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ЭПИГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ КАРДИОПРОТЕКЦИИ: В ФОКУСЕ — АКТИВАЦИЯ СИРТУИНОВ

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Epigenetic Mechanisms of Cardioprotection: Focus is on Activation of Sirtuins

Резюме

Окислительный стресс является общим признаком старения и сердечно-сосудистых заболеваний (ССЗ), включая атеросклероз, сердечную недостаточность, гипертонию, сахарный диабет и другие заболевания сосудистой системы. В этой связи, в последние годы исследователи проявляют повышенный интерес к сиртуинам (SIRT) — адаптерам стресса и эпигенетическим ферментам, участвующим в клеточных механизмах контроля возрастных патологий, рака и ССЗ. Среди сиртуинов, которых у млекопитающих семь (SIRT1-SIRT7), кардиопротекторными, противовоспалительными, атеропротекторными и антивозрастными свойствами в наибольшей степени обладают SIRT1 и SIRT6. В данном обзоре мы представляем всесторонний анализ последних событий в области клеточных и молекулярных сигнальных путей, контролируемых двумя посттрансляционными модификаторами — SIRT1 и SIRT6, которые доказали свою ценность в качестве инструментов для ослабления воспаления и окислительного стресса на уровне сердечно-сосудистой системы. Более глубокое понимание эпигенетических механизмов, через которые оказывают своё кардиопротекторное действие SIRT1 и SIRT6, будет иметь широкие последствия и ускорит разработку селективных и эффективных фармакологических препаратов для модуляции сиртуинов с целью профилактики и лечения ССЗ.

Ключевые слова: *SIRT1, SIRT6, окислительный стресс, эндотелиальная дисфункция, старение сосудов, сердечно-сосудистые заболевания*

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Abstract

Oxidative stress is a common sign of aging and cardiovascular disease (CVD), including atherosclerosis, heart failure, hypertension, diabetes mellitus and other diseases of the vascular system. In this regard, in recent years, researchers have shown increased interest in sirtuins (SIRTs) — stress adapters and epigenetic enzymes involved in cellular mechanisms for controlling age-related pathologies, cancer and CVD. Among sirtuins, of which there are seven in mammals (SIRT1-SIRT7), SIRT1 and SIRT6 possess the most cardioprotective, anti-inflammatory, atheroprotective and anti-aging properties. In this review, we present a comprehensive analysis of the latest developments in the field of cellular and molecular signaling pathways controlled by two post-translational modifiers — SIRT1 and SIRT6, which have proven their worth as tools to reduce inflammation and oxidative stress at the level of the cardiovascular system. A deeper understanding of the epigenetic mechanisms through which SIRT1 and SIRT6 exert their cardioprotective effect will have widespread implications and will accelerate the development of selective and effective pharmacological agents for modulating sirtuins for the prevention and treatment of CVD.

Key words: *SIRT1, SIRT6, oxidative stress, endothelial dysfunction, vascular aging, cardiovascular disease*

Conflict of interests

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BCA — ATP-binding cassette subfamily A, ABCG — ANP-binding cassette subfamily G, Akt — protein kinase B, AMPK — AMP-activated protein kinase, Ang II — angionensin II, ApoE — apolipoprotein E, AP-1 — activator protein 1, ATIR — angiotensin II type I receptor, Bcl-2 — B cell lymphoma 2, Bcl xL — B cell lymphoma-extra-large, CVD — cardiovascular diseases, CAT — catalase, CCR7 — C-C chemokine receptor 7, COL1A2 — collagen type 1, EC — endothelial cells, eNOS — endothelial nitric oxide synthase, ECP — endothelial cell precursors, EPCs — endothelial progenitor cells, ERR — estrogen-related receptors, ERK — extracellular signal-regulated kinase, FOXO — forkhead box O, I/R — ischemia-reperfusion, ICAM-1 — intercellular adhesion molecule-1, IGF — insulin-like growth factor, JNK — c-Jun N-terminal kinase, LKB1 — liver kinase B1, Lox-1 — lectin-like oxLDL receptor 1, LXR — liver X-receptor, MCP-1 — monocyte chemoattractant protein 1, MMP-9 — matrix metalloproteinase-9, MnSOD — manganese superoxide dismutase, NAD — nicotinamide adenine dinucleotide, NADPH — nicotinamide adenine dinucleotide phosphate, NAMPT — nicotinamide phosphoribosyltransferase, NBS-1 — Nijmegen breakage syndrome-1, NFkB — nuclear factor-kappa B, NKG2D — natural-killer group 2 member D, NO — nitric oxide, NRF1 — nuclear respiratory factor1, ox-LDL — oxidized low density lipoproteins, PARP1 — poly-(ADP-ribose) polymerase 1, PGC-1α — proliferator-activated receptor g coactivator-1α, PI3K — phosphoinositide 3-kinases, PIP3 — phosphatidylinositol-3,4,5-triphosphate, PCSK9 — proprotein convertase subtilisin/kexin type 9, PDK1 — 3-phosphoinositide-dependent kinase 1, PPAR-α — peroxisome proliferator-activated receptor coactivator-α, ROS — reactive oxygen species, SERCA2a — sarcoplasmic calcium ATPase, SIRT — sirtuin, SOD — superoxide dismutase, SREBP — sterol regulatory element-binding proteins, STAT3 — signal transducer and activator of transcription 3, TG — triglycerides, TIMP3 — tissue inhibitor of metalloproteinase, TNFSF4 — tumor necrosis factor superfamily member 4, VCAM-1 — vascular cell adhesion molecule-1

