between reproduction and aging was given.

The results supporting these notions were reported in [10, 11]. It was found that the number of age-related damages of DNA helix strands (determined by the cell lysis on the surface of alkaline sucrose gradient) in actively proliferating tissues (spleen, regenerating liver) was significantly lower than in mitotically inactive tissues (intact liver, kidneys).

In most theories of aging, the leading role is given to the well-proven idea on the importance of telomeres and telomerase activity in the mechanisms of cell aging and life span. Telomeres are molecular structures consisting of repetitive sequences of DNA and proteins located at each end of each chromosome. Their role, among other functions, is to protect chromosomes from various damages (mainly from nucleolysis), undesirable recombination, repair and fusion with neighboring chromosomes. Hence, they play an important role in preserving information in genome. Under intact conditions, a small part of telomeric DNA is lost at each cell division. When the critical limit of telomere length is reached, a cell undergoes senescence and apoptosis [12].

Thus, the length of telomeres can serve as a biomarker of biological clocks that determine the life span of cells and organisms. Some factors (refer to epigenetics; in particular, to individual's life style) can negatively affect the length of telomeres, that is, truncating them (causing DNA damage, and thus, affecting life span extension). These factors are: smoking, lack of physical activity, obesity, stress, toxic effects, etc. On the contrary, the factors such as calorie restriction, diet high in fiber/antioxidants; low-fat and low-protein food, food containing soy protein, as well as regular physical activity can potentially reduce the rate of telomere shortening and, hence, reduce the risk of age-related pathology and the rate of aging.

The enzyme telomerase is terminal transferase, ribonucleoprotein that adds species-specific nucleotide repeat sequences to the 3' end of telomeres. Telomerase is active in normal stem cells; however, it is inactive or its activity is very low in most normal somatic cells [12]. Thus, it is obvious that increasing its activity, using various methods, is one of the approaches to prolong life. These statements are illustrated in Fig. 3. As it can be seen, the telomere length is regulated by telomerase, which is active in germ (stem) cells, and is repressed in normal somatic cells, and is also reactivated in most cancer cells. Telomeres are lost during cell division, followed by senescence and death. With age, the length of telomeres decreases.

The theory of somatic mutations

Among the modern theories of aging, based on the assumption that DNA is the main target for age-related damaging agents, the theory of somatic mutations dominates. According to this theory aging is the result of the interaction of various endogenous and exogenous damaging agents with the cell genetic material, and the gradual accumulation of random mutations in the genome of somatic cells [13]. Damages of nuclear and mitochondrial DNA of somatic cells, such as point mutations, deletions and translocations, leads to activation or inactivation of specific genes involved in the regulation of the cell cycle and growth control. Accumulation of such mutations in various organs and tissues with age determines development of age-related pathology, including cancer.

Understanding the anti-aging mechanisms is associated with several aspects. First, researchers working in this field (researchers-biogerontologists) agree that these mechanisms are determined by genes (or groups of genes). It is evidenced, firstly, by differences in life span between species, which, as we know, differ in the genome primary structure. Secondly, as it has been shown recently, both the premature aging (progeria) symptoms and the time of manifestation of the most typical age-related pathology (cardiovascular: atherosclerosis, infarcts, strokes; neurologic: Alzheimer's disease, parkinsonism; hormonal disorders: insulin resistance) are determined by specific genome sequences, induced at certain stages of ontogenesis, at that, the time of this onset is determined by both endogenous and exogenous factors [14, 15]. Of note, both these directions (the connection between the slowing of aging rate and manifestations of typical age-related

pathology) are closely connected and are determined by the same genes.

Non-biotechnological (traditional) methods to extend lifespan

The influence of epigenetic (non-genomic) factors

Earlier the importance of some exogenous epigenetic factors that prolong life (moderation in everything — moderate lifestyle, balanced diet, physical activity, etc.) was underlined in [16]. Currently, these factors are commonly referred to non-genomic (epigenetic) ones. In the work, the aging process was considered as a gradual loss of tissue its ability to regenerate, what, in many respects, coincides with modern conceptions of nature of this process.

Cells in multicellular organisms, being genetically homogeneous, yet are structurally and functionally heterogeneous due to different gene expression. Many of these differences are realized during ontogenesis and further persist during mitosis. Such stable changes are considered as "epigenetic" since they are not inherited; they exist for a short time, and are not mutations that affect DNA structure [17]. Currently, two epigenetic molecular mechanisms are known: DNA methylation (a stochastic process that occurs with age) and histone modifications.

