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Sirtuins and Aging

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The sirtuin family of proteins (SIRT proteins) are involved in DNA repair, chromatin remodeling, epigenetic regulation of the expression of metabolism genes, the antioxidant system, apoptosis, immuno- and neurogenesis, etc. The aim of this review is to analyze the geroprotective properties of sirtuins in normal and age-associated pathologies. SIRT1, 2, 3, 4, and 6 contribute to increases in life expectancy. SIRT1, 2, 6, and 7 slow cellular aging and maintain the stem cell pool. Sirtuins are potential targets for the treatment of neurodegenerative, oncological, and cardiovascular diseases, metabolic syndrome, and diabetes mellitus. All these diseases are in most cases characteristic of elderly and old people, so the geroprotective effects of sirtuins, realized at the molecular and cellular levels, may play an important role in the treatment of these conditions.

Keywords: sirtuins, cellular aging, geroprotection, age-associated diseases.

Introduction. Sirtuins (SIRT) are a family of NAD-dependent histone deacetylases which regulate cellular functions and various metabolic pathways in normal conditions, aging, and age-associated pathology [17]. Sirtuins are class III histone deacetylases. The main difference between sirtuins and other classes of these proteins is the need for nicotinamide adenine dinucleotide (NAD^+) as cofactor for reactions to occur.

Phylogenetic analysis divides the seven mammalian sirtuins (SIRT1–7) into four classes: SIRT1–3 belong to class I, SIRT4 to class II, SIRT5 to class III, and SIRT6 and 7 to class IV [24]. In addition, mammalian sirtuins can also be categorized on basis of their subcellular location: SIRT1, 6, and 7 are located in the nucleus, SIRT3, 4, and 5 in mitochondria, and SIRT2 mainly in the cytoplasm [34]. These differences in subcellular location and expression patterns, along with the diversity of substrates, determine the wide range of biological functions of sirtuins.

Sirtuins were originally described as histone deacetylases in the yeast *Saccharomyces cerevisiae* [38, 43]. In addition to their function of histone deacetylation, sirtuins also deacetylate lysine in a wide range of non-histone cellular proteins, regulating their activity. The spectrum of known functions of sirtuins has expanded since their discovery; data have been obtained on the roles of sirtuins in carrying out post-translational modifications [71]. SIRT3, 4, 5, and 6 can function as ADP-ribosyltransferases [29, 56, 90], while SIRT5 catalyzes desuccinylation and demalonylation [19, 76].

In addition to NAD^+ availability and subcellular localization, there are several additional regulatory mechanisms that contribute to sirtuin activity. Thus, various sirtuins can be activated, with subsequent stimulation of a diversity of substrates. Additional mechanisms of regulation of sirtuin functions include transcription factors, micro RNAs, post-translational modifications, protein–protein interactions, and regulation by "small molecules" such as short peptides [34, 48, 101]. Environmental stimuli such as calorie

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restriction control the expression and/or activity of sirtuins through these regulatory mechanisms. Sirtuins are therefore regarded as stress-sensitive enzymes which regulate cell adaptation to changes in homeostasis by modulating the protein acetylation profile. Sirtuins have been shown to regulate the lifespan of various types of organisms, including yeast, nematodes, *Drosophila* [12, 28], and mammals [40].

Many studies of sirtuins have addressed their role in aging and the development of age-related diseases. The variety of proteins whose activity can be altered by acetylation at lysine residues suggests that sirtuins are major regulators of cell activity, which roles in gene expression, metabolism, telomerase activity, the cell cycle, differentiation, apoptosis, proliferation, DNA repair, cellular aging, and responses to oxidative stress [70].

The aim of the present review was to analyze the geroprotective properties of proteins of the sirtuin family in normal and age-associated pathologies.