Introduction

Sirtuins (SIRT), nicotinamide adenine dinucleotide (NAD+)-dependent deacetylating enzymes, first found in yeast, are class III histone deacetylases. They all have a highly conserved NAD+ dependent catalytic core domain of 250–270 amino acid residues. Mammals have seven sirtuins (SIRT1–SIRT7). SIRT1 is localized in the nucleus and translocated to the cytosol under special conditions. It has been proven that SIRT6 is localized not only in the nucleus, but also in the cytosol. SIRT2 is primarily found in the cytosol, SIRT3, SIRT4 and SIRT5 in mitochondria, and SIRT7 is nuclear and nucleolar. Besides performing the well-known deacetylase function, sirtuins also function as mono-ADP-ribosyltransferase, lipoamidase (SIRT4), hydrolase (SIRT6), demalonylase, decrotonylase (SIRT3) and desuccinylase (SIRT5).

Sirtuins regulate important molecular pathways in eubacteria, archaea, and eukaryotes, and have a positive effect on life expectancy. They are involved in a variety of metabolic and homeostatic processes, including gluconeogenesis, fatty acid oxidation, oxidative phosphorylation, urea cycle, and endothelial homeostasis. Accumulated data have shown that sirtuins play an important role in cell adaptation to nutritional stress and are not only important sensors of energy status, but also counteract cellular metabolic stress by acting as stress adapters [1]. They play a central role in the development of age-related metabolic disorders, as well as stress resistance [2]. In addition to histone modifications, sirtuins directly modulate non-histone substrates, including DNA repair enzymes and other repair factors. The role of sirtuins in maintaining vascular homeostasis and in the development of cardiovascular diseases (CVD) is interesting. In endothelial cells (ECs), SIRT1 regulates cellular physiology in a unique way by controlling endothelial homeostasis and the functional state of blood vessels by modulating the activity of endothelial nitric oxide synthase (eNOS), p53, angiotensin II receptor (Ang II) of type 1 (AT1R, Ang II type 1 receptor) and transcription factor forkhead box O (FOXO) 1. SIRT2 is involved in vascular remodeling due to arterial hypertension [3], while SIRT3 controls systemic levels of oxidative stress and increases the survival rate of ECs in response to hypoxia [4]. SIRT4 and SIRT7 exacerbate

cardiac hypertrophy and negatively affect the proliferation and migration of ECs and vascular smooth muscle cells (VSMCs) [5]. The cardioprotective role of SIRT6 in the development of atherosclerotic plaque was recently established [6].

In this review, we discuss new views on cellular and molecular signals regulated by SIRT1 during the onset and development of CVD, as well as by SIRT6 during the formation of atherosclerotic plaques. In particular, we highlight their role in protection from pathological processes mediated by oxidative stress, including ischemia-reperfusion (I/R) heart damage, arterial wall remodeling, inflammation, vascular aging, and atherosclerosis.