DNA methylation and its role in the processes of aging and extension of lifespan, as well as proteins that are responsible for similar effects (including typical age-related pathology) were described in [17]. A key

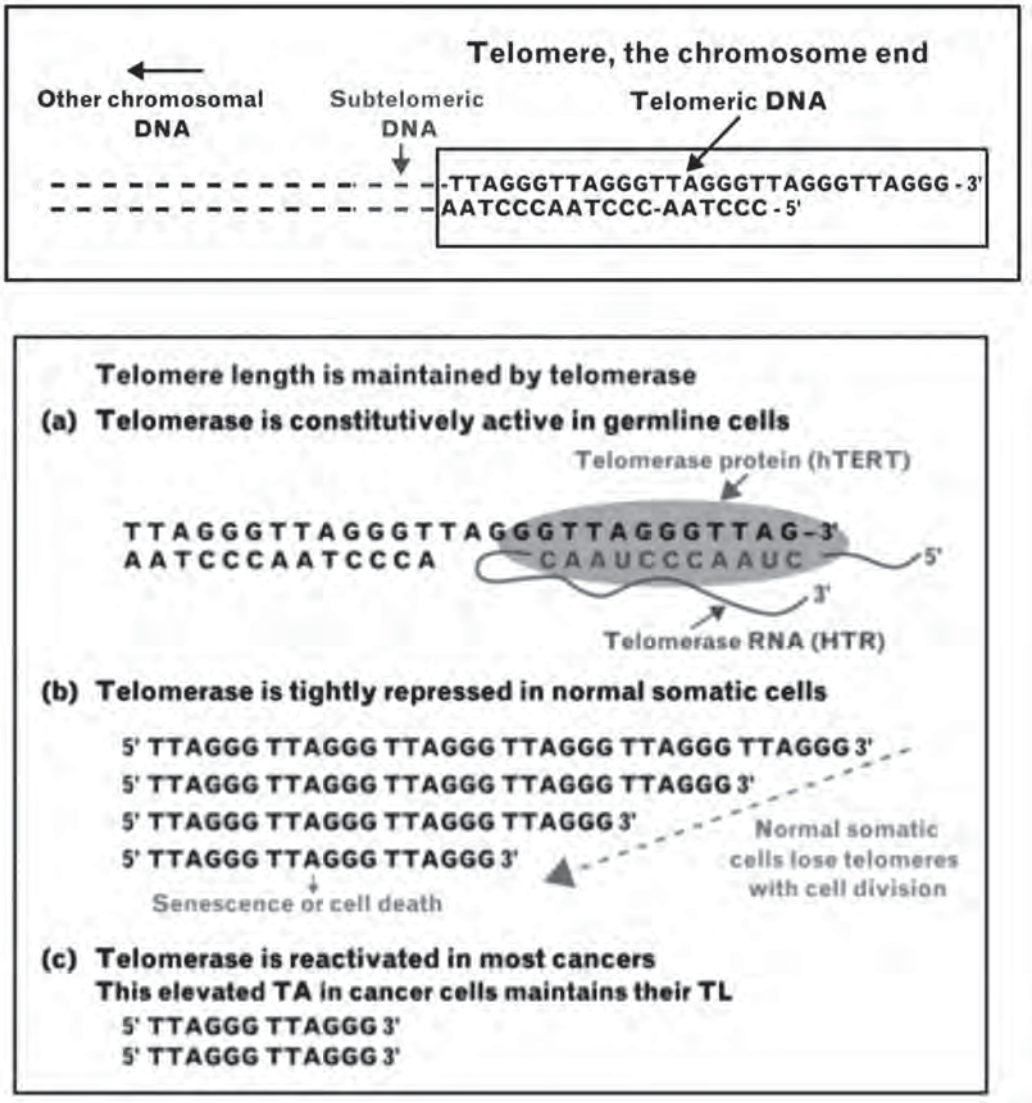

Fig. 3. **Importance of length of telomeric DNA in determination of cell life span:**
A— schematic structure of the region of telomeric DNA on a chromosome; *B* — alterations in the telomere length and in the activity of telomerase during cell life cycle and cancer [12]

conclusion reached in similar researches was that the organism reacts (via epigenetic mechanisms) to environmental influence by changing gene expression.

It was also concluded that genetic information of an organism is expressed differentially with respect to time and space through specific mechanisms. Specific adaptive genes remain active or silent by means of epigenetic mechanisms.

This is achieved by direct modification of the DNA region or proteins close to the given locus. Various factors, ranging from ontogeny and aging progression to a viral infection and diet, may be epigenetic activators of such modifications. To date, more attention is given to signal systems responsible for such epigenetic programming. It might be possible, knowing these mechanisms, to regulate, to some extent, the functioning of genome, including changing of lifespan, that is evidenced by the observed positive effect of epigenetic factors (physical activity, calorie-restricted, though adequate nutrition; positive emotions, etc.) or negative effect (smoking, alcoholism, long-term negative stress, etc.) on lifespan extension or reduction respectively.

However, at the same time, it should be noted that a genetic program, which is "recorded" in genome and unique for each individual, is the leading pattern of aging and prolongation of life, whereas epigenetic factors only modify realization of this program within certain limits.

One of the examples of the impact of epigenetic factors on lifespan is the effect of biologically active substances (BAS), in the first place — therapeutic agents — taking drugs.

