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Possibilities of gene, cellular and pharmacological approaches to correct age-related changes

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ABSTRACT

Improvement of the human habitat has led to an increase in average life expectancy. Long life goes hand in hand with old age, which reduces the quality of human life and it is an acute social problem. Thus, the search for approaches that can improve the quality of life, the ability to live it without age-related diseases is an extremely urgent task. Aging of the body begins with the aging of cells, in which the activation of the aging process occurs through the induction of specific signaling pathways, which irreversibly divides the life of any cell into "before and after". Aging cells are able to influence their microenvironment, secreting more inflammatory signaling molecules and inducing pathological changes in neighboring cells. The accumulation and long-term preservation of aged cells lead to deterioration of the condition of tissues and organs, and ultimately to a decrease in the quality of life and an increased risk of death. Among the most promising approaches to the correction of aging and age-related diseases are pharmacological, gene and cell therapy. Increasing the expression of aging suppressor genes, using certain populations of native and genetically modified cells, as well as senolytic drugs can help delay aging and associated diseases for a more distant future. This review examines currently studied approaches and achievements in the field of anti-aging therapy, in particular gene therapy using adeno-associated vectors and approaches based on cell therapy.

Keywords: aging; senolytic; senescent cells; anti-aging therapy; cell therapy; gene therapy.

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Возможности генных, клеточных и фармакологических подходов для коррекции возрастных изменений

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АННОТАЦИЯ

Улучшение среды обитания человека привело к увеличению средней продолжительности жизни. Длинная жизнь идёт рука об руку со старостью, которая снижает качество жизни человека и представляет собой острую социальную проблему. Таким образом, поиски подходов, которые способны улучшить качество жизни, возможность прожить её без возрастных заболеваний представляет собой крайне актуальную задачу. Старение организма начинается со старения клеток, в которых происходит активация процесса старения через индукцию специфических сигнальных путей, что необратимо делит жизнь любой клетки на «до и после». Стареющие клетки способны влиять на своё микроокружение, секретируя больше воспалительных сигнальных молекул и индуцируя патологические изменения в соседних клетках. Накопление и длительное сохранение постаревших клеток приводят к ухудшению состояния тканей и органов, а в конечном итоге к снижению качества жизни и повышению риска смерти. Среди наиболее перспективных подходов к коррекции старения и возрастных заболеваний — фармакологическая, генная и клеточная терапия. Повышение экспрессии генов-супрессоров старения, использование определённых популяций нативных и генетически-модифицированных клеток, а также сенолитических препаратов способно помочь отсрочить старение и связанные с ним заболевания на более отдалённую перспективу. В представленном обзоре рассмотрены исследуемые на сегодняшний день подходы и достижения в области антивозрастной терапии, в частности генная терапия с использованием аденоассоциированных векторов и подходы, основанные на клеточной терапии.

Ключевые слова: старение; сенолитик; сенесцентные клетки; антивозрастная терапия; клеточная терапия; генная терапия.

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INTRODUCTION

Population aging is a serious societal problem, especially in developed countries where the proportion of elderly people is increasing annually [1]. The idea, which was first proposed by Peter Medawar and later embodied in the antagonistic pleiotropy hypothesis of American evolutionary biologist George Williams in 1957, remains popular and mainly explains the evolution of aging [2]. From the perspective of classical medicine and common logic, aging is a degenerative, progressive process that leads to tissue dysfunction and death [3]. The signs of aging that manifest at the cellular and molecular level are common to all organisms and include genomic instability, telomere attrition, mitochondrial dysfunction, epigenetic noise, and stem cell depletion and dysfunction (Figure 1) [4].

Senescent cells can be eliminated by the immune system under physiological conditions, promoting processes such as tumor suppression, embryogenesis, differentiation, and wound healing [5]. Currently, targeted aging of cells in malignant neoplasms is under investigation; the removal of uncontrolled tumor cells from tissues through their controlled aging and subsequent apoptosis may become the key to cancer treatment [6].

The promising approaches to rejuvenate the body include gene and cell therapies combined with pharmacological interventions aimed at rejuvenating senescent cells, eliminating senescent dysfunctional cells, and blocking signaling pathways involved in cellular aging.