Protective Role of SIRT1 and SIRT6 in Cases of Atherosclerosis

Aging processes are closely associated with atherosclerosis, which is the most common cause of death in elderly people, diabetes mellitus, dyslipidemia, metabolic syndrome, and hypertension. Atherosclerosis is triggered by SIRT1 deficiency in endothelial cells, smooth muscle cells, and monocytes/macrophages, which activates such processes as oxidative stress, inflammation, development of foam cells and impaired autophagy in the vascular wall. In turn, excessive autophagy triggered by high level of inflammation or oxidative stress contributes to decreased collagen synthesis, thinning of the fibrous cap and plaque destabilization, restenosis, and the development of acute coronary syndrome. In recent years, a link was also demonstrated between SIRT6 and the vulnerability of atherosclerotic plaque [6, 7].

Studies have shown that SIRT1 has an atheroprotective effect by increasing the nitric oxide (NO) level, degradation of serine-threonine kinase LKB1 (liver kinase B1), blocking NF-*k*B (nuclear factor-kappa B) — mediated inflammatory process, reducing the intensity of oxidative stress and control of autophagy [8]. In apolipoprotein E knockout (ApoE –/–) mice, endothelium-dependent vasorelaxation is usually reduced. However, if these mice are crossed with SIRT1-transgenic (SIRT1-Tg) mice, the endothelium-dependent vasorelaxation in their offspring, i.e. in SIRT1-Tg/ApoE (–/–) mice, is significantly improved and is accompanied by increased aortic eNOS [9]. Overexpression of endothelial SIRT1 in these mice, along with activation of eNOS expression, also prevents the expression of endothelial adhesion molecules and inhibits the development of aortic plaques in response to a high-fat diet [10].

Along with these data, SIRT1 involvement in preventing the progression of atherosclerotic lesions is evidenced by increased aortic eNOS activity and SIRT1 expression in hypercholesterolemic mice after oral administration of low doses of red wine as a source of resveratrol, a SIRT1 activator [11]. SIRT1 levels and activity were also significantly reduced in the lungs of ApoE –/– mice prone to atherosclerosis, which caused lung endothelium dysfunction due to increased acetylation and inactivation of eNOS [12]. Moreover, SIRT1 counteracted neointima development by suppressing the activity of the transcription factor AP-1 (activator protein 1) and decreasing the expression of cyclin D1 and MMP-9 (matrix metalloproteinase 9) [13].

At the level of smooth muscle cells, SIRT1 protects DNA from damage and inhibits atherosclerosis, in part, by activating NBS-1 (Nijmegen breakage syndrome-1) repair protein. It is notable that ApoE –/– mice expressing inactive truncated SIRT1 (Dex4) in smooth muscle cells demonstrate progressive atherosclerosis and signs of plaque vulnerability (relatively thin fibrous cap and media degeneration). In patients with type 2 DM, atherosclerotic plaques are usually characterized by increased MMP9 activity and decreased expression of TIMP3, tissue inhibitor of metalloproteinase 3. These changes in atherosclerotic plaques have been shown to be associated with significantly reduced SIRT1 levels [14]. In particular, overexpression of SIRT1 in smooth muscle cells increased the activity of gene promoter TIMP3, whereas inhibition of SIRT1 activity decreased TIMP3 expression. It is worth noting that SIRT1 in smooth muscle cells supports collagen synthesis and prevents the process of destabilization and destruction of plaque by promoting nuclear displacement and proteasomal degradation of the activity of the X-box transcription factor (RFX5, regulatory factor X5), thus weakening its binding to the promoter of the collagen I gene (COL1A2) [14]. In response to atheroprotective pulsatile shear stress, co-regulation of AMPK (adenosine monophosphate-activated protein kinase) and SIRT1 by CaMKKb (Ca2+ / calmodulin-dependent protein kinase b) promotes the development of an atheroprotective phenotype. In the proposed cell mechanism, AMPK and SIRT1 act in coordination in the cytoplasm in order to activate eNOS, thereby stimulating NO-mediated anti-inflammatory effects through the suppression of MCP-1 (monocyte chemoattractant protein-1), adhesive molecules VCAM-1 (vascular cell adhesion molecule-1), ICAM-1 (intercellular adhesion molecule-1) and E-selectin. Furthermore, AMPK and SIRT1 in the nucleus activate PGC1a (peroxisome proliferator-activated receptor gamma, coactivator 1 alpha), resulting in an increase in the level of antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) [15]. AMPK/NADPH (nicotinamide adenine dinucleotide phosphate)-oxidase / Akt (serine/threonine protein kinase B) / eNOS signaling pathway is also modulated

by quercetin, an antioxidant that activates SIRT1 and suppresses endothelial oxidative damage caused by oxidized low density lipoproteins (ox-LDL) [16]. Resveratrol, similarly to quercetin, reduces endothelial vascular inflammation and ox-LDL-induced damage by increasing the activity of AMPK/SIRT1 or cAMP-PRKA (serine/threonine protein kinase)-AMPK-SIRT1 signaling pathway [17]. In particular, ox-LDL inhibit autophagic flow due to a mechanism that includes ox-LDL-induced SIRT1-dependent lysosomal dysfunction [18].