Medicinal therapy— taking drugs (medicines based on medicinal plants; antioxidants, vitamins, adaptogens, probiotics, geroprotectors, senolytics)

Earlier in the study [16], the state connective tissue was considered as one of the factors of longevity. It was shown that the connective tissue disorders in old age led to metabolism violations in most important tissues and, as a result, to aging and death. The administration of antireticular cytotoxic serum (ACS) that intensified antitoxic response of connective tissue was expected to result in drastic extension of human lifespan.

Modern research gives hope that appropriate pharmacological preparations (agents) that are able, to some extent, to increase life span will be developed in the near future.

The author in the work [3] convincingly substantiated the prospects of using plant-based medicines for the prolongation of human life. This statement is based on high toxicity of synthetic drugs and small toxicity in phytomedicinal drugs. Moreover, the latter was found to have a wide range of pharmacological activities that allows using them upon various age-related diseases.

Now we can name some of known prototypes of drugs— geroprotectors (in addition to mentioned above): metformin and acarbose (used in the treatment of type 2 diabetes mellitus patients), rapamycin (an immunosuppressant that suppresses mTOR pathway), a protein called GDF11 (myostatin analog). Until recently, resveratrol and melatonin have also been in this list. In the future this list will be replenished with synthetic analogs of "starvation hormone"— FGF21, which increases level of adiponectin and thus, extends lifespan through AMP-induced protein kinase-, mTOR- and sirtuin-independent pathways [18].

One of such BAS capable of increasing life span can be curcumin, which is intensively studied recently. Although the work [19] focused mainly on biotechnology, it also summarized data on the prospects of the use of curcumin as a component for creating biologically active nanocomplexes with anti-inflammatory and antioxidant activity— potential drugs that prolong life. The effectiveness of such drugs depends on the solubility in water and the metabolism rate slowing in the body. Current direction is the development of methods for design of hydrophilic nanostructures based on curcumin to increase the time of its biological action. Such multifunctional nanocomplexes will facilitate targeted delivery of medicines to the sites, where pathological processes localized, and reduce their side effects, that is one of the key moments at development of geroprotectors.

In work [20], the effect of human growth hormone-2 (GH-2)— protein, consisting of 191 amino acid residues, expressed and incorporated into the proteoliposome, was studied. It was shown that such a structure can increase tissue stability, as well as the efficiency of tissue regeneration in the vertebrate animal model that makes possible to use it as a geroprotector.

More detailed information on the effect of BAS, including pharmacological agents, on genome-controlled aging and life span can be found in many works, e.g. in [3, 21].

Changing the way of life (maintenance and stimulation of the body's defense system)—physical activity

The significance of physical activity and, particularly moderate physical exercises, in slowing the aging process and increasing lifespan has been demonstrated and proven in numerous works. For example, it was shown in the recent study [22] that gradual muscle degradation, a decrease in muscle tone, and subsequent decrease in muscle function occur with age. Muscle mass begins to decline after 25–30 years of age and 40% of muscle is lost by the age of 80 years old. In turn, the quantitative loss in muscle occurs mainly due to loss in the cross-sectional muscle tissue that causes intensive decrease in the muscle length after 60–70 years of age. Regular physical exercises have a multifunctional anti-aging effect. The researchers in the field emphasize that, besides numerous attempts to develop novel medicines targeted to slow the aging process, more research efforts should be aimed at stimulating endogenous factors that increase lifespan, first of all, physical activity, decoding of molecular mediators underlying the rejuvenating effect of physical exercises on organism.

Alterations in the genome during physical training

In some recent researches [23, 24] endurance training was shown to affect the activity of thousands of genes and give a rise to the altered DNA and RNA copies. The results of the research, focused on the study of muscle memory, were published in the *PLOS Genetics*. Regular endurance training is beneficial for the human body: it can prevent cardiovascular diseases, diabetes, obesity and many other problems. The study of molecular processes in muscles consisted of the analysis of DNA and RNA copies in muscle tissue, before and after training. Thus, about 3400 RNA variants in association with 2600 variants of genes, changed in response to training, were found. Training causes an increase in the production of one RNA variant and a decrease in the production of another. This suggests that genes can change their functions in response to training and, for example, increase the synthesis of a certain variant of protein to the detriment of other.

The role of physical activity as an important epigenetic factor in slowing the aging and in lifespan extension was also shown in other works. Thus, the research conducted as randomized clinical trial in Australia was aimed to analyze effect of several physical activity programs on the rate of aging, evaluated on the basis of several integral indices, in patients aged over 70 years [25]. This work was carried out within the framework of a three-group, randomized, parallel clinical trial. The control group had a usual sedentary lifestyle. The base indices were assessed at 6 and 12 months after the beginning of the research. The obtained results were computer processed. As the participants Sydney residents were chosen. The main conclusion of this work was: the performance of both common strengthening exercises and special exercises of power fitness (if the patients have the necessary functional capabilities) is essential epigenetic factor for slowing down the aging processes and attenuating the age-related pathology.