The Geroprotective Properties of Sirtuin 1. Sirtuins were first mentioned as regulators of cellular senescence in 1997, when they were found in the yeast *Saccharomyces cerevisiae*: yeast overexpressing the *sir2* gene underwent a larger number of divisions than the control strain [38, 43]. Furthermore, the protein encoded by the *sir2* gene in yeast was shown to regulate gene expression through epigenetic mechanisms and also to be involved in DNA repair. In animals and humans, the protein homologous to yeast *Sir2* is SIRT1. Subsequent studies have shown that increased expression of the *Sirt1* gene also increases the lifespan of *Caenorhabditis elegans*, flies and hookworms. Overexpression of SIRT1 homologs in mice may increase lifespan [79].

SIRT1 expression decreases with age in the human liver, heart, kidneys, brain, and lungs [1, 2, 8, 15, 41]. SIRT1 synthesis in endothelium and smooth muscle cells has been found to decrease with aging [16, 19, 46]. Use of the SIRT1 activator resveratrol inhibited apoptosis and promoted the survival of C2C12 myoblast cells [33]. Increased expression of SIRT1 seems to play an important role in slowing down the aging process of nucleus pulposus cells, promoting their proliferation and reducing apoptosis [27].

SIRT1 overexpression in the mouse brain correlates with an increase in lifespan [79]. Activation of SIRT1 slows the accelerated aging of human dermal fibroblasts induced by ultraviolet radiation [54].

Transcription factor p53 is one of the key targets of SIRT1 in the processes of cellular aging [14]. Acetylation of p53 is known to occur in the nucleus during stress and inflammation due to DNA damage, hypoxia, and formation of reactive oxygen species (ROS); acetylation stabilizes it and increases its DNA-binding activity. This leads to an increase in the transcription of genes involved in proapoptotic cascades. The protective role of SIRT1 consists of an interaction with p53 protein via deacetylation of the lysine^{382} residue at the C-terminus of the protein [91]. NAD^+ operates as cofactor and binds to p53 tetramers, changing their conformation and preventing binding to DNA. This reduces p53-mediated transcriptional activity and the expression of pro-apoptotic proteins such as the cell cycle inhibitor p21. In this way, SIRT1 can inhibit p53-dependent cell cycle arrest and apoptosis, enhancing DNA repair and helping to maintain genome integrity and cell survival.

Along with p53, NF-κB protein is a transcription factor involved in the regulation of cell aging and apoptosis. NF-κB activation is observed in many pathological processes, such as diabetes, Alzheimer's disease (AD) and Parkinson's disease (PD). Long-term activation of NF-κB is not only associated with cellular aging, but also accelerates it [105]. SIRT1 is a negative regulator of the NF-κB signal pathway [21], deacetylating the lysine^{310} residue of p65 protein – a subunit of NF-κB. p65 acetylation increases the transcriptional activity of the NF-κB complex, and SIRT1 mediates deacetylation and suppresses NF-κB signaling [100]. SIRT1 has an antiatherosclerotic effect mediated by inhibition of NF-κB signaling in the vascular endothelium [16]. SIRT1 deficiency in osteoblasts and osteoclasts in mice has been shown to activate NF-κB by increasing p65 acetylation at lysine^{310}, leading to a decrease in bone mass and acceleration of bone aging [21].

The next pathway in which SIRT1 is involved is the AMPK signal pathway. AMPK is a highly conserved serine/threonine protein kinase that regulates energy metabolism and cell survival [36]. Activation of AMPK contributes to an increase in the lifespan of *C. elegans* by 13% [11]. SIRT1 and AMPK can mutually enhance each other's activity [85]. AMPK enhances SIRT1 activity by increasing the cellular NAD^+ level by deacetylation of PGC1α, the downstream target of SIRT1 [106]. In addition, AMPK activation slows cell aging by inducing autophagy [22].