The atheroprotective effect of SIRT1 is also mediated through the subtle modulation of the aging of endothelial cell precursors (ECP) and migration of adventitial fibroblasts [19]. In particular, in ECP, NAMPT (nicotinamide phosphoribosyltransferase), a rate-limiting enzyme in the NAD + biosynthetic pathway, diminishes ox-LDL-induced aging by increasing SIRT1 expression through the channel PI3K (phosphoinositide 3-kinases) / Akt / ERK (extracellular signal-regulated kinases) [19]. In peripheral blood mononuclear cells of individuals with metabolic syndrome, high glucose and palmitate-dependent damage to SIRT1 is associated with decreased NAMPT expression, subsequent depletion of cellular NAD+, and increased generation of reactive oxygen species (ROS).

The key event in atherogenesis is the infiltration of macrophages of monocytic origin into subendothelial space. The uptake of ox-LDL via lectin-like Lox-1 receptors determines the accumulation of cholesterol in macrophages and the subsequent development of foam cells. SIRT1 +/+ ApoE −/− mice demonstrated reduced rates of foam cell development and ox-LDL uptake that were accompanied by decreased Lox-1 receptor expression via NF-*k*B signaling pathway [20]. Accordingly, increased SIRT1 expression and decreased Lox-1 expression were also observed in ox-LDL-stimulated endothelial cells of the human umbilical vein that were exposed to ginkgolide B (biologically active terpene lactone found in Ginkgo biloba) — a platelet activating factor inhibitor with anti-inflammatory properties [21]. It is interesting that Lox-1 regulation of thrombus formation in vivo depended on the degree of ox-LDL activation. In particular, at low levels of ox-LDL, Lox-1 activated the SIRT1 protective pathway, whereas at higher levels of ox-LDL, it switched to the thrombogenic ERK1 / 2-dependent pathway [22].

SIRT1 controls the development of foam cells by deacetylation and activation of liver X-receptor (LXR), which, in turn, triggers the activity of member 1 of ATP-binding cassette subfamily A (ABCA1) and member 1 of ATP-binding cassette subfamily G (ABCG1), as well as C-C chemokine receptor 7 (CCR7), thereby contributing to the reverse transport of cholesterol and slowing down the development of foam cells [23].

SIRT6 inhibits triglyceride (TG) synthesis and fat metabolism, contributes to the β-oxidation of fatty acids, and maintains low LDL cholesterol levels through deacetylation of histone H3 at the lysine 9 (H3K9) position in the promoter of several genes involved in these metabolic processes [24]. Under nutritional stress, SIRT6 is positively modulated by SIRT1 through the development of SIRT1 / FOXO3a / nuclear respiratory factor 1 (NRF1) complex at the SIRT6 promoter, which, in turn, negatively regulates TG synthesis, lipogenesis, and glycolysis [24]. Accordingly, SIRT6-mediated histone deacetylation suppresses the transcription of proprotein convertase subtilisin / kexin type 9 (PCSK9) and transcriptional regulators SREBP (sterol regulatory element-binding proteins) 1 and 2. In particular, SIRT6 and FOXO3 can coordinate the regulation of cholesterol homeostasis through FOXO3-mediated recruitment of SIRT6 to the gene promoter *SREBP1/2* where it deacetylates histone H3 in lysine positions 9 (H3K9) and 56 (H3K56) and promotes the repressive state of chromatin [25]. Also, SIRT6 regulates cholesterol metabolism through suppression of lipogenic cholesterol transcription factors SREBP1 and SREBP2 and their target genes, inhibition of SREBP1/SREBP2 cleavage into their active forms, and activation of AMPK enzyme that phosphorylates and inhibits SREBP1 [26].