This review focuses on gene therapies based on recombinant adeno-associated viruses (AAVs) and drug and cell therapies.

USE OF SENOLYTIC AGENTS

Senolytic agents eliminate senescent cells, which are cells that can no longer function but continue to exist and negatively affect surrounding healthy cells. Senolytic research is aimed at discovering substances that can induce apoptosis (programmed death) of senescent cells, thereby preventing their negative effects on healthy cells and tissues.

Over 46 potentially senolytic compounds that target anti-apoptotic pathways in senescent cells have been identified, including the SRC tyrosine kinase inhibitor dasatinib, which has been approved and widely used since 2006, and the natural flavonoids quercetin and fisetin [7]. These agents are first-generation senolytics and act on various molecular targets and signaling pathways, such as tyrosine kinase receptors, growth factors, ephrin B1, SRC family kinases, phosphoinositide 3-kinase (PI3K) /protein kinase B (AKT) signaling pathway, heat shock protein 90 (HSP-90), members of the BCL-2 family (apoptosis regulators), caspases, and p53 [8].

Dasatinib, a well-known senolytic agent, which was originally developed to treat leukemia, has been shown to be effective in killing senescent cells. Type 2 diabetes mellitus is known to be an age-related disease, and insulin resistance accelerates beta cell aging [9]. Senolysis of $p21^{high}$ cells in

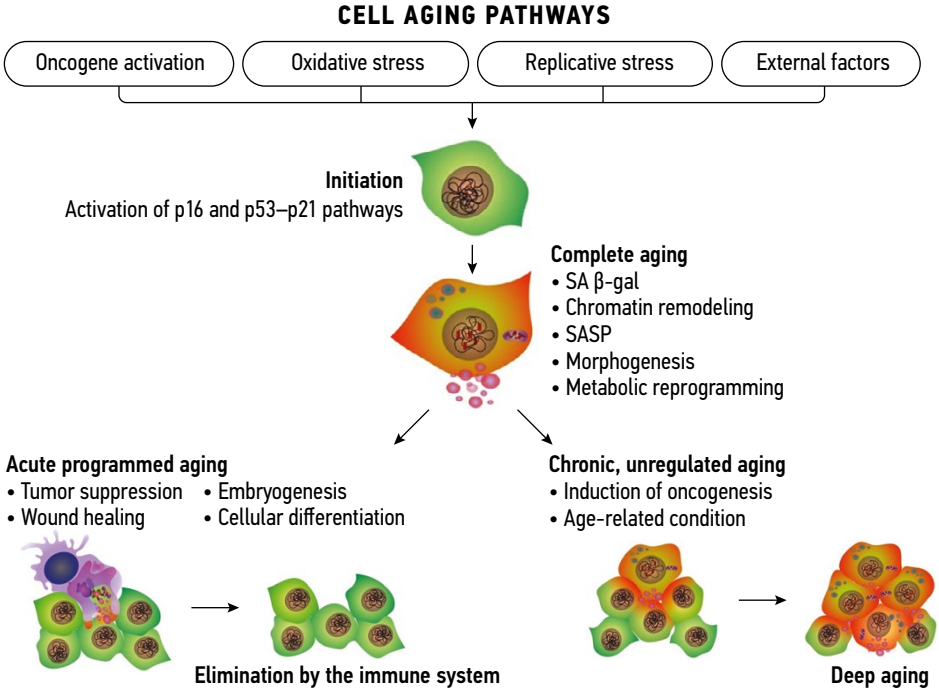

Fig. 1. General scheme of the cell aging pathway. The impact of a number of factors triggers the activation of the p16 and p53–p21 signaling pathways, which leads to complete aging of the cell, which can be completed by the elimination of the cell from the tissue by the immune system or by long-term preservation of the pathologically functioning cell and its pathological effect on the microenvironment in the tissue

human fat ex vivo xenografted into immunodeficient mice using a cocktail of dasatinib + quercetin reduces insulin resistance [10].