Cellular senescence has been shown to be closely associated with mitochondrial dysfunction [92]. Mitochondrial dysfunction promotes synthesis of ROS and exacerbates oxidative stress, and this progresses with age [78]. PGC1α is the main transcriptional coactivator in the regulation of mitochondrial functions and maintenance of cell homeostasis. SIRT1 deacetylates PGC1α and is thus involved in regulating mitochondrial function and increasing mitochondrial biogenesis [47]. Activation of SIRT1 prevents endothelial aging by deacetylating PGC1α and PPARα, leading to suppression of NADPH oxidase-mediated ROS production and inactivation of nitric oxide [102].

mTOR is another key regulator of the body's aging process. Suppression of mTOR activity increases lifespan in various organisms [6, 18, 95]. SIRT1 and mTOR are involved in the regulation of aging via control of autophagy. In conditions of oxidative stress, the processes of autophagy are disrupted; SIRT1 restores them to a normal level and improves the survival of embryonic stem cells by blocking the mTOR pathway [72]. In addition, inhibition of SIRT1 activates mTOR signaling, leading to impaired autophagy. SIRT1 has ben shown to interact with TSC2 protein, which

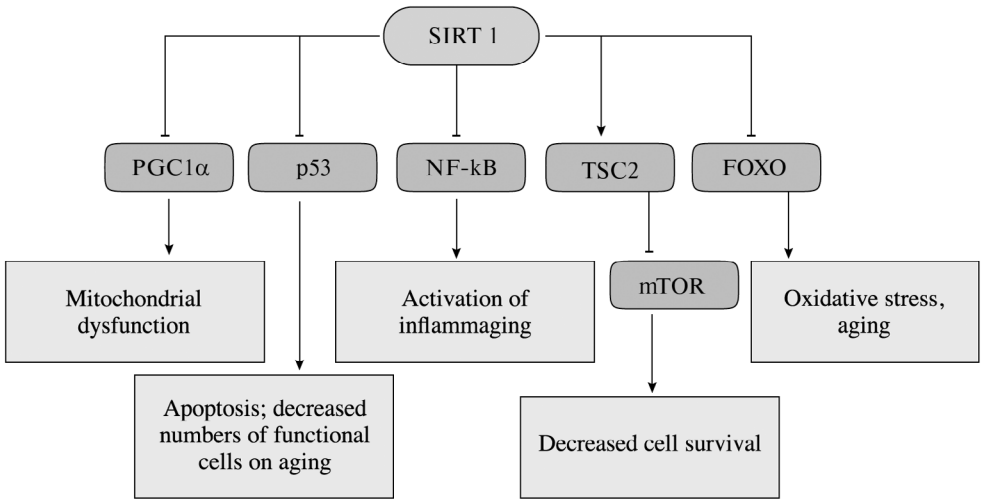

Fig. 1. Geroprotective effects of Sirt1. Arrowheads indicate positive regulation and horizontal line terminators indicate negative regulation.

is an upstream inhibitor of TORC1 and negatively regulates mTOR signaling in a TSC2-dependent manner [26]. Suppression of SIRT1 increases TSC2 acetylation in its N-terminal domain, which is accompanied by an increase in its ubiquitination protein status and leads to activation of mTORC1 [25].

FOXO transposition factors are a family of proteins that function as sensors in the insulin signal pathway. FOXO is involved in various physiological and pathological processes, including oxidative stress, DNA repair, autophagy, and cell cycle arrest. The FOXO family in mammals consists of FOXO1, FOXO3, FOXO4, and FOXO6 [4]. FOXO transcriptional activity is affected by post-translational modifications, such as phosphorylation and acetylation [60]. FOXO1, FOXO3, and FOXO4 are acetylated by CBP/p300 acetyltransferase in response to cellular stress. SIRT1 regulates the functions of FOXO proteins by deacetylation, preventing oxidative stress and aging [67].

Thus, the geroprotective effect of SIRT1 is mediated via the regulation of the p53, NF-ϰB, mTOR, PGC1α, and FOXO signal pathways (Fig. 1). These regulatory mechanisms involving SIRT1 contribute to slowing aging at the level of cells, organs, and tissues. This is expressed as slowing of the aging of the brain, heart, liver, lungs, skin, smooth muscle, and vascular endothelium, along with an increase in life expectancy.

