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Sirtuins: Role in the Regulation of Oxidative Stress and the Pathogenesis of Neurodegenerative Diseases

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Sirtuins (SIRTs) are a family of histone deacetylases which epigenetically regulate major cell functions. This review analyzes the role of SIRTs in controlling oxidation-reduction reactions in cells in stress. Oxidative stress and mitochondrial dysfunction are among the causes of the development of neurodegenerative pathologies – Alzheimer's disease (AD) and Parkinson's disease (PD). SIRTs supporting the antioxidant defense of neurons may play an important role in the pathogenesis of AD and PD. This article summarizes the molecular mechanisms of the neuroprotective properties of SIRT1, 2, 3, and 6 in AD and SIRT1 and 3 in PD. The roles of other proteins of the SIRT family in the pathogenesis of neurodegenerative diseases requires further study. SIRTs may have potential as diagnostic markers and treatment targets in AD and PD.

Keywords: sirtuins, oxidative stress, Alzheimer's disease, Parkinson's disease.

Introduction. Sirtuins (SIRTs) are class III histone deacetylases and are universal regulators of cell functions. Histone deacetylases produce hypoacetylation of lysine residues in histone proteins. This leads to a reduction in the distance between nucleosomes and DNA and induces changes in gene transcription. SIRTs use nicotinamide adenine dinucleotide (NAD^+) as a cofactor, while "classical" deacetylases of classes I, II, and IV regulate gene expression without using NAD^+. In addition, class I, II, and IV proteins are homologous to each other but have no homology with SIRTs [62, 80]. It is interesting that the targets of histone deacetylases may not only be histones, but also various other proteins, such as transcription factor p53 [51].

SIRTs were discovered as regulators of the transcription of inactive ("silent") genes in the yeast *Saccharomyces cerevisiae*, such that they were termed "silent information regulators." In 1999, Kaeberlin and McVey showed that overexpression of the *sir2* gene increased the lifetime of the yeast *Saccharomyces cerevisiae* by 30% [42]. In 2000, Imai et al. identified SIR2 protein as an NAD-dependent histone deacetylase (HDAC), which deacetylates lysine residues K9 and K14 in histone H3 and K16 in histone H4. The authors suggested that the ability of protein SIR2 to modify histones might be linked with the increased lifetime of yeasts and the excessive number of copies of the *sir2* gene [36]. Acetylation and deacetylation of histones at lysine residues are known to constitute a key method for the regulation of gene expression in particular histone areas [90]. SIRTs, apart from deacetylase activity, also have other enzymatic activities: ADP-ribosylation, demalonylation, and desuccinylation [26].

Later studies of SIRTs demonstrated similarity in the sequences of these proteins in prokaryotes and eukaryotes, which is evidence that they are highly conserved [28]. Each of the seven SIRTs in mammals has a conserved NAD^+-

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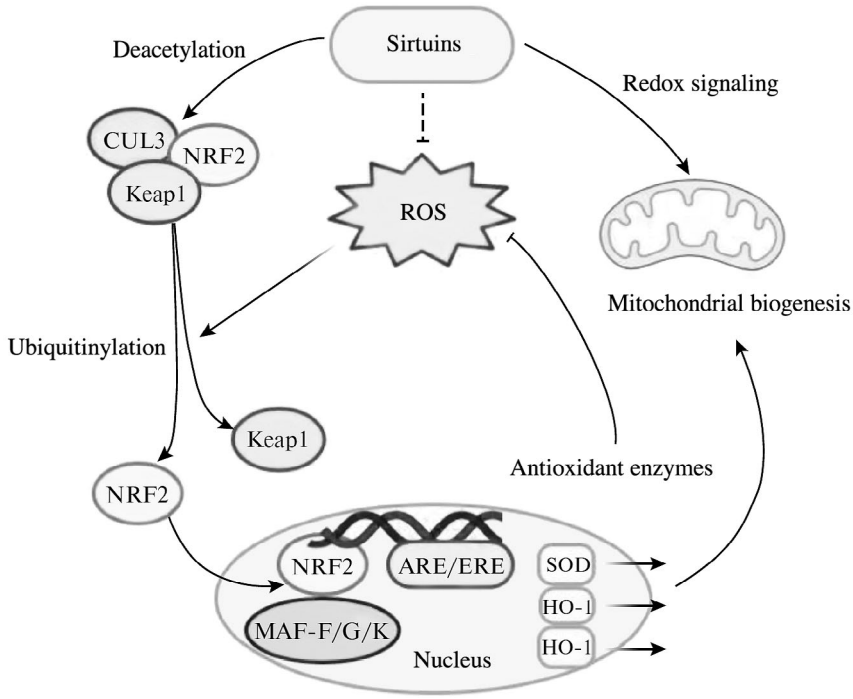