In addition, to dasatinib and quercetin, other agents have great potential, and some of them are antitumor agents. For example, rapamycin (sirolimus) and its analogs (i.e., everolimus, temsirolimus, and deforolimus) bind the FKBP12 cytosolic protein and inhibit the mammalian target of rapamycin (mTOR) complex 1, thereby reducing malignant neoplasm incidence in patients after transplantation [11].

mTOR is a serine/threonine kinase that is crucial in the regulation of cellular metabolism and growth by phosphorylating various substrates in response to growth factors, stress, nutrient availability, and other stimuli [12]. Therefore, targeting the mTOR pathway is a promising way to slow aging. Adding the FOXO4-related peptide to senescent human IMR-90 fibroblasts reduces their viability more than 10-fold compared to non-senescent IMR-90 fibroblasts or other cell types.

The mechanism of action of the FOXO4-related peptide is characterized by preventing the binding of the transcription factor FOXO4 and p53 in the nucleus, which leads to the release of the p53 protein into the cytosol and initiation of caspase-dependent apoptosis of aging cells [13].

Hsp90 is a cytoplasmic protein that prevents AKT proteasomal degradation and promotes tumor cell survival. Hsp90 inhibitors are being actively investigated as therapeutic agents for malignant neoplasm treatment [14]. In addition, to antitumor activity, Hsp90 inhibitors such as geldanamycin induce senolytic activity against senescent cells [15]. However, further research is required to find the most effective combinations and test their safety in humans before these agents can be widely used in clinical practice.

Table 1 lists the most common senolytic agents.

CELL AND GENE/CELL THERAPY

Cell therapy is a promising approach in treating age-related diseases. It involves the use of the regenerative and immunomodulatory properties of cells to restore tissue and functions and improve well-being. However, in antiaging cell therapy, some specific aspects should be considered when selecting a treatment strategy.

Notably, the ability of tissues to regenerate decreases with age. A study showed that when bone marrow-derived cells were used, young recipients showed statistically better skin healing than older recipients [31]. This characteristic manifests at the level of individual organs. Another study reported that in adult recipients, young donor kidneys demonstrate better engraftment and lower rejection risk than older ones [32]. Moreover, organs from older donors had a negative effect on recipients, accelerating aging of their bodies [33].

Skin xenografts from elderly human donors transplanted into young immunodeficient mice showed morphological rejuvenation within 1 month of transplantation. However, within the following year, skin rejuvenation regressed and the transplanted areas in the mice returned to their pretransplant condition [34].

Data from transplantation studies are consistent with and supported by *in vitro* studies. Co-culturing epithelial progenitors isolated from aged mice with mesenchymal stem cells (MSCs) or membrane vesicles isolated from MSCs of young mice resulted in “old” epithelial progenitor rejuvenation [35].

Cardiosphere-derived cells, which are cardiac progenitor cells from neonatal rat hearts, have been shown to reproduce the juvenile gene expression pattern when injected into the hearts of aged animals. Furthermore, telomeres in heart cells were longer in animals after transplantation of cells isolated from cardiospheres [36].

Direct brain injection of cerebrospinal fluid from young mice induced oligodendrocyte proliferation and long-term memory consolidation in aged mice [37]. These data indicate that using cells isolated from young donors or placing senescent cells in an environment containing factors characteristic of a young organism may be beneficial in achieving tissue rejuvenation.

The use of stem cells has proven to be effective owing to their ability to differentiate into different types of cells and regenerate or replace damaged tissues and organs [38]. For example, adding MSCs to the standard therapy of the early phase of acute severe pancreatitis in middle-aged patients (i.e., approximately 44 years) allows a targeted and relatively rapid action on abnormal homeostatic processes. It inhibits toxic reactions, restores immune response, and improves microcirculatory flow [39].

Positive results were obtained using bone marrow cells expanded *in vitro* and injected into the defect site along with biphasic calcium phosphate granules, which induced new bone formation. Additionally, the volume of regenerated bone was sufficient to place a dental implant in patients aged 52–79 years with satisfactory esthetic and functional results and no side effects (NCT02751125) [40].

Moreover, MSCs and adipose-derived stem cells are effective alternatives for reducing or slowing the aging process of the face [41]. In a study, sirtuin-3-overexpressing MSCs improved cardiac function in rats and increased vascular endothelial growth factor A levels and vascular density [42]. However, despite the flexibility and safety of MSCs, their use in the treatment of certain diseases, such as osteoarthritis, is debatable [43].