Protein-balanced but calorie-restricted diet and lifespan

Another epigenetic exogenous factor affecting lifespan is a calorie-restricted, but providing needed nutrients, diet. It was found in [26, 27] that diet low in calories increase the maximum and average lifespan of rats and mice. In recent years, this model, due to its simplicity and reproducibility, has become the most widely used model in studying the fundamental mechanisms of aging and prolongation of life. The calorie restriction diet was also found to extend lifespan of fish, amphibians, daphnia, insects and other invertebrates. It is still unknown whether the low-calorie diet slows the aging or prolongs life in human. Preliminary results of three large-scale experiments on primates (mainly on rhesus monkeys) showed that at least some of the physiological effects namely, a decrease in the level of blood glucose and insulin, a decrease in body temperature and energy expenditure were also observed in monkeys [28–30].

It was demonstrated that the geroprotective effect is attained by reducing the total calorie consumption, not by selective nutrients exclusion [29]. It was examined about 300 parameters, including behavior and learning, immune response, gene expression, enzyme activity and hormone action, glucose tolerance, DNA repair efficiency, protein synthesis rate in rats on low-calorie diet and alterations in 80–90% of them indicated slowdown in aging rate [30]. It is important to note that such a diet stimulates apoptosis, which eliminates pre-neoplastic cells in body tissues, slows the accumulation of mutations in them, as well as the development of other age-related pathology.

It was suggested that such factors as a decrease in body fat, slowdown in growth, neuroendocrine or immunological age-associated shifts, increased DNA repair, a decrease in protein biosynthesis rate and gene expression, as well as body temperature, basal metabolism rate, and oxidative stress play the main role in mechanisms of life prolongation at calorie-restricted diet. Some of these factors appear to be of less importance than others. The calorie-restriction started at the age of 12 months was found also to increase the maximum lifespan of monkeys [29]. The effect of reduction in body fat itself on maximum lifespan has not yet evidenced, since there is no obvious connection between a reduction in body fat and maximum lifespan in normally fed rodents, however in calorie-restricted animals this connection is directly proportional [29, 30]. The data on role of a decrease in metabolism rate at calorie-restricted diet are rather contradictory.

The most significant effect of calorie restriction was found to be a decrease in rate of free radical processes. It was observed that, in calorie-restricted rodents, the age-related increase in the rate of superoxide and H_2O_2 formation, as well as the age-related decrease in cell-membrane fluidity slowed, and, thus, oxidative damages reduced. Previously similar patterns were established in other experimental models of aging [31].

The activity of antioxidant enzymes in various tissues is not altered uniformly; however malnutrition decreases tissue vulnerability to accelerated oxidative reactions *in vitro*. The greatest protective effect of calorie restriction diet was observed in postmitotic cells of brain, heart and skeletal muscles. This is understandable, given the fact that the amount of DNA damages in postmitotic tissues is higher than in mitotically active ones [10, 11]. At a calorie-restriction regimen, the age-related decrease in the function of the epiphysis cerebri (whose hormones play an important role in the organism's antioxidant reactions and exhibit distinct geroprotective effect) does not occur.

Biotechnological methods to extend life of humans and multicellular animals

It is necessary to stress that in this review just the main molecular-genetic methods (from all existing biotechnological approaches) for lifespan extension, which ensure preservation of the general and individual features of certain type of organisms, will be considered. The data on the prospects of prolonging life of plants with the aid of biotechnological approaches, as well as the data on the extension of human lifespan with the use of medicines (biopreparations) can be found in the monograph by V. A. Kunakh [3].

Genetic engineering, gene therapy (including genome editing and reprogramming)

Aging and lifespan are extremely complex, genetically programmed processes, which, nevertheless, can be affected by certain epigenetic factors, and thus, individual's lifespan can be changed, in particular, towards its prolongation.

Clinical trials of genetic engineering techniques in aging and extension of lifespan (gene therapy) have been conducted since the 1990s, and are still under study. This area of research draws high attention and is widely discussed due to possibility of very serious interventions in the human body. Gene therapy is aimed to prevent or treat human diseases by altering the related gene expression. The target for gene therapy can be either somatic cells or gametes (ova or sperm). The genome modifications in somatic cells are not inherited. In gene therapy of sex cells, modifications in genome function are transmitted to next generations. This type of gene therapy has not been sufficiently studied yet, although similar researches on animals and humans are actively discussed [32].

It was shown in various experimental models that interventions in genome can lead to an increase in life longevity, even in laboratory conditions [33]. In general, such interventions involve partial or complete switching off of genes and inhibiting of gene products that play a well-established important role in metabolic processes.

Such genetic interventions are easy to apply in human, irrespective of their effects on growth, development, maturation, reproduction and other characteristics. Studies on the correlation between single nucleotide polymorphism and multiple polymorphism (haplotype) in human genes responsible for life longevity allowed to identify several genes whose frequencies increase or decrease with age. Whether genetic remodeling can be achieved by epigenetic factors that effectively determine the life course and lifespan of individuals still remains unknown.