Fig. 1. Diagram showing interactions of sirtuins with NRF2: regulation of expression of antioxidant defense genes (from [93]). CUL3 – cullin 3, ARE – antioxidant response element; ERE – electrophilic response element; GSH – glutathione; – HO-1 – hemoxygenase 1; Keap1 – kelch-like ECH-associated protein 1; NRF2 – nuclear factor E2; ROS – reactive oxygen species; SOD – superoxide dismutase.

binding catalytic core domain consisting of 250–270 amino acid residues. The core domain contains a large domain, the Rossman fold (a region required for NAD^+ binding), and a small domain – a zinc ribbon with a flexible spiral subdomain. Lying between these domains is the region responsible for catalysis [22].

All known SIRTs are subdivided into five classes (I–IV and U). In mammals, there are seven members of the sirtuin family (SIRT1-7), which are members of classes I–IV and have different enzymatic activity profiles and subcellar compartmentalization [22]. SIRT1 is located in the nucleus but can circulate in the space between the cytoplasm and the nucleus [3]. SIRT2 is mainly located in the cytoplasm but can bind to chromatin in the process of mitosis [66]. SIRT3 is located in mitochondria and translocates to the nucleus in response to stress (for example, DNA damage) [88]. SIRT4 and SIRT5 are located in mitochondria, while SIRT6 and SIRT7 are present in the heterochromatin areas and nucleolus [66]. The main activity of SIRT4 and SIRT6 is ADP-ribosylation, while SIRT5 shows demalonylation and desuccinylation activities [18].

In mammals, SIRTs have been shown to take part in forming heterochromatin, silencing transcription, regulating ion channels, and modulating oxidation-reduction processes. SIRTs are known to be involved in controlling insulin secretion, glycolysis, the ornithine cycle, mitochondrial biogenesis, glycogenesis, and fat oxidation [10, 13, 31, 34, 99]. SIRTs are involved in the pathogenesis of various age-associated diseases, including neurodegenerative disorders [30, 97]. Some SIRT target proteins, such as KeapI and CUL3, are effectors for the main pathways of oxidative stress (Fig. 1) [65, 95, 104, 108]. Nonetheless, the mechanisms underlying the actions of each SIRT on these effectors and on antioxidant and oxidation-reduction signal transmission provide an actively developing area of research.

The aim of this review is to analyze the role of SIRTs in oxidative-reductive regulation, oxidative stress, and the pathogenesis of neurodegenerative diseases.

The role of SIRTs in the oxidation-reduction balance. Free radicals (reactive oxygen species (ROS) and reactive nitrogen species) are generated by numerous metabolic and biosynthetic pathways, including the mitochondrial respiratory chain, phagocytosis, prostaglandin synthesis, and the cytochrome P450 system. In addition, nonenzymatic cellular reactions can also be sources of free radicals. Examples of such reactions include the interaction of oxygen and organic compounds and reactions initiated by ionizing radiation. In health, ROS and nitrogen are required for some biochemical reactions and stimulation of signal cascades. However, excess free radicals can damage DNA, RNA, and other biologically important molecules within cells.

Antioxidants generally act via one of two pathways: either interrupting the free radical formation cascade or preventing its occurrence. The main antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione reductase, prevent triggering of the oxidative cascade, cleaving the molecules responsible for forming free radicals. Another important type of antioxidant enzyme, peroxiredoxins, control intracellular peroxide levels.

The idea that SIRTs are involved in regulating the oxidation-reduction balance was confirmed by their interaction with various molecules – antioxidant response elements (ARE), which mediate signal cascades regulating gene transcription in cells subjected to oxidative stress. ARE molecules have biological and structural characteristics allowing them to trap changes in the oxidation-reduction status of cells. They then activate transcriptional responses mediated mainly by NRF2 molecules [113, 115]. In the absence of stress, NRF2 protein is located in the cytoplasm, where it is degraded by clusters of specialized Keap1 and CUL3 proteins via ubiquitinylation. In oxidative stress, the Keap1-CUL3 ubiquitinylation system is impaired, NRF2 accumulates in the cytoplasm and is translocated to the nucleus, where it initiates the transcription of antioxidant genes and their proteins simultaneously with one of the Maf proteins (MAFF, MAFG, MAFK) [49]. In the nucleus, NRF2 binds with electrophilic response element (ERE), which additionally modulates the expression of genes involved in the detoxification and elimination of electrophilic agents, leading to increases in the antioxidant activity of cells (Fig. 1) [119]. Dysregulation of ARE/ERE has the result that oxidative stress can lead to the development of neurodegenerative, autoimmune, and cardiovascular diseases, cancerogenesis, and accelerated body aging [87].