The use of reprogrammed and genetically modified cells is an option for cell therapy. Cellular reprogramming is aimed at reversing cellular aging and restoring cellular function. For instance, the use of induced pluripotent stem cells is a promising treatment option for age-related macular degeneration with retinal pigment epithelium degeneration, which is a leading cause of irreversible vision loss worldwide.

Some studies have proposed differentiated allogeneic-induced pluripotent stem cells of the retinal pigment epithelium as a treatment for this disease. Successful trials have been performed in various animal models, including cynomolgus macaques [44].

Table 1. List of the most common pharmacological senolytic agents

Name	Mechanism of action	Used model	Effect	Reference
A-1155463	Selective BCL-XL inhibitor	SCID beige mice xenografted with Bcl-2/xl-dependent NCI-H146 lung cancer cells	Induces reversible thrombocytopenia in mice and inhibits growth of small cell lung cancer xenografts *in vivo* after repeated administration	[16]
		Gastric cancer cell lines (23132/87, SNU216, NCI-N87, MKN1, AGS, HGC27, and SNU719). Human multiple myeloma cell lines MM1S, KMS12PE, and KMS12BM	A cytostatic effect on tumor cells	[17]
		Glioblastoma multiforme cells (U251 and SNB-19 lines)	A cytostatic effect on cells	[18]
Cardiac glycosides	Na^+/K^+-ATPase inducers of apoptosis	PDX-immunodeficient NMRInu/nu mice with xenografts of A549 (lung adenocarcinoma) and IMR90 (normal human lung cells) cells	*In vivo* inhibition of tumors xenografted in mice after treatment	[19]
Curcumin	Downregulation of the opioid nociceptin receptor gene *OPRL1*	T98G human neuroglial cell line	Reduces *OPRL1* gene expression associated with pain syndromes	[20]
	Inhibition of the mitogen-activated protein kinase (MAPK)/ nuclear transcription factor κB pathway	C57BL/6 mice and primary hepatocytes isolated from the liver of C57BL/6 mice	Inhibits the MAPK signaling pathway in the liver of aged mice and p38 signaling pathway in aged mice with diet-induced obesity Improves insulin homeostasis and reduces body weight in aged mice	[21]
Dasatinib + quercetin	Suppression of the effect of inhibitors of the SRC kinase family	Human prostate cancer cells	Inhibits adhesion, migration, and invasion of prostate cancer cells at low nanomolar concentrations	[22]
Fisetin	Blocks the PI3K/ AKT/mTOR/p16INK4a signaling pathway	*Ercc1*$^{-/\Delta}$ mice (a model of human progeroid syndrome) and aged wild-type mice, human fibroblasts (IMR90)	Provides tissue-specific reduction of cellular aging in mouse adipose tissue and human cells	[23]
FOXO4-related peptide	Blocks the interaction of the FOXO4 transcription factor and p53, leading to apoptosis	Early and late passage of human chondrocytes	Removes (eliminates) senescent cells in a late-passage chondrocyte population *in vitro*	[24]
Luteolin	mTOR pathway inhibitor	Human bladder cancer cell lines T24, 5637 (mutated p53), RT-4, and rat bladder cancer cell line BC31 (mutated p53) *in vitro*/rat bladder cancer model *in vivo*	Inhibits cell survival and induces cell cycle arrest in the G2/M phase and p21 activation in bladder cancer cells	[25]
Navitoclax (formerly ABT263)	BCL-2 inhibitor	Human skin xenografted immunodeficient mice	Causes selective elimination of senescent dermal fibroblasts	[26]
Nutlin-3a	E3 ubiquitin ligase MDM2/p53 inhibitor	Chemically induced mouse model of aging, Alu-induced geographic retinal atrophy model, and aged mice	Provides senolytic effect and reduces levels of aging markers, SASP components, and pigment deposits of the fundus	[27]
Piperlongumine	Extracellular signal-regulated kinase (ERK) 1/2 inhibitor	Senescent human fibroblast WI-38 cell line	Demonstrated moderate selectivity in reducing the viability of ionizing radiation-induced senescent fibroblasts of the WI-38 line	[28]

Table 1 (continued).