Genome reprogramming via epigenetic interventions is considered as the most important biotechnological approach to extent lifespan. Some researchers [34] used for this purpose induced pluripotent stem cells (iPSC). It was noted that aging is the main risk factor for many diseases. Studies *in vitro*

demonstrated that cellular reprogramming to pluripotency allowed to reverse the age-related degradation processes; however such effects *in vivo* experiments have not been revealed. In this work authors reported that partial reprogramming by short-term cyclic expression of *Oct4*, *Sox2*, *Klf4* and *c-Myc* (OSKM) diminishes the cellular and physiological signs of aging and leads to prolongation of lifespan in mice with progeria (rapid aging syndrome). Similarly, expression of OSKM *in vivo* led to remission of various chronic metabolism and muscular disorders in very old mice.

The finding that somatic cells can be transformed into a pluripotent state by induction of reprogramming factors has a great potential for therapy and modeling of human diseases. There are controversial data regarding these cells, regarding the extent to which telomeres are elongated, telomerase activity is reprogrammed, and mitochondria are reorganized. Though, some research groups reported that the reprogramming process decreases with age and is inhibited by age-activated genes, others successfully created similar cells from senescent ones [35, 36].

Approaches to reprogramming the genome functioning are based on totipotency of embryonic stem cells.

Insulin-like growth factor (IGF-I) is considered as a potential neuroprotective agent in the brain and spinal cord [37]. Intracerebroventricular IGF-I gene therapy was shown to be an effective strategy for increasing the level of this factor in cerebrospinal fluid (CSF). Since aging in rats manifests itself as motor impairment, the authors applied IGF-I gene therapy to very old rats (30–31 months) and evaluated its effect on motor function. Recombinant adenovectors (RAds) expressing either a green fluorescent protein (GFP) or rat IGF-1 were used. Injections into the lateral fourth ventricle, as well as the spinal cord led to transgene expression in the ependymal cells. In RAd-GFP-injected rats compared to the control uninjected rats, a significant increase in the CSF IGF-1 level was detected. The expected age-related motor impairment in old rats was confirmed by motor tests. However, the appropriate gene therapy during 17 days showed a significant improvement in this parameter in aged, but not in adult animals. These results indicate that IGF-1 molecule can be used as a geroprotector in the brain and spinal cord, and that ependymal route can be effective approach for protective IGF-I gene therapy for the aging central nervous system.

As it was stated in [38], there is a large number of evidence that the age-related decline in ovaries function in female rats is defined by abnormal response of the nervous system cells to the hormonal signal. Since IGF-I acts as a signal allowing proper response of GnRH (gonadotropin releasing hormone) system to the estrogen-positive effect, and the IGF-I level in the hypothalamus of aging rats is reduced, the authors assessed the effectiveness of long-term IGF-1 gene therapy targeting mediobasal hypothalamus of aging female rats to prolong the ovarian cyclicity and preserve the ovarian structure. Although menstrual cycle disorders and occurrence of enlarged ovaries without yellow bodies were observed in control, such abnormalities in the experiment animals were not observed. The level of luteinizing hormone was found to be higher in serum of experimental animals compared to control, whereas hyperprolactinemia was lower. These results indicate that IGF-1 gene therapy prolongs the ovarian function in aging rats. Therefore, application of hypothalamic multigene therapy assisting in activation of numerous regulatory factors is expected to allow prolonging normal ovarian function in rats. Although senescence of reproductive system in rats occurs in the middle of life cycle, in nonhuman primates, such as rhesus monkeys, this process occurs in later life, these interspecies differences are not an obstacle to understanding the hypothalamus-controlled mechanisms that trigger aging of reproductive system, and thus, gives us hope to elucidate such mechanisms in humans.

Another cell reprogramming approach to impair or reverse the aging process is the transfer of nuclear material from intact cells to damaged cells [39]. In this work, authors applied such technique on mouse oocytes, which rapidly lose their ontogenetic potential after ovulation. This phenomenon, called oocytes postovulatory aging, is often accompanied by such phenotype manifestations as cytofragmentation, abnormal spindle shape, and chromosomal imbalance. The authors attempted to reconstruct mouse oocytes using somatic cell nucleus transfer (SCNT)to investigate the effect of the nuclei from these cells on oocyte aging processes. The aging of SCNT oocytes was found to be slowed. The aging of these cells was slowed down in the conditions of the transfer: in control cells, cytofragmentation occurred 24 h after oocyte collection, whereas, in the SCNT cells— after 48 h, suggesting a positive effect of the transfer on cell physiology. In aging cells, there were

no differences in acetylated α-tubulin (Ac-Tub) and α-tubulin (Tub) between control and SCNT oocytes, but the latter did not have astral microtubules. In the experiment there was a scatter of chromosomes in form and location. Thus, the differences in the modified cells may indicate that they not only contain epigenetically altered nuclei, but differ in their physiology from the control ones.