Studies have shown that SIRT2 deacetylates NRF2, leading to decreased total and nuclear NRF2 levels [112]. In addition, SIRT2 can also regulate NRF2 levels in the nucleus by controlling the phosphorylation of Akt kinase, which leads to modulation of total glutathione and glutamate cysteine ligase levels. Thus, SIRT2 may be a key modulator of this aspect of the antioxidant response [14]. SIRT1 also appears to be involved in this process. Knockdown of SIRT1 inhibits the expression of the *NRF2*, *HO-1*, and *SOD1* genes. The antioxidant resveratrol, a SIRT1 activator, modulates the expression of NRF2-dependent genes, which promotes neuroprotection in cerebral ischemic damage [109].

SIRT6 has been shown to coactivate NRF2 for protection of human mesenchymal stem cells (hMSC) from oxidative stress [79]. It is interesting that the signal pathways associated with oxidative stress evidently take part in modulating SIRT activity and influence their expression, posttranslational modifications, and protein-protein interactions [86].

Thus, most SIRTs in mammals may be linked with signal transmission in oxidative stress. Existing data on the involvement of each human sirtuin in controlling the oxidation-reduction balance will be discussed in detail below.

SIRT1 is the best studied of all mammalian SIRTs. SRT2014, a synthetic activator of SIRT1, decreases the level of lipid peroxidation markers in the liver and muscles and increases SOD2 levels in muscle tissue in C57BL/6 mice [64]. This action of SIRT1 may thus be mediated by key redox-sensitive transcription factors, including FOXO3a and p53. The FOXO transcription factor family is involved in regulating a wide spectrum of genes associated with antioxidant defense [48]. SIRT1 is known to deacetylate FOXO3a protein, which induces antioxidant responses by activating SOD2 and catalase. Deacetylation of FOXO3a protein by SIRT1 leads to its activation. This promotes increases in antioxidant defense. In addition, FOXO3a regulates the expression of mitochondrial genes, leading to modulation of ROS levels [20]. p53, usually regarded as a tumor suppressor protein, is also a redox-sensitive protein and SIRT1 substrate [61]. In the absence of cellular stress, p53 can decrease intracellular ROS levels and increase the production of antioxidant proteins such as SOD2 and glutathione peroxidase-1. Impairments to p53 regulation lead to increases in intracellular ROS levels and oxidation of DNA [77].

SIRT1 has been shown to regulate the acetylation of transcription factor *PGC-1α*, the major regulator of mitochondrial biogenesis [71].

Oxidative stress can evidently induce impairments to the functioning of SIRT1. The response to oxidative stress includes redistribution of SIRT1 at the chromatin level, impairing the regulation of transcription. Excess hydrogen peroxide leads to activation of genes linked with SIRT1, including those involved in metabolism, apoptosis, ion transport, cell mobility, and signal transmission via G protein [74]. Hydrogen peroxide-induced oxidative stress suppresses SIRT1 synthesis in keratinocytes depending on the dose and time of exposure. Treatment of cells with the SIRT1 activator resveratrol prevents oxidizer-associated cell death and prevents cell aging [14]. The SIRT1 inhibitors sirtinol and nicotinamide increased cell apoptosis induced by hydrogen peroxide [35]. These data provide evidence that SIRT1 is a key molecule in preventing oxidative damage to cell structures.

SIRT2 is expressed in the brain, kidneys, pancreas, ovaries, liver, and fatty tissue in mammals [25]. In the cytoplasm, SIRT2 functions to organize the cytoskeleton and deacetylates α-tubulin. In the nucleus, SIRT2 deacetylates lysine K16 residues in histone H4, which is involved in regulating the cell cycle [26]. In addition, SIRT2 takes part in forming the nuclear membrane by means of deacetylation of ANKLE2 protein – a regulator of nuclear envelope assembly [44]. SIRT2 activity and expression change depending on the energy status of the cell: activation occurs in the low-energy state and suppression in the high-energy state [25]. This suggests that SIRT2 is involved in regulating energy metabolism and cellular homeostasis.

SIRT2 also activates mitochondrial biogenesis regulator PGC-1α, which leads to increased expression of antioxidant enzymes and decreased levels of ROS. Like SIRT1, SIRT2 deacetylates FOXO3a in response to oxidative stress [50].