The Geroprotective Properties of Sirtuin 2. SIRT2 is expressed in a wide variety of central nervous system (CNS) structures, including the hippocampus, striatum, cerebral cortex, and spinal cord. The SIRT2.3 isoform has been shown to accumulate in the CNS of mice during aging [9]. More than 40 proteins involved in various intracellular signal pathways regulating carcinogenesis, redox balance, cell proliferation, and differentiation have been found to be SIRT2 substrates [93].

SIRT2 slows the aging of hematopoietic stem cells (HSC). With age, HSC become more sensitive to mitochondrial stress, and they show elevated activation of the main inflammasome component, NLRP3. This is probably due to the suppression of SIRT2 expression. Overexpression of SIRT2 can inhibit NLRP3 activation and slow aging of GSK [59]. SIRT2 expression decreases with aging in bovine oocytes. Treatment of oocytes with a SIRT2 inhibitor resulted in high levels of oxidative stress, an abnormal distribution of mitochondria, and low ATP production. Oocyte aging was accompanied by apoptosis; inhibition of SIRT2 increased the intensity of oocyte apoptosis during aging. SIRT2 inactivation is thus the key mechanism underlying cellular senescence in oocytes [96].

Mice which are hypomorphic for the mitotic checkpoint protein kinase gene, *BubR1*, have a shorter lifespan than animals overexpressing this gene. As wild-type mice age, synthesis of *BubR1* protein decreases in many tissues. This process is thought to underlie normal aging and age-related diseases. The age-related decreases in the *BubR1* protein level in various organs and tissues with age have been shown to occur as a result of a decrease in the NAD^+ level and the ability of SIRT2 to maintain $lysine^{668}$ in the *BubR1* protein in a deacetylated state. Overexpression of SIRT2 increases the amount of *BubR1* protein in vivo in male mice and also increases their life expectancy [69].

SIRT2 may prevent intervertebral disc degeneration associated with cell aging in the nucleus pulposus. IL-1β was found to contribute to an increase in the extent of intervertebral disc cell degeneration and a reduction in the level of expression of the *Sirt2* gene in these cells. At the same time, *Sirt2* overexpression can abolish the effects of IL-1β, leading to an increase in the expression of the gene for the antioxidant enzyme superoxide dismutase (SOD) and reducing the level of oxidative stress. In addition, *Sirt2* overexpression inhibits the p53/p21 pathway, preventing cell senescence and degradation of nucleus pulposus cells [99]. The interaction of SIRT2 with the cell aging marker p53 has been confirmed by results obtained by chromatin immuno-

precipitation, which revealed the presence of p53 binding sites on the SIRT2 promoter [5].

Thus, the geroprotective effects of SIRT2 are associated with its ability to regulate signal cascades involving NLRP3, BubR1, IL-1β, and p53/p21. As a result, SIRT2 slows down the aging of stem cells, has antioxidant, anti-inflammatory and neuroprotective effects, and increases lifespan in animals.

The Geroprotective Properties of Sirtuin 3. SIRT3 is mainly located in the cells of tissues with high metabolic activity and is regarded as a regulator of mitochondrial metabolism [68]. The SIRT3 level is reduced by 40% in the cells of various organs and tissues in elderly people with a sedentary lifestyle, but its synthesis can be activated by calorie restriction [52].

Mice with knockout of the *Sirt3* gene showed myocardial hypertrophy and fibrosis, with decreases in life expectancy [7]. This is probably because one of the targets of SIRT3 is the FOXO3 protein, the deacetylation and activation of which lead to increased transcription of the antioxidant genes SOD and catalase [84].

SIRT3 activates a variety of protein targets, modulating key cellular and physiological processes, leading to increases in lifespan. Many of these processes are mediated by decreases in ROS production due to deacetylated SOD2 and IDH2. [58].