Cell therapy using stem cells

An overview analysis of the use of stem cells to prolong life was given in [40]. In this case stem cell therapy is based on the introduction of immature stem cells, which can differentiate into required cells that were damaged during the aging process, or can repair them. Stem cells in organism are the cell pool designed specifically to reach these goals. The research on stem cells showed that these cells have sufficient potential to differentiate into various cell types and, therefore, can be considered as a sort of reparative system in the body. Stem cells can divide, in theory, for any length of time (through the whole life) replacing damaged cells, which are unable to function properly.

It was shown in [41] that stem and progenitor cells undergo the natural aging process typical for all somatic cells. The authors emphasized that tissue-specific stem cells were, at first, believed to be immortal; however, the recent studies have shown that effectiveness of stem cells is limited by natural aging.It means that the age of the donor should be taken into account at the therapy with these cells. Although stem cells from the old organism retain some activity, the age-related changes in them and in their microenvironment inhibit the regenerative potential. The effect of aging on various tissue populations of stem cells differs in degree, and depends on endo- and exogenous factors, including systemic changes associated with the immune system modifications. The authors analyzed the mechanisms of stem and progenitor cells aging and techniques that are commonly used to identify signs of aging. The influence of aging on the proliferative potential, differentiation and clinical use of stem cells was studied. Particular attention was paid to aging of embryonic, mesenchym, and induced pluripotent stem cells with an emphasis on the mechanisms of their aging and rejuvenation.

As it was underlined in the work [42], direct reprogramming of somatic cells into induced pluripotent stem cells (iPSCs) provides a unique opportunity to use patient-specific stem cells (hESCs) in tissue replacement therapy without ethical dilemma over human embryonic stem cells (hESCs). However, cellular senescence, which determines aging of the organism and limits its lifespan, is considered as an impediment to such iPSCs application. The authors showed, using an optimized protocol, that cellular senescence does not limit reprogramming and that age-related cell physiology is reversible. They demonstrated that iPSCs generated from senescent cells have characteristics of young cells regarding the telomere size, gene expression profiles, oxidative stress and mitochondrial metabolism. By these parameters they are not distinguishable from hESCs. Thus, pluripotent cells derived from senescent cells are capable of redifferentiating into fully rejuvenated cells. These results provide a new view on iPSC technology and indicate this can be a new method in regenerative medicine for aged patients.

In another paper [43] it was stated that, since aging is a major risk factor for the onset of many human diseases, *in vitro* generation of neurons is a promising approach to modeling age-related changes in the brain. However, the modeling of aging in differentiated human neurons appeared to be very difficult. Neurons were obtained from donors of different ages using iPSC-based reprogramming technique, as well as by differentiation or by direct conversion into induced neurons (iNs). While iPSC and derived neurons do not bear “mark of age” at the molecular level and iNs retain age-associated transcriptional profiles, it was possible to reveal age-related decrease in the transcription of the nuclear transport receptor RanBP17. An age-dependent loss of nucleoplasmic compartmentalization (NCC) in donor fibroblasts and corresponding iNs, and a decrease in the transcription of nuclear transport receptor RanBP17, that suppress NCC in young cells, while iPSC-rejuvenation restored the altered NCC in aged cells were found in this research. These results showed that iNs retain age-related changes at the molecular level, and this allows modeling the aging process *in vitro*, suggesting an age-related decrease in NCC as an important mechanism of human aging.

The ability to repair skeletal muscles is gradually lost with age. Such a repair requires functionally active muscular satellite (or stem cells) and progenitor cells. A positive correlation between a decrease in the number of stem cells and a gradual loss in muscle strength during aging was observed [44]. Recent studies

have established a link between a loss of stem cell numbers and the entering in old age, or the loss of self-renewal ability due to an inability to maintain mobility resulting from depletion of the stem cell pool. It was previously shown that administration of certain factors from blood of young animals can restore function of muscle stem cells (SMSCs). However, cells in a presenescenent stage were found to be resistant to the impact of these factors when transplanted into a young cell medium. Entering this stage leads to loss of autophagy, which in turn leads to an increase in reactive oxygen species (ROS) level and epigenetic modification at CDKN2A locus due to an increase in H2Aub, leading to a loss of the regulatory function of aging biomarker p16ink4a. However, the number of presenescent SMSCs can be restored to the level in young animals by agents that stimulate autophagy, such as mTOR inhibitor ripamycin. Autophagy plays a key role in SMSC homeostasis. These results can be used for development of old age therapy aiming to destroy cells expressing p16ink4a, since such therapy could help destroy a reservoir of non-functional regenerative stem cells. It was shown that in humans, loss of ability to SMSC self-renewal is associated with a decrease in the expression of growth factor. Growth factor downregulation is caused by DNA hypomethylation at the SPRY1 gene locus that lead to inability to maintain stem cells population. This hypothesis suggests that during humans aging, loss in the number of stem cells occurs, but remaining SMSCs are still in presenescence stage during transition into the very old cells [44].