Other targets of SIRT2 include metabolic enzymes: glucose-6-phosphate dehydrogenase (G6PD), phosphoglycerate mutase (PGAM2), and transcription factor NF-ϰB [25]. In conditions of oxidative stress, SIRT2 activates G6PD, a key enzyme in the pentose phosphate pathway, which produces NADPH in the cytosol. NADPH is a molecule required to counter oxidative damage, maintaining glu-

tathione in the reduced form. In addition, SIRT2 activates transcription factor NF-κB. Transcription of several NF-κB-dependent genes has been shown to affect intracellular ROS levels. In turn, NF-κB activity is regulated by the ROS level. NF-κB controls the synthesis of enzymes able to produce ROS, such as NADPH oxidase, xanthine oxidoreductase, inducible NO synthase, cyclooxygenase-2, and cytochrome P450. NF-κB also regulates the activity of the enzymes SOD1, SOD2, thioredoxins, and glutathione-S-transferase, which help inhibit ROS. SIRT2 evidently supports the regulation of NF-κB depending on the oxidation-reduction state of the cell. These data provide evidence that SIRT2 plays a critical role in modulating oxidative stress, protecting the body from metabolic impairments.

SIRT3 is located in the nucleus, but responds to stress signals, such as DNA damage, by being transported into mitochondria, where is it cleaved by peptidase to the active form. SIRT3 modulates mitochondrial metabolism and increases the longevity of experimental animals. Mice not synthesizing SIRT3 have reduced oxygen consumption and a simultaneous increases in intracellular ROS production, a well as higher levels of oxidative stress in muscles [40]. Analogous results were obtained using MCF7, T47D, and CAMA cell cultures, which do not synthesize SIRT3. These cells show elevated expression of ROS, which can induce DNA damage and activate the HIF1α molecules involved in the mechanism of impaired vascularization and angiogenesis, energy metabolism, cell survival, and tumor invasion [21]. In conditions of restricted calorie intake, SIRT3 activates the enzymes 3-hydroxy-3-methylglutaryl-CoA synthase and acyl-CoA dehydrogenase, ketone body formation, and long-chain fatty acid oxidation, which are associated with increases in longevity [92].

Polymorphisms in the *SIRT3* gene are more commonly encountered in the long-lived [6, 7]. The variable number of tandem repeats in the enhancer region of intron 5 of the *SIRT3* gene evidently affects the activity of this enhancer. Studies led to the conclusion that people carrying the allele with the least active enhancer have a lower probability of living to old age. This variant of the allele is virtually absent in males over 90 years old living in Italy [6]. Nonetheless, later studies in large cohorts have not supported this conclusion. This suggests that the effects of *SIRT3* on longevity are less significant than previously thought [53].

Like other sirtuins, SIRT3 deacetylates enzymes responsible for decreases in intracellular ROS, leading to protection from oxidative stress and its associated pathology (neurodegenerative, cardiovascular disease, cancerogenesis) and accelerated aging [2]. SIRT3 activates isocitrate dehydrogenase (IDH2), SOD2, and catalase – enzymes neutralizing ROS [65]. Mice with *SIRT2* knockout on a high-cholesterol diet show increased ROS levels in the vascular endothelium [106]. Increased intracellular ROS levels stimulate *SIRT3* transcription and may thus lead to deacetylation of SOD2 by means of a feedback loop [65].

Decreased SIRT3 levels were seen in human epidermal keratinocytes after exposure to ozone, which correlated with DNA damage, higher hydrogen peroxide levels, and decreases SOD2 concentrations within cells [63]. The lack of regulation of ROS in keratinocytes, which form and maintain a protective layer of skin cells, influences their differentiation. When dysregulation of SIRT3 occurs in keratinocytes, levels of the superoxide anion increase, promoting expression of differentiation markers. The opposite is seen in keratinocytes with induced SIRT3 overexpression. Superoxide anion and differentiation marker levels in these cells are decreased. Thus, SIRT3 takes part in suppressing the differentiation of the epidermis by decreasing oxidative stress [4]. SIRT3 modulates mitochondrial functions, regulating the NAD^+ level, and may be a factor protecting against acute liver and kidney disease [67]. Thus, SIRT3 has been shown to have a role in protecting cells from oxidative damage and genotoxic stress.

SIRT4 is located in mitochondria and is involved in ribosylation of adenosine diphosphate (ADP) [1]. High levels of *SIRT4* expression are seen in heart, kidney, liver, and brain tissues. It was initially believed that SIRT4 lacks NAD-dependent deacetylase activity. However, recent studies have established that SIRT4 is able to deacetylate lysine, allowing it to control insulin secretion. Mice with *SIRT4* knockout have elevated insulin secretion [1].