Hypoxia in cultured endothelial cells stimulates SIRT3 expression and SIRT3-dependent antioxidant signaling, preventing mitochondrial damage and promoting cell survival. SIRT3 deficiency causes mitochondrial dysfunction in pulmonary artery smooth muscle cells in rodents and humans, leading to vascular remodeling and pulmonary hypertension [77]. Knockout of the *Sirt3* gene contributes to the development of metabolic syndrome, which is a factor in the occurrence of cardiovascular diseases. Old mice show a 50% reduction in SIRT3 synthesis in kidney tissue as compared with the level in young animals [55]. Decreased SIRT3 synthesis in mitochondria is associated with a number of age-related pathologies, including cancer, insulin resistance, heart disease, fibrosis, and neurodegeneration [63].

SIRT3 expression is reduced in some forms of breast, liver, and stomach cancer [23, 98], and is associated with poor survival in hepatocellular carcinoma [104]. These studies demonstrate the ability of SIRT3 to slow tumor growth.

Decreases in mitochondrial function during aging are accompanied by the development of hyperglycemia and hyperinsulinemia. The liver of SIRT3KO mice, which have knockout of the *Sirt3* gene, accumulates long-chain acylcarnitine forms of coenzyme A dehydrogenase, disrupting fatty acid oxidation and leading to the development of metabolic pathology [32]. SIRT3KO mice on a high-fat diet experience accelerated development of metabolic syndrome, with pancreatic β-cell dysfunction, impaired glucose tolerance, insulin resistance, and weight gain [31]. Temporary knockdown of SIRT3 in pancreatic β-cell cultures leads to increased ROS generation and impaired insulin secretion, while overexpression of SIRT3 eliminates lipotoxic disorders [44]. SIRT3 expression and activity in the liver are reduced by a high-fat diet, which leads to protein hyperacetylation, increased lipotoxic conditions, and hepatic steatosis [41]. Diabetics show decreased SIRT3 synthesis in the islets of Langerhans of the pancreas. The processes of lipid β-oxidation in cardiomyocytes are disrupted in *Sirt3* gene knockout mice and the activity of the oxidative phosphorylation complex and ATP production are reduced [3]. These data suggest that SIRT3 plays important roles in the development of metabolic syndrome, diabetes mellitus, and cardiovascular disease, all of which are age-related diseases.

SIRT3 is expressed in the brain and other nervous system tissues [103]. As SIRT3 regulates metabolic homeostasis, it has been suggested that it may contribute to protection against the development of neurodegenerative diseases. SIRT3 can restore neuron loss in various models of neurodegeneration. Apoptosis develops in primary cortical neuron cultures when the toxic peptide Aβ42 is added. Pituitary adenylate cyclase-activating polypeptide (PACAP) protects neurons from Aβ42 exposure by upregulating SIRT3. The PACAP-mediated neuroprotective effect is lost when SIRT3 expression is suppressed in cultured neurons. Overexpression of SIRT3 makes neurons resistant to oxidative stress and increases their viability [30]. Amyotrophic lateral sclerosis is associated with mitochondrial dysfunction, which can be modeled in neuron cultures expressing the SOD1 G93A gene mutant. This mutant SOD1 gene causes mitochondrial dysfunction and neuronal apoptosis, which is inhibited by overexpression of SIRT3 and PGC1α, a transcription factor which regulates SIRT3 expression [82].

Thus, SIRT3 regulates the synthesis of FOXO3, PGC1α, PACAP, catalase, and SOD, preventing the development of a number of age-related pathologies: diabetes mellitus, metabolic syndrome, cardiovascular dysfunction, cancer, and neurodegenerative diseases (Fig. 2).

Sirtuin 4: Geroprotector or Aging-Accelerating Protein? Data on the role of SIRT4 in aging processes are controversial. There is evidence that *Drosophila melanogaster* individuals with knockout of *Sirt4* have a reduced lifespan, increased sensitivity to starvation, reductions in fertility, glycolysis, branched chain amino acid metabolism, and fatty acid catabolism. *Drosophila* overexpressing *Sirt4* displayed increased lifespan [94]. Other data indicate that knockout of the *Sirt4* gene in *Drosophila melanogaster* leads to a reduced lifespan and impaired motor function [75].