The results of similar research are presented in [45]. The paper emphasizes that an individual while aging develops, gradually loses muscle strength and the ability to repair skeletal muscles. Such muscle repair requires a functional skeletal muscle satellite or stem cells (SMSCs) or progenitor cells. A decrease in number of stem cells and progressive dysfunction correlate with the observed decline in muscle strength with age. The authors attribute this to a decrease in number of stem cells and loss of their functional state due to their entry into presenescence phase, or loss of their ability to self-renewal due to stem cell pool depletion, leading to immobility. In this research it was also shown that administration of factors from blood of young animals, or similar procedures can facilitate preserving the SMSC function. However, at that, cells in presenescenent phase and factors of refractoriness to rejuvenating signals also enter to a medium containing similar factors from young cells. Though, SMSCs in presenescenent phase can be rejuvenated by agents that stimulate autophagy, such as rapamycin inhibitor mTOR. Autophagy plays a key role in the homeostasis of SMSC. These results are related to cenolytic therapy, the aim of which is to attempt to destroy cells expressing p16ink4a, due to the destruction of a reservoir of potentially regenerative stem cells. In this work it was also found that loss of the SMSC ability to self-replication in humans is primarily associated with a decrease in sprouty1 expression. DNA hypomethylation at SP RY1 gene locus led to a decrease in sprouty1 regulation that resulted in an inability to maintain immobility and to depletion of the stem cell pool. The authors hypothesized that senescence in humans begins with the loss of stem cell mobility and therefore, the pool of these cells in presenescent phase is considered to be a target for the therapy [44].

In work [46] it was emphasized that the molecular mechanisms of stem cells senescence, resulting in a decline in their number and function, are poorly understood. The authors demonstrated that the ability of mouse muscle stem cells to self-renewal reduced in the progenitor population. They linked aging to an increase in methylation of the SPRY1 gene, a known regulator of stem cell mobility at aging. Replenishment of the reserve cell pool was modulated experimentally by demethylation or knockdown of siRNA SPRY1. The authors suggested that SPRY1 suppression by age-related methylation in humans inhibits the replenishment of the reserve muscle stem cell pool that is one of the causes of a decreased regenerative response with age. The researchers also assumed that stem cells in humans do not undergo aging.

The contribution of mitochondria-based biotechnologies

Relevance of both the free radical theory of aging and the role of mitochondria in these processes was confirmed in work [47]. The authors used a transgenic system (FLP-out) based on yeast FLP recombinase that allows overexpression of manganese-dependent superoxide dismutase (MnSOD) in adult *Drosophila melanogaster*. With this system, by brief heat pulse (HP) induction, regrouping and subsequent overexpression of transgenic MnSOD was reached in young and adult flies through their lifetime. Control flies and flies exposed to heat pulse had an identical genetic background. In six transgenic lines, overexpression reached 75% compared to control. The flies' lifespan increased

proportionally to this indicator. An average increase was 16%, with the maximum for some lines of 30–33%. The maximum increase was on average 15%, and in one line— 37%. Simultaneous overexpression of catalase gene did not exhibit a positive effect on this parameter that is consistent with previous results indicating an excessive amount of catalase in adult flies, regardless of the life cycle phase. Overexpression of copper-zinc-dependent enzyme (Cu/ZnSOD) also increased mean and maximum life span.

The authors explained these findings by one of the current theories of aging that suggests the intensity of natural positive selection decreases with age making possible age-related accumulation of harmful mutations resulting in damage to essential cells' macromolecules, primarily DNA [48]. This, in turn, induces an imbalance between the rate of accumulation of damage and the possibility of its repair. In this process ROS, as it is posited in one of the most widely recognized theory of aging, have a leading role to play. Superoxide dismutase and catalase are antioxidant enzymes in every cells of an organism. Mitochondrial superoxide is considered to be the main radical producer, thus, superoxide dismutase converts it into hydrogen peroxide, and hydrogen peroxide— by catalase into molecular oxygen and water. Due to insufficient cell defense against free radicals with, free radical induced damage to proteins and DNA is accumulated with age causing vast majority of age-related pathologies. In particular, this statement is true for fruit flies.

Development of biotechnology allowed researchers to find further evidence of accumulated with age free-radical damages using transgenic organisms with high activity of antioxidant enzymes. Furthermore, it was also able to prove the positive impact of this approach on life span (in the direction of its increase [47]). It is interesting to note that an increase in life span depended on the type of transgenes. In tissue-specific or inducible transgenic systems with Cu/ZnSOD overexpression, an life span increase was found to be 48%. It is evidenced that the level of Cu/ZnSOD-enzyme (that increased at overexpression), but not the level of catalase (that is already rather high to be such limiting factor) was the limiting factor in this case.

Thus, the aging process in multicellular organisms is an adaptive mechanism of evolution, aimed a preparation of organism excretion from the population to prevent clogging of the gene pool with the genes of old organisms that carry harmful mutations, and that does not have beneficial mutations of offspring allowing adapting to the variable environment.