All sirtuins other than SIRT4 play key roles in decreasing mitochondrial oxidative stress on a restricted calorie diet [103], though this does not alter the role of SIRT4 in controlling oxidative stress.

SIRT4 is involved in regulating ROS production in mitochondria, though it remains unclear whether it affects activation of the antioxidant enzymes located in the mitochondrial matrix. In angiotensin II (AngII)-induced cardiac hypertrophy in mice, SIRT4 overexpression reduced ROS content in cardiomyocyte mitochondria. Knockout of the *SIRT4* gene in this model led to increased ROS synthesis in cardiomyocyte mitochondria [59]. Similar results were obtained in rat cardiomyocytes, suggesting that SIRT4 may control ROS synthesis in heart cells. SIRT4 has been shown to inhibit SOD2 binding to SIRT3, leading to increases in the acetylation and decreases in the activity of this enzyme [59]. These results provide evidence that SIRT4 may play an important role in controlling signal molecules involved in antioxidant reactions.

SIRT4 has been shown to be an essential factor in fatty acid oxidation in liver and muscle cells. Knockdown of *SIRT4* increases fatty acid oxidation and oxygen consumption in mouse hepatocytes, possibly via regulation of SIRT1 expression [70]. Fatty acid oxidation is a key source of mitochondrial ROS and impaired regulation of this process is linked with kidney damage in diabetes mellitus [83].

SIRT4 has been studied as a biomarker for coronary heart disease. Patients with cardiovascular pathology, obesity, and fatty hepatosis have lower blood SIRT4 than healthy

people [94]. There are few such studies, so it is unclear whether SIRT4 can serve as a biomarker for ischemic heart disease. In addition, SIRT4 expression differs depending on cell type, which has to be considered before it can be used as a biomarker for various diseases.

SIRT5 is located in mitochondria and its function consists of deacetylation, demalonylation, and desuccinylation of proteins [26]. SIRT5 expression is seen in brain, heart, and liver tissues and in lymphoblasts, where it accumulates in the intermembrane spaces of mitochondria [58]. SIRT5 has a role in cellular metabolism, detoxification, and the regulation of oxidative stress and energy balance, and it also functions as a mediator in apoptosis [56]. Nonetheless, there is no consensus as to the role of SIRT5 in these processes.

SIRT5 is known as a regulator of fatty acid β-oxidation in mitochondria, the urea cycle, and cellular respiration [110]. SIRT5 deacetylates and activates carbamoylphosphate synthetase (CPS1), which catalyzes the first step in the urea cycle. Studies in mice with SIRT5 knockout have demonstrated increased urinary ammonia levels during starvation. Mice overexpressing *SIRT5* show elevated CPS1 activity, promoting conversion of ammonia to the less toxic urea [75]. Ammonia activates ROS synthesis and decreases intracellular glutathione content [11], which is evidence for the indirect involvement of SIRT5 in controlling oxidative stress.

It is interesting that SIRT5 protects cardiomyocytes from apoptosis induced by oxidative stress [56]. Suppression of oxidative stress is regarded as a possible mechanism for preventing apoptosis in SH-EP neuroblastoma cells [54]. These results are consistent with data obtained in lung tumor and epithelial cells [55, 101]. SIRT5 has been shown to bind SOD1 and to desuccinylate it, increasing its activity. SOD1-mediated decreases in ROS are seen on coexpression of SOD1 and SIRT5. SIRT5 probably mediates the post-translational regulation of SOD1 in lung tumor cells [55].

ROS concentrations decrease in cells transfected with SIRT5. This suggests that SIRT5 suppresses the development of oxidative stress within cells. The function of SIRT5 probably consists of supporting cell responses to oxidative stress.

SIRT6 is located in the cell nucleus and its function consists of NAD^+-dependent deacetylation of lysines K9 and K56 of histone H3 (H3K9 and H3K56) [96]. SIRT6-mediated deacetylation of histone H3 mediates regulation of gene expression via recruitment of transcription factors, e.g., NF-ϰB [117]. In addition to the fact that SIRT6 plays an important role in controlling chromatin structure and recruitment of transcription factors, it also participates in DNA repair [38]. SIRT6 regulates aging rate in mammals [26]. Mice with knockout of *SIRT6* had decreased longevity and a phenotype with premature aging, including decreased blood glucose and insulin-like growth factor (IGF-1) levels [68]. Considering the important role of SIRT6 in cell homeostasis, impairments to the synthesis of this enzyme evidently influence the development of a variety of pathological processes [5, 84]. SIRT6 is regarded as an important metabolic sensor supporting the connection between signals from the environment and metabolic homeostasis and stress responses in mammals [5, 100].