Recent *ex vivo* and *in vivo* studies demonstrated the direct involvement of SIRT6 in the development of atherosclerotic plaques in patients with diabetes and animal models of atherosclerosis [6]. In the carotid atherosclerotic plaques of patients with type 2 diabetes, SIRT6 expression was reduced compared to plaques in nondiabetic patients [6]. Also, decreased expression of SIRT6 protein in these atherosclerotic plaques was associated with decreased interstitial collagen content and increased levels of oxidative stress, pro-inflammatory cytokine NF-*k*B and MMP-9 [6]. All of these molecular events that characterize the phenotype of atherosclerotic carotid plaques in patients with asymptomatic type 2 diabetes are positively modulated by therapy with glucagon-like peptide-1 receptor agonists, a new class of antihyperglycemic agents with pleiotropic effects on arterial wall function.

Therefore, the short term *in vitro* effect of high glucose on EPCs (endothelial progenitor cells) and ECs induced suppression of SIRT6 and increased NF-*k*B [6]. *In vivo* studies of animal models of atherosclerosis confirmed the role of SIRT6 as a negative regulatory factor in the development of endothelial dysfunction and atherosclerosis. The expression of the SIRT6 gene and protein was suppressed in atherosclerotic plaques of ApoE −/− mice on a high cholesterol diet. In particular, SIRT6 knockdown ApoE −/− mice demonstrated impaired endothelium-dependent vasodilation,

increased size and increased vulnerability of plaques as evidenced by increased necrotic region of the nucleus, accumulation of macrophages, and decreased collagen amount.

In addition, SIRT6 heterozygous (SIRT6 +/–) mice demonstrated increased expression of natural killer (NKG2D) group 2 member D ligand on macrophages and ECs, which promoted activation of killer cells and increased levels of inflammatory cytokines. Finally, another key piece of evidence for the atheroprotective role of SIRT6 is the observation that SIRT6 +/– / ApoE –/– mice on a high-fat diet demonstrated significantly accelerated progression of atherosclerotic lesion along with increased expression of pro-inflammatory cytokine VCAM-1.

Analysis of potential targeting genes of SIRT6 revealed that SIRT6 binds to the promoter of the proatherogenic gene of tumor necrosis factor superfamily member 4 (TNFSF4) where it deacetylates histone H3 at the lysine 9 (H3K9) position, leading to SIRT6-dependent suppression of TNFSF4 transcription in ECs. However, we still have to figure out whether overexpression of SIRT6 and/or its modulation by specific activators can suppress vascular inflammation and slow down the development of atherosclerotic plaques. It was found just recently that SIRT6 protected against atherosclerosis by reducing the development of foam cells via the autophagy-dependent pathway [27]. Under ox-LDL conditions, SIRT6 reduces the development of foam cells of macrophages through the induction of autophagy and cholesterol efflux. In particular, overexpression of SIRT6 in foam cells increased ABCA1 and ABCG1 levels, activated cholesterol efflux, and reduced miR-33 levels. Moreover, transfection of miR-33 into cells with SIRT6 overexpression reduced the development of foam cells and resulted in reverse induction of the flow of autophagy.

SIRT1 and SIRT6 in Cardiac Diseases

SIRT1 and SIRT6 have different roles in maintaining cardiac function, especially in terms of protecting it from oxidative and ischemia-reperfusion (I/R) damage, as well as hypertrophic stimuli. SIRT1, which is the most important part in the pathogenesis of heart failure and regulation of cardiac electrical activity, was proposed as a tool for predicting the incidence of new myocardial infarctions.

In cardiac tissue, SIRT1 negatively regulates pro-apoptotic proteins Bax (BCL-2-associated X protein) and positively regulates the expression of anti-apoptotic protein of large B-cell lymphoma (Bcl-xL, B-cell lymphoma-xL) through FOXO activation. It is worth noting that SIRT1 has a protective effect via specific control of the acetylation and transcriptional activity of p53 in cardiomyocytes. In a chronic model of type 1 diabetes, decreased cardiac SIRT1 level is associated with decreased cardiac Ca-ATPhase levels of the sarcoplasmic reticulum (SERCA2a, cardiac sarcoplasmic calcium ATPase) [28]. More recently, Prola et al. reported that SIRT1 protects cardiomyocytes from endoplasmic reticulum (ER) stress through physical interaction and deacetylation of the eukaryotic protein translation initiation factor 2α (eIF2a) at lysine positions 141 (K141) and 143 (K143) [29]. In contrast, inhibition of SIRT1 induces nuclear fragmentation and cleavage of caspase-3, while SIRT1-deficient mice demonstrate abnormal heart development and prenatal mortality [30]. SIRT6 is valuable in cases of heart failure and control of cardiac fibrosis, a pathological condition that is critical in the development of heart failure [31]. SIRT6 negatively regulates the differentiation of cardiac fibroblasts into myofibroblasts; its depletion increases the proliferation of cardiac fibroblasts and the accumulation of extracellular matrix, and also stimulates genes associated with adhesion and fibrosis via the NF-*k*B signaling pathway [31].