Special genetic program recorded in each individual's genome for aging process regulation. Despite common features, this program is run in each person by its own way differ as qualitatively (various age-related diseases leading to death), and also quantitatively (different life span, the concept of "calendar" and "biological" age). This program is accomplished via affecting relevant genes ("gerontogenes") by both endogenous (genomic) and exogenous (epigenetic) factors. They affect gerontogenes through numerous signaling pathways and systems, in which the relevant proteins encoded by nuclear genome involve.

The effect of genome factors is carried out through the corresponding so-called "senile" pathologies, named so because their emergence and rate increase with age. These include cardiovascular, oncological, neurological, endocrinological pathology, etc. Their implementation is carried out by so-called "silent" genes, activated by endogenous factors — gerontogenes (genetic predisposition inherited from parents — heredity), and by harmful epigenetic factors (smoking, alcoholism, chronic stress and some others — variability).

It is obvious that since the genetic aging program is encoded in the nuclear genome [49], the main targets of the damaging factors, leading to a reduction of life span, are DNA, nuclear chromatin and chromosomes. There are numerous proofs of the postulate that the primary and the main target of aging is DNA and the theories of aging based on this postulate, the main of which were considered in the first part of this review. Therefore, all attempts to slow and reverse the aging process are focused on DNA protection by either stimulation of natural DNA repair, or replacing damaged DNA sites using biotechnology techniques.

Thus, aging is rigidly programmed in genome of the organism. "Hacking" this genetic program is very difficult, but possible.

There are several approaches to reach this goal, which can be divided (that is done in this work) into traditional, non-biotechnological and biotechnological.

The traditional, non-biotechnological approaches include a number of long time known epigenetic impacts. Nevertheless, these approaches do not allow substantially extend life span (by only up to 15%) [3].

The biotechnological approaches include genetic engineering methods that has the potential to "edit" the genome. This method, the most progressive and intensively developed, is believed by researchers working in this field to allow "reversing" the genetic aging program, that is, rejuvenating the body. The biotechnological approaches also include the gene therapy method, which allows researcher to replace damaged genes and introduce new ones that also have potential in prolongation of life. However, the results obtained with the application of these approaches are rather modest given the presence of numerous side effects observed at the time of their application.

This group of approaches also includes a method with the use of stem cells. Stem cells exhibit reparative impact on the organs and the body as a whole replacing damaged cells and thus, have a rejuvenating effect. This approach became possible owing to the production of pluripotent stem cells from embryonic stem cells.

However, the achievements of this method in questions of prolonging life are rather modest. So, this method has also not give yet the expected results in the problem of life span extension.

In conclusion, it should be noted that the biotechnological approaches to extend life span of multicellular organisms, primarily human beings, considered in this paper, have only recently been applied and their development is quite obscure, and achievements in practical application are less than modest. However, there is no alternative to their use.

Therefore, theoretical development and possibility of successful practical application of these methods require much attention and appropriate funding [3].

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СУЧАСНІ БІОТЕХНОЛОГІЧНІ ПІДХОДИ ДО ЗБІЛЬШЕННЯ ТРИВАЛОСТІ ЖИТТЯ ТВАРИН І ЛЮДИНИ

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Метою роботи було проаналізувати сучасні дані, що стосуються проблеми збільшення тривалості життя багатоклітинних тварин і людини. Наведено уявлення про процеси старіння та продовження життя. При здійсненні аналізу акцент був зроблено на генетичних механізмах старіння і головним чином, біотехнологічних підходах (генетична інженерія, генна терапія, використання стовбурових клітин, репрограммування геному) до збільшення тривалості життя багатоклітинних організмів. Для порівняння наведено деякі традиційні методи (лікарська терапія, фізичні вправи, калорійно обмежене харчування). Проведений аналіз дає підстави зробити висновок про перспективність та переваги застосування біотехнологічних методів збільшення тривалості життя порівняно з традиційними.

Ключові слова: старіння, збільшення тривалості життя, стовбурові клітини, репрограммування геному.

СОВРЕМЕННЫЕ БИОТЕХНОЛОГИЧЕСКИЕ ПОДХОДЫ К УВЕЛИЧЕНИЮ ПРОДОЛЖИТЕЛЬНОСТИ ЖИЗНИ ЖИВОТНЫХ И ЧЕЛОВЕКА

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Целью работы было проанализировать современные данные, касающиеся проблемы продления жизни многоклеточных животных и человека. Приведены представления о процессах старения и продления жизни. При осуществлении анализа акцент был сделан на генетических механизмах старения и, главным образом, биотехнологических подходах (генетическая инженерия, генная терапия, использование стволовых клеток, репрограммировние генома) к продлению жизни многоклеточных организмов. Для сравнения описаны некоторые традиционные методы (лекарственная терапия, физические упражнения, калорийно ограниченное питание). Проведенный анализ позволяет сделать вывод о перспективности и преимуществах применения биотехнологических методов продления жизни по сравнению с традиционными.

Ключевые слова: старение, продление жизни, стволовые клетки, репрограммирование генома.