SIRT6 has been proposed to have a role as mediator of oxidative stress and a marker for myocardial damage in ischemia-reperfusion. *SIRT6* overexpression protects cardiomyocytes from damage in ischemia-reperfusion by decreasing oxidative stress and activating endogenous antioxidants via the AMPK-FOXO3α axis, ensuring resistance to oxidative stress [100].

SIRT6 has been shown to protect hMSC from oxidative stress by activating NRF2. Oxidation-reduction metabolism is impaired in hMSC not synthesizing SIRT6, which leads to increased sensitivity to oxidative stress. It has been suggested that SIRT6 is a coactivator of NRF2, triggering the antioxidant response pathway of oxidative stress [79].

In addition, SIRT6 and NF-ϰB demonstrated protective effects in relation to accelerated endothelial aging mediated by high glucose levels. Decreases in SIRT6 levels during short-term exposure to high glucose levels led to increased NF-ϰB expression, while SIRT6 overexpression decreased NF-ϰB expression. The protective effects of the antioxidant ergothioneine are linked with increased quantities of SIRT1 and SIRT6 within cells and their negative regulation of NF-ϰB. This indicates that both SIRTs have high potential in relation to regulating redox signals [17]. SIRT6 also takes part in controlling inflammation in diabetic atherosclerotic endothelial damage [57]. SIRT6 repression is seen in stress responses, leading to acetylation of histones and increases in gene expression [116]. The functions of SIRT6 are evidently antiglycolytic and antioxidant, protecting cells from ROS [33].

SIRT7 is expressed in the nucleolus and mediates positive regulation of transcription of ribosomal DNA (rDNA) by binding to histones [26]. Different levels of SIRT7 mRNA expression are seen in all tissues but higher levels are seen in tissues with higher metabolic activity. In humans, SIRT7 expression decreases with age [46], while mice with SIRT7 knockout show premature aging [98]. In physiological aging, SIRT7 can translocate from the nucleolus to the cytoplasm and chromatin, where it inhibits rDNA transcription [47].

SIRT7 overexpression has been shown to activate transcription mediated by RNA polymerase I, while knockdown or inhibition of SIRT7 decreases it. SIRT7 plays a key role in cellular energy balance and, in stress conditions, promotes reductions in rDNA transcription. SIRT7 has been seen to have a role in regulating mitochondrial homeostasis by deacetylating GABPβ1 protein, which is one of the subunits of the complex involved in regulating the expression of mitochondrial genes *Clpp*, *Polrmt*, *Mfn1*, *Fars2*, *Elac2, and Nt5m* [85].

Thus, SIRTs constitute a class of epigenetic transcription regulators, which determines their important role in modulating the expression of a wide spectrum of genes. The most important function of SIRTs is their role in maintain-

ing the intracellular oxidation-reduction balance. Interest in the role of SIRTs in the development of neurodegeneration and the pathogenesis of Alzheimer's and Parkinson's diseases continues to increase.

The role of SIRTs in brain aging and the development of neurodegenerative diseases. The aging process is characterized by numerous changes at the body, tissue, and cellular levels. With age, senescing cells accumulate in the tissues, impairing their normal functioning. Senescent cells modify the microenvironment, secreting cytokines, chemokines, and inflammatory mediators. This secretory phenotype is one of the causes of the chronic inflammation seen in elderly and old people (inflammaging) and may also accelerate the rate of replicative aging of neighboring cells. Senescent cells, apart from the secretory phenotype, have a series of characteristics such as elevated levels of secretion of cell cycle inhibitors, β-galactosidase activity, and DNA damage. Age-related increases in DNA damage result from impairment to the effectiveness of the DNA repair system. DNA damage is believed to be the main cause of cell aging. This applies to both replicative and stress-related (oxidative, genotoxic) aging. DNA damage impairs normal cell functioning, but in normal conditions the effectiveness of the repair system is sufficient to protect cells from the accumulation of DNA damage. However, age-related decreases in DNA repair lead to the accumulation of damage and, as a result, cell aging [72].

As noted above, the main functions of SIRTs are DNA repair, control of inflammation, and support of antioxidant defense. SIRTs are therefore regarded as factors able to slow age-related changes in the body by supporting physiological levels of DNA repair and controlling the oxidation-reduction balance.