Oxidative and Ischemia–Reperfusion (I/R) Damage

SIRT1 responds differently to various cardiac stresses. The expression of this protein increases during pressure overload, nutritional deficiencies, exercise and acute ischemic preconditioning and decreases with underlying I/R damage. SIRT1 protects cardiomyocytes from oxidative stress-mediated damage through the activation of CAT and MnSOD by deacetylation and activation of PGC-1a and FOXO [32].

SIRT1 expression in cardiac tissue decreases after I/R, while SIRT1 overexpression improves function recovery after I/R damage through increased MnSOD, thioredoxin-1 (Trx1), and Bcl-xL, as well as decreased activity of the proapoptotic protein Bax [32]. SIRT1 activation by resveratrol diminishes I/R damage to the heart by increasing ERK phosphorylation and decreasing p38 and JNK (c-Jun N-terminal kinase) expression. Also, exogenous administration of nicotinamide mononucleotide protects the heart from I/R damage by mimicking the cardioprotective effect of ischemic preconditioning and NAMPT overexpression, i.e. through a SIRT1-dependent mechanism. In contrast, autophagic flow in cardiac myocytes is impaired by a decrease in NAMPT, probably in conjunction with SIRT1 signaling pathway.

However, the effect of SIRT1 against oxidative stress in the heart depends on its concentration. In fact, at baseline, high cardiac expression of SIRT1 in mice, on the contrary,

induces oxidative stress through dysregulation of mitochondrial function. Hearts of male Wistar-Kyoto rats subjected to I/R were characterized by increased apoptosis of cardiomyocytes, cleavage of caspase 3, transient increase in SIRT1 level, increased expression of FOXO1 and binding to the SIRT1 promoter region, suppression of SIRT6 expression and AMPK-dependent reduction of NAD+ amount, reflecting a complex molecular network to protect the heart during I/R [33]. Moreover, in diabetic mice, resveratrol-enhanced autophagic flux prevented oxidative stress damage to the myocardium via the SIRT1/FOXO1/Rab7 pathway [34].

The protection provided by SIRT6 against cardiac I/R involves activation of FOXO3 in an AMPK-dependent manner, followed by the development of a complex with FOXO3 in the nucleus. Like SIRT1, the SIRT6-FOXO3 complex enhances the transcription of FOXO-dependent antioxidant genes (MnSOD and CAT) to counteract damage due to I/R [35]. Also, overexpression of SIRT6 protects cardiomyocytes from hypoxic stress by activating AMPK, increasing Bcl2 level, suppressing NF*k*B activity, and decreasing cell levels of ROS (reactive oxygen species) [36]. SIRT6 directly binds to PARP1 (poly-[ADP-ribose] polymerase 1) and increases its poly-ADP-ribosylase activity, thereby stimulating the restoration of double-strand break under oxidative stress [37]. Since excessive PARP1 activation can deplete NAD+ levels in cardiomyocytes, it is important to limit the excessive activation of SIRT6 in the heart to optimize its cardioprotective effects.

Finally, SIRT6 also protects against hypoxia/reoxygenation-induced damage by reducing hypoxia-induced apoptosis and mitochondrial defects through suppression and translocation of the p65 subunit of NF-β*k*B [38].

Cardiac Hypertrophy

Both SIRT1 and SIRT6 protect the heart from hypertrophy, although SIRT1 also demonstrates opposite effects depending on the interaction with other factors and stress severity [39]. Pressure overload in the heart causes cardiac hypertrophy and failure through an increase in PPAR-a (peroxisome proliferator-activated receptor coactivator-α) -SIRT1 complex and suppression of estrogen-related receptors (ERRs) of the transcriptional pathway [39]. Also, SIRT1-dependent activation of ACT exacerbates cardiac hypertrophy. In particular, SIRT1-mediated deacetylation as a plextrin homology (PH) domain of A*k*t and its upstream kinase PDK1 (3-phosphoinositide-dependent kinase 1) facilitates their interaction with phosphatidylinositol-3,4,5-trisphosphate (PIP3) in the plasma membrane where PDK1 phosphorylates and activates Akt, causing cardiac hypertrophy. SIRT1-deficient hearts demonstrated decreased Akt activation and less development of cardiac hypertrophy in response to exercise and Ang II stimulation.