Rapamycin	mTOR pathway inhibitor	Nrf2 KO fibroblasts (knockout for the nuclear factor Nrf2) *in vivo* and Nrf2 KO mice *in vitro*	Reduces the induction of cellular senescence *in vitro* by increasing the levels of Nrf2, which activates autophagy. In mice, Nrf2 KO reduces pro-inflammatory cytokine levels in serum and adipose tissue *in vivo*	[29]
Tanespimycin	Hsp90 inhibitor	Isogenic BAX knockout model in human colon cancer cell line HCT116 *in vitro* and in tumor xenografts *in vivo*	Provides cytostatic antiproliferative effect on tumor cells through the inhibition of oncogenes	[30]

Note: ATP, adenosine triphosphate.

However, not all attempts to use these cells have been successful. Aged rats injected with neural progenitor cells derived from human-induced pluripotent stem cells at the site of a chronic cervical spinal cord injury did not perform well in behavioral tests. Additionally, high mortality rates were reported during behavioral training (41.2%), after injury (63.2%), and after cell injection (50%). Histological analysis showed that the injected cells survived and were present at the transplantation site and did not cause tumors, confirming their safety [45].

GENE THERAPY USING RECOMBINANT ADENO-ASSOCIATED VIRUSES

There are three major approaches to gene therapy for age-related diseases: epigenetic modulation, genome editing, and gene replacement therapy using viral vectors such as recombinant AAVs. Recombinant AAVs are small, non-enveloped viruses wherein the *rep* and *cap* genes are deleted and the transgene of interest is inserted. Viral vectors contain 4.7 kbp single-stranded genomic deoxyribonucleic acid with two palindromic GC-rich inverted terminal repeats at the chain ends [46].

Recombinant viruses are cassettes containing a promoter, genes of interest, and a terminator, making them more suitable for clinical use. Such recombinant AAVs are a relatively safe tool to ensure long-term transgene expression after a single infection because they cannot replicate. AAVs have emerged as efficient carriers of genetic modifications because of their efficient *in vivo* infectivity, lack of pathogenicity, broad tissue tropism, rare genomic integration, and ability to infect and maintain in non-dividing cells [47].

Several genes have been identified as potential targets for gene therapy to extend life expectancy and improve health of patients. These genes are often involved in signaling pathways that are crucial in regulating cellular metabolism, oxidative stress, and inflammation, which are believed to contribute to the aging process. Some of them are discussed below, as well as options for using AAVs to treat age-related diseases.

Telomerase is an enzyme that helps maintain the length of telomeres, which are protective caps at the ends of chromosomes. Telomere shortening is believed to contribute to the aging process. Some studies have investigated the use of viral vectors to deliver telomerase-expressing genes into cells in an attempt to slow telomere shortening and promote longevity. Telomere length varies widely among individuals; however, it shortens with age and cell division [3].

A method to extend life expectancy using a cytomegalovirus vector encoding the telomerase reverse transcriptase (TERT) gene and follistatin has been proposed, showing high efficacy in a mouse model of natural aging. Gene therapy extended life expectancy (by >32%), improved glucose tolerance and exercise capacity, and prevented weight loss and alopecia when administered intranasally or by injection [48].

The use of gene therapy to express active human TERT in human cells potentially treats several age-related neurodegenerative diseases, including Alzheimer's disease. Some clinical trials, for example, studies by Libella Gene Therapeutics, employed this strategy. This trial involved treatment with human TERT delivered by AAV transduction (NCT04133454). It aimed to lengthen telomeres to prevent, delay, or reverse the progression of Alzheimer's disease.

Telomere lengthening induces a direct impact on cognitive function and quality of life in patients with age-related neurodegenerative disease such as Alzheimer's disease. However, the use of human TERT is associated with the risk of malignant transformation of cells. For example, the human TERT/MDM2-FOXO3a-integrin β1 signaling pathway is involved in human TERT-driven gastric cancer invasion. This indicates that this pathway is a novel target for the prevention and treatment of gastric cancer metastasis [49].

Aging-suppressor gene klotho. Animal models have demonstrated its association with longevity. Klotho levels decrease with age in humans and mice, and increasing klotho expression slows or reverses age-related changes [50].