Data have also been obtained on the role of SIRT4 in the formation of an aging-associated phenotype (SASP) in the skin. Ultraviolet radiation, which accelerates the aging of dermal cells, activates *Sirt4* expression. SIRT4 inhibits the activation of SOD2 [61], which may contribute to the formation of SASP by increasing ROS generation. Exposure of human dermal fibroblasts to ultraviolet radiation has been shown to increase their SIRT4 mRNA and protein levels,

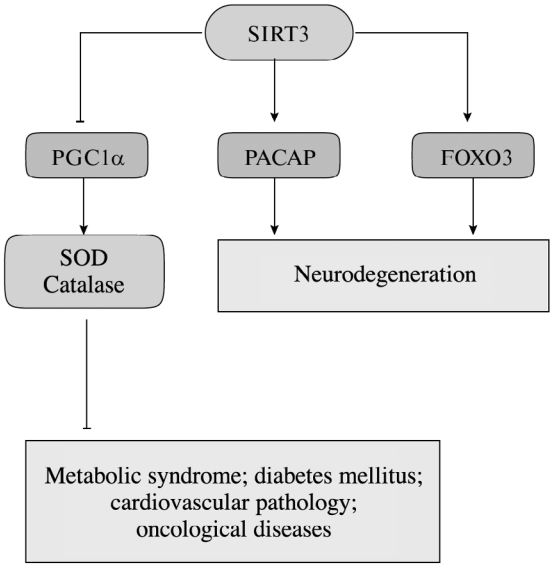

Fig. 2. Geroprotective effects of SIRT3. Arrowheads indicate positive regulation and horizontal line terminators indicate negative regulation.

which inhibits microRNA-15b, leading to the formation of SASP [51]. SIRT4 has also been shown to be able to increase ROS synthesis in mouse cardiomyocytes [61].

Overexpression of SIRT4 in vascular endothelial cultures inhibited the nuclear translocation of NF-κB, triggering the expression of proinflammatory cytokines IL-1β and IL-6 and adhesion molecule ICAM-1 [87]. SIRT4 may thus have anti-atherosclerotic and anti-inflammatory properties.

We note that SIRT4 is a tumor suppressor, which is explained by its ability to regulate mitochondrial metabolism during oncogenesis [64]. *Sirt4* mRNA levels are decreased in lung, pancreatic, ovarian, stomach, intestinal, prostate, kidney, liver, and endometrial cancers, as well as hematological tumors. Lower *Sirt4* expression levels in tumor tissues are often associated with reduced survival in cancer patients [89].

SIRT4 promotes longevity in *Drosophila* but activates an aging-related phenotype in human skin fibroblasts. These conflicting data require more research detailing the molecular mechanism of action of SIRT4. Furthermore, SIRT4 normalizes mitochondrial metabolism, which is expressed in its oncostatic effect, and regulates cytokine synthesis.

The Geroprotective Properties of Sirtuin 5. SIRT5 has neuroprotective properties, slowing the development of epilepsy and the age-related condition Parkinson's disease. SIRT5 deficiency causes reactive astrogliosis, exacerbates neuron loss and hippocampal degeneration, increases the severity of epileptic seizures, and increases mortality in mice in a model of epilepsy [80]. The expression of mitochondrial SIRT5 is increased when the hippocampus is damaged. This indicates the ability of SIRT5 to increase the survival of hippocampal cells [53]. Mice with *Sirt5* gene knockout displayed more severe nigrostriatal dopaminergic degeneration in a model of PD than animals without mutation in this gene. Deletion of the *Sirt5* gene in mice with PD leads to decreased SOD2 synthesis. These data show that SIRT5 slows nigrostriatal dopaminergic degeneration by maintaining the functions of the neuronal antioxidant system [57].

The Geroprotective Properties of Sirtuin 6. SIRT6 is a histone deacetylase which targets acetylated lysine residues K9, K56, and K18 (H3K9ac, H3K56ac, and H3K18ac) in histone H3. Deacetylation of these amino acid residues by SIRT6 is required for chromatin compaction, transcriptional repression, and regulation of DNA repair. SIRT6 acts as a corepressor of several transcription factors – NF-κB, HIF-1, and c-Myc – which slow aging, prevent carcinogenesis, and regulate metabolism. SIRT6 promotes the chromatin remodeling required for DNA repair and maintenance of telomere structure to prevent genomic instability and cellular senescence [49].