A number of studies have demonstrated the role of SIRTs in the pathogenesis of Alzheimer's disease (AD) and other neurodegenerative diseases. Decreases in SIRT1 and SIRT3 mRNA and protein levels in the brain in patients with AD correlate with the stage and duration of illness [41, 60]. Similar data on decreases in SIRT1 levels were obtained in vitro using SH-SY5Y neuroblastoma cells treated with neurotoxic amyloid Aβ25–35 [52]. Studies in a mouse model of AD showed increased expression of SIRT3 mRNA, which corresponded to the spatial and temporal profiles of amyloid Aβ accumulation. In elderly patients with AD, high levels of SIRT3 mRNA are seen in the temporal lobes of the brain [105]. SIRT5 was identified in activated brain microglia from AD patients [60]. Interaction of amyloid Aβ42, sphingosine kinases, and mitochondrial SIRT3-5 may play an important role in the pathogenesis of AD [15]. Excessive expression of amyloid β-precursor (APP) and presenilin-1 led to decreased SIRT3 mRNA and protein expression in the brains of mice with AD. This suggests a more complex mechanism for the interaction of SIRTs and the main molecules involved in the pathogenesis of AD [111].

SIRT1 has been suggested to support the balance between the amyloidogenic and nonamyloidogenic processing of APP, preventing the development of AD [82]. In addition, SIRT1 can promote Aβ degradation via the LKB1/AMPKα pathway, the main function of which is to control neuron metabolism and growth [81].

It has also been reported that activation or overexpression of *SIRT1* affects the toxicity of Aβ mediated by microglial cells, due to its ability to inhibit NF-ϰB signal transmission [89]. SIRT1 can protect neurons from the synapse loss typical of the early stages of AD [24].

A SIRT2 inhibitor, the AGK2 molecule, shifts the balance between α- and β-secretases, decreasing the cellular amyloid load and leading to improvement in cognitive functions in models of transgenic mice with AD [8]. AGK2 decreases amyloid Aβ42-mediated glial activation [89]. Thus, SIRT1 and SIRT2 regulate the processing of APP, probably in opposite ways.

Apart from the amyloid hypothesis of the development of AD, there is also the τ hypothesis. It has been suggested that the accumulation of pathologically modified τ protein, which is associated with microtubules, leads to the formation of neurofibrillary tangles, which cause impairments to axonal transport and axon damage. Some data indicate that SIRTs mediate the leptin-dependent inhibition of τ protein phosphorylation [27]. SIRT1 also deacetylates τ protein. Changes in the activity of SIRTs may therefore decrease the number of neurofibrillary tangles [16]. Furthermore, SIRT1 and τ protein have a common bottom-up regulatory mechanism, being targets for microRNA-132 and AMPK kinase [32, 81].

SIRT3 evidently also participates in the pathogenesis of AD via modulation of τ protein phosphorylation. Knockdown of *Sirt3* in ex vivo and in vivo models increased τ protein phosphorylation. In addition, autopsy material showed that *Sirt3* expression was reduced in brains from AD patients. Increased Aβ levels can probably decrease *Sirt3* expression, leading to increases in its acetylation and the formation of neurofibrillary tangles [114]. On the other hand, it has been reported that *Sirt3* overexpression prevents Aβ-induced pathological changes in the brains of mice with AD, so the direction of the interaction between SIRT3 and Aβ remains to be explained [114].

Four-month-old mice with deficiency of SIRT6 synthesis show impairments to behavior and learning. Histological studies of the brains of these animals show large amounts of DNA damage and hyperphosphorylation of τ protein. SIRT6 probably regulates the stability and phosphorylation of τ protein by activating kinase GSK3α/β [43].

Apart from Aβ and τ protein, the two most important molecular factors in the pathogenesis of AD, SIRTs can influence the pathways involved in neuroprotection. It has been suggested that SIRT1, acting via interaction with the type β retinoic acid receptor (RAR-β) and subsequent activation of ADAM10 metalloprotease, induces cleavage of the Notch receptor. Release of the intracellular domain of Notch activates the transcription of genes associated with

neurogenesis and neuronal differentiation in response to pathological damage. In addition, Notch targets include genes important for synaptic plasticity, learning, and memory, as well as for generating synapses [12]. Thus, among all SIRTs, SIRT1 is the best studied in the context of the pathogenesis of AD. The neuroprotector action of SIRT1 in AD probably operates at multiple levels and is mediated both by activation of the Notch signal pathway and influences on APP processing and τ protein metabolism.

It has been suggested that the pathogenesis of Parkinson's disease (PD), which affects dopaminergic structures in the brain, also involves SIRTs. As in the case of AD, SIRT1 has neuroprotective properties in models of PD. Thus, the SIRT1 activator resveratrol decreased signs of parkinsonism in mice in a model of PD induced by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) [9]. Use of resveratrol in mice with MPTP-induced parkinsonism produced SIRT1-mediated activation of PGC-1α protein, increasing resistance to oxidative stress and neurodegeneration [69]. In addition, variants of the *SERT1* gene promoter linked with decreased SIRT1 protein synthesis correlated with the occurrence of sporadic forms of PD [118].