The potential of gene therapy to enhance klotho activity in humans using AAVs is currently being investigated. For example, AAV-Klotho was injected into the bilateral hippocampus of rat models of temporal lobe epilepsy, and after 9 weeks, AAV-Klotho was found to induce *klotho* overexpression in the hippocampus and ameliorate cognitive impairment and have a neuroprotective effect. Additionally, klotho significantly increased glutathione peroxidase-4 and glutathione levels while suppressing reactive oxygen species levels

in a rat model of temporal lobe epilepsy [51]. Utilizing AAV-Klotho in a mouse model of temporal lobe epilepsy significantly reduced hippocampal neuronal damage and cognitive impairment [52].

AAV-mKlotho (murine klotho) prevented the progression of spontaneous arterial hypertension, abolished renal tubular atrophy and dilation, and decreased renal damage in rats with spontaneous arterial hypertension [53]. Neuroprotective and anti-inflammatory effects and restoration of the epigenetic landscape were confirmed when AAV9-Klotho was administered to a mouse model of rapid aging [54].

The use of AAV encoding a soluble form of the klotho protein reduced arterial stiffness in aging mice, including by restoring the B-cell population and serum immunoglobulin-G levels, and decreased age-related vascular inflammation and arterial remodeling [55]. There was a study using AAV vectors encoding *hTERT* and *klotho*, which involved patients with mild to moderate dementia. It showed the safety of the vectors and improvement in cognitive function; however, formal data on this trial are not yet available [56].

Fibroblast growth factor 21 (FGF21) is a hormone involved in the regulation of glucose and lipid metabolism. Animal studies have shown that increased FGF21 activity can improve metabolic function and life expectancy. Gene therapy is currently being investigated to increase FGF21 activity in humans; FGF21 is considered a promising treatment for type 2 diabetes mellitus and obesity. In long-term high-fat diet-fed and obese mice, gene therapy with AAV-FGF21 significantly reduced body weight, adipose tissue hypertrophy, and inflammation and improved liver steatosis and insulin resistance for >1 year. This therapeutic effect was achieved without side effects despite persistently elevated serum FGF21 levels [57].

However, in rodents and humans, it was noted that circulating FGF21 levels increase with age. The beneficial metabolic effects of FGF21 use are associated with elevated FGF21 levels in obesity and diabetes, which may be related to altered tissue sensitivity to FGF21 [58].

Positive results were obtained in a gene therapy trial with three different AAVs encoding genes *FGF21*, *αKlotho*, and a soluble mouse TGF-beta type II receptor. The ability of these genes to mitigate the effects of four age-related diseases, namely, obesity, type 2 diabetes mellitus, heart failure, and kidney failure, was evaluated in animal models. Heart function was improved by 58% in heart failure-induced ascending aortic stenosis; alpha-smooth muscle actin expression was reduced by 38% and renal medullary atrophy by 75% in mice subjected to unilateral ureteral obstruction; and obesity and diabetes phenotypes were completely reversed in mice fed a chronic high-fat diet [59].

CONCLUSION

Increasing life expectancy is a positive trend in human history. However, aging has become a major issue that should be addressed using new technologies and advanced scientific tools.

Senolytics are receiving much attention owing to successful clinical trials of some of these agents. Senescent cells play a key role in age-related diseases, and eliminating them may have significant therapeutic benefits. However, most senolytics have serious side effects that have not yet been overcome.

Moreover, cell therapy, which uses stem and specialized cells to repair damaged and aging tissues, has the potential to slow the aging process and improve overall health. However, autologous stem cells from older patients are subject to uncertain therapeutic effects because of their intrinsically senescent nature.

Using AAVs to deliver genetic material and a gene that can slow the aging process could transform the approach to treating aging and discover new ways to slow and even reverse these processes, provided that side effects are avoided and manufacturing costs are reduced. While the abovementioned studies show encouraging success in improving the health of animal models and patients, the search for a true "youth pill" is far from over.

ADDITIONAL INFORMATION

Authors' contribution. K.V.K. — writing — original draft, conceptualization, visualization; V.V.S. — writing — review & editing; I.Yu.F. — resources; Ya.O.M. — project administration; A.A.R. — supervision.
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