SIRT6 overexpression leads to increases in the lifespan of male mice [40]. Mice with impaired SIRT6 synthesis develop progeria and die four weeks after birth. This is due to the instability of the cellular genome and systemic metabolic defects [66]. Human embryonic stem cells (hESC) with impaired *Sirt6* expression differentiated into mesenchymal stem cells (hMSCs), had elevated sensitivity to oxidative stress, and showed signs of accelerated cellular senescence [73]. The authors suggested that SIRT6 positively modulates the antioxidant pathway regulated by NRF2 and heme oxygenase-1 in hMSC.

Data have been obtained on the involvement of SIRT6 in the regulation of circadian rhythms [62] and its ability to suppress tumor growth [49]. SIRT6 interacts with protein BMAL1, which regulates the expression of circadian genes and is involved in chromatin remodeling. SIRT6 also interacts with the deacetylated form of PER2 protein, preventing its degradation [83]. Another study demonstrated that SIRT6 interacts with CLOCK and BMAL1 proteins, which regulate circadian rhythms, and also with SREBP-1 protein, which regulates the periodicity of fatty acid metabolism [62]. Thus, the geroprotective effects of SIRT6 may be mediated by regulating the expression of circadian genes involved in the maintenance of metabolism.

SIRT6 has been shown to inhibit the growth of pancreatic carcinoma. Impaired SIRT6 expression leads to hyperacetylation of the Lin28b histone gene promoter, activation of the Myc gene, and positive regulation of the synthesis of HMGA2, IGF2BP1, and IGF2BP3 proteins, which are expressed during the growth and metastasis of pancreatic carcinoma [50]. SIRT6 suppresses the expression of genes involved in the development of colorectal cancer by modulating the PTEN/AKT signaling cascade, which may be important for the development of new therapies for this pathology [88].

High levels of SIRT6 expression have been found in mammalian cerebral neurons [11]. Decreases in this indicator with age have been noted [9]. *Sirt6* gene knockout mice

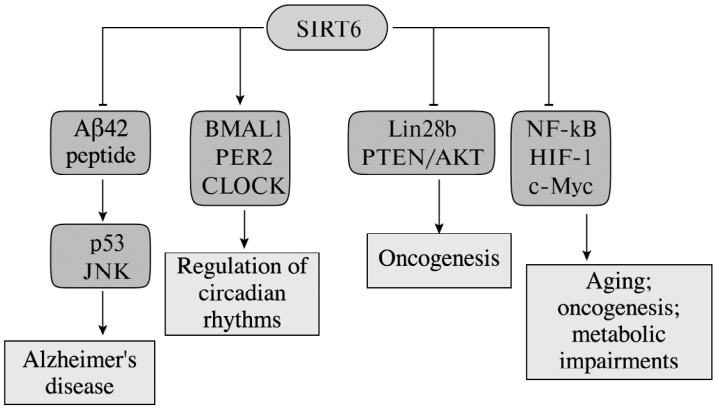

Fig. 3. Geroprotective effects of SIRT6. Arrowheads indicate positive regulation and horizontal line terminators indicate negative regulation.