Studies of PD in animal models have linked SIRT1 deficiency with α-synuclein aggregation. The neuroprotective effect of resveratrol in in vitro models of PD are explained by its ability to induce autophagic degradation of α-synuclein via SIRT1 [107].

Chaperonins may also be targets of SIRT1 in PD; these promote correct protein folding. Chaperonin Hsp70 has been shown to prevent α-synuclein aggregation. SIRT1 deacetylates heat shock factor I (HSF1), which promotes its long-term binding with the target sequence in the gene encoding Hsp70. This leads to increased Hsp70 expression in stress conditions and probably prevents excessive accumulation of α-synuclein in neurons [102].

Conversely, use of a SIRT2 inhibitor in MPTP-induced parkinsonism in mice decreases loss of dopaminergic neurons and improves neurological and behavioral deficit [29]. The SIRT2 inhibitor AGK2 blocks the toxic effects of α-synuclein in an in vitro model of PD [78].

Data published by de Oliveira et al. (2017) showed that SIRT2 overexpression in substantia nigra neurons in rats leads to blockade of α-synuclein acetylation, inducing its aggregation and increasing toxicity. In addition, SIRT2 probably facilitates the transport of aggregated α-synuclein via acetylation of α-tubulin [19]. From this point of view, acetylation is a key mechanism regulating α-synuclein aggregation and toxicity and facilitating its axonal transport, demonstrating the potential therapeutic value of inhibiting SIRT2 in synucleinopathies [76].

SIRT3 and SIRT1 display neuroprotective properties in PD, stabilizing the electron transport chain and decreasing oxidative stress in substantia nigra dopaminergic neurons. Gleave et al. demonstrated that even when SIRT3-myc vector transduction was performed after induction of PD and development of cell stress and behavioral anomalies, increases in SIRT3 synthesis decreased the extent of degeneration of dopaminergic neurons by decreasing acetylation of mitochondrial proteins [23].

Deletions in the *Sirt3* gene increased oxidative stress and decreased membrane potential in mitochondria in substantia nigra dopaminergic neurons. Some authors take the view that age-associated decreases in the protective function of SIRT3 protein constitute the main factor underlying increases in mitochondrial oxidative stress and the apoptosis of substantia nigra dopaminergic neurons in PD [91, 120].

SIRT6 can increase neurodegenerative effects in PD. A small number of studies on this theme have demonstrated that SIRT6 protein levels in the brains of patients with PD are higher than those in healthy people [37]. SIRT6 knockout mice with MPTP-induced parkinsonism had less severe neurological and behavioral changes than animals with normal SIRT6 expression [73]. SIRT6 probably plays a proinflammatory role in the pathogenesis of PD, promoting the production and secretion of proinflammatory cytokines [39]. However, some authors believe that decreased SIRT6 expression in the brain is a sign of accelerated aging and is linked with the progression of neurodegenerative diseases [37, 43, 45], whereby increased neurodegeneration in PD under the influence of SIRT6 requires further investigation.

Conclusions. Existing published data indicate that the main functions of SIRTs in mammals are to support the oxidation-reduction balance in cells and provide antioxidant defense. The authors of many studies emphasize the existence of an interaction between SIRT activity and longevity in experimental animals and humans.

A no less interesting and relevant research direction is that of studying the role of SIRTs in the pathogenesis of neurodegenerative disorders. The mechanism of the pathogenesis and methods of in-life diagnosis of neurodegenerative diseases such as AD and PD thus far remain controversial. The most widespread theories for the occurrence of AD are the amyloid and τ hypotheses, while that for PD is the synuclein hypothesis. Overall, these explain the mechanisms of development of these diseases, though it is unclear what is the trigger for accumulation of pathogenic Aβ42, τ, and α-synuclein proteins. Impairment of the functions of SIRTs leads to dysregulation of the oxidation-reduction balance. This induces impairments to neuron function. The best studied in the context of the pathogenesis of AD and PD are SIRT1, 2, 3, and 6. SIRT1 and SIRT3 evidently play an important role as neuroprotectors, while SIRT2 exacerbates the course of PD and AD and SIRT6 has differently directed effects. The effects of SIRT4, 5, and 7 on the occurrence and development of AD and PD have received essentially no study. A potential direction in molecular medicine is provided by further studies of the effects of SIRTs on the development of neurodegenerative diseases. This allows SIRTs to be regarded as potential targets for the pharmacotherapy of AD and PD.

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