In neonatal rat cardiomyocytes, inhibition of SIRT6-dependent NF-*k*B suppresses cardiomyocyte hypertrophy, and overexpression of wild-type SIRT6 diminishes Ang II-induced cardiac hypertrophy [40]. Interestingly, the overexpression of nicotinamide mononucleotide adenylyl transferase 2 (Nmnat2) prevented the development of Ang II-induced cardiac hypertrophy. Among all sirtuins, elevated mRNA levels in response to Ang II stimulation were observed for SIRT6 and SIRT1, with the predominant role of SIRT6 [40]. Therefore, a new PARP1 inhibitor, AG-690/11026014, a compound that can prevent Ang II-induced cardiomyocyte hypertrophy, reverses the depletion of cellular NAD+ and SIRT6 deacetylase activity. It is noteworthy that under normal conditions SIRT6 blocks the expression of genes associated with IGF (insulin-like growth factor) signaling, which is responsible for heart failure by deacetylation of H3 at Lys-9 (H3K9) and suppression of c-Jun activity. In contrast, the reduction of SIRT6 expression in the heart in cases of pathological stress leading to the development of cardiac hypertrophy, fibrosis, and heart failure was associated with increased H3K9 acetylation on the IGF signaling gene promoters and c-Jun-mediated transcriptional activation.

The attenuation of Akt signaling through SIRT6-dependent activation of FOXO3 also contributes to the pro-autophagic effect of SIRT6 in suppressing isoproterenol-induced cardiac hypertrophy. More recently, the protective role of SIRT6 with underlying cardiomyocyte hypertrophy was confirmed by the observation that the suppression of the signal transporter and transcription activator 3 (STAT3), critical for the development of cardiac hypertrophy and heart failure, was involved in signaling, which mediated the protective effect of SIRT6 [41].

SIRT1 and SIRT6 Modulators in Preclinical and Clinical Conditions

Today, intensive studies are focused on modulating SIRT1 and SIRT6 using pharmacological and natural food compounds, as well as miRs [42]. SIRT1 activation by resveratrol derivatives such as BTM-0512 demonstrated a beneficial effect on high glucose-induced dysfunction of ECs [43]. According to these results, eight-week male C57BL/6 mice treated with resveratrol demonstrated less significant development of insulin resistance and endoplasmic reticulum stress induced by a high-calorie diet through increased SIRT1 expression and reversal of adipokine expression in both subcutaneous and visceral adipose tissues. Another compound,

icariin, an important active ingredient in Herba Epimedii (horny goat weed), also acts as a SIRT6 activator and NF-inhibitor*k*B and demonstrated its potential efficacy in the treatment of CVD [44].

As was widely reported [42], the following clinical trials are currently underway or have been completed (http://clinicaltrials.gov): safety, efficacy, pharmacodynamics, and pharmacokinetics of natural and synthetic compounds that can modulate SIRT1 and SIRT6 in several diseases, including cardiovascular, inflammatory, metabolic syndrome, insulin resistance, type 2 diabetes and obesity. In this regard, clinical evaluations of the pharmacological activators of SIRT1 (SRT1720, SRT3025, SRT2104 and SRT501) have resulted in the prevention of metabolic diseases, decreased atherosclerotic plaque formation, improved lipid profile in cigarette smokers, and improved glucose tolerance in patients with type 2 diabetes [45]. Also, the results of a double-blind, placebo-controlled study in patients with carotid atherosclerosis revealed that treatment with metformin reduced the state of proinflammation in peripheral blood mononuclear cells through the induction of SIRT1, p65, as well as the blockade of NF-*k*B [46].

However, the problem of controlling SIRT1 and SIRT6 activity by specific compounds in order to achieve protection against CVD remains unresolved. And there is still a long way to go before sirtuin modulators can be used for therapeutic purposes. This is because clinical evaluations of SIRT6 are still limited, and clinical results on the effectiveness of SIRT1 modulators are contradictory. Nevertheless, studies on sirtuin modulation by pharmacological compounds remain significant today and are being carried out quite intensively. A sulfonylurea compound (G004) was recently synthesized. It had a positive impact on hyperglycemia and atherosclerosis due to