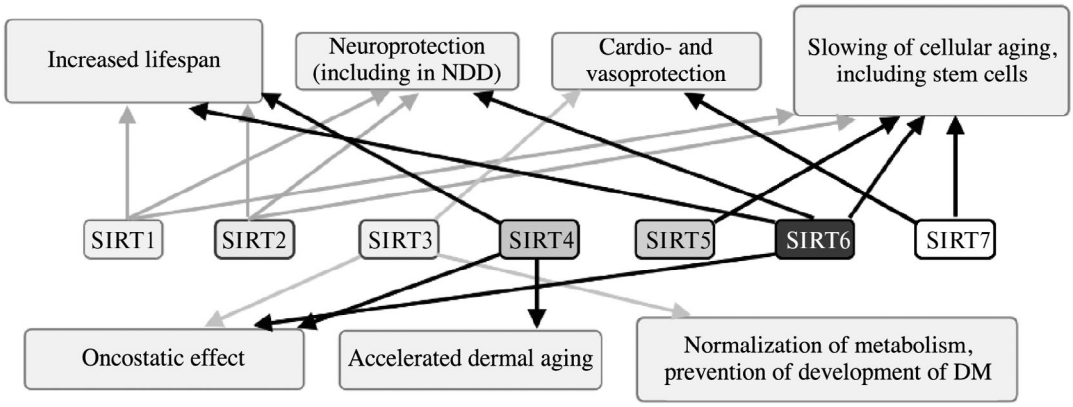

Fig. 4. The geroprotective effects of sirtuins and their potential roles in the treatment of age-related diseases. Abbreviations: NDD – neurodegenerative diseases; DM – diabetes mellitus.

display defects in the transmission of nerve impulses to the retina, which are associated with decreased numbers of ionotropic and metabotropic glutamate receptors [81]. SIRT6 expression is decreased in the brains of patients and mice with AD. Amyloid plaques formed by Aβ42 peptide conjugates suppressed SIRT6 synthesis in cerebral cortex neurons in mice with AD, as well as in the mouse hippocampal neuron line HT22. This was accompanied by acetylation of histones H3K9 and H3K56. Peptide Aβ42 suppressed the expression of SIRT6 in HT22 cells by a mechanism involving JNK kinase and p53 protein [37]. A decrease in SIRT6 synthesis in the brains of mice with a deletion in the *Sirt6* gene leads to hyperphosphorylation of τ-protein, which is also a link in the pathogenesis of AD [39, 86].

Thus, SIRT6 has the widest range of geroprotective effects among the sirtuin family. SIRT6 regulates the activity of circadian genes, slows down the process of cellular aging (including aging in human stem cells), has oncostatic and neuroprotective effects, regulates metabolism, and prolongs lifespan (Fig. 3).

The Geroprotective Properties of Sirtuin 7. SIRT7 is a regulator of rRNA synthesis and is involved in maintaining cellular homeostasis. Proteins p53, H3K18, PAF53, NPM1, and GABP-β1 are substrates of SIRT7 deacetylase activity [45]. SIRT7 promotes cell survival under stress conditions, including aging, by regulating the synthesis of HIF-1 and IRE1α [35]. Increased rDNA instability is a phenotype associated with aging in humans. Being the only sirtuin located mainly in the nucleolus, SIRT7 counteracts aging in hMSC by maintaining rDNA stability in heterochromatin regions [74]. SIRT7 represses LINE1 retrotransposons, regulates the expression of rDNA gene clusters in heterochromatin regions, and promotes the survival of hematopoietic stem cells [65]. SIRT7 has a cardioprotective effect by participating in GATA4 deacetylation in cardiomyocytes [97]. Thus, SIRT7 plays an important role in slowing cellular aging, maintaining the stem cell pool, and cardioprotection.

Conclusions. Sirtuins play key roles in providing antioxidant protection and regulating ROS synthesis and DNA repair. Prevention of oxidative stress helps to slow cellular aging and to maintain the stem cell pool. The geroprotective properties of SIRT1, 2, 3, 6, and 7, mediated by a variety of cellular signal cascades, have been described in detail in the literature. In the case of SIRT4, there is as yet no consensus as to whether it has a geroprotective effect or accelerates aging. SIRT5 remains insufficiently studied, though data on its neuroprotective activity and antioxidant properties have been obtained, allowing this protein to be seen as a potential

geroprotector. It has been suggested that human sirtuins are potential targets for the treatment of a variety of age-related diseases: diseases of the cardiovascular system (hypertension and heart failure), the nervous system (AD, PD), metabolic disorders (type 2 diabetes, metabolic syndrome), and oncopathology (Fig. 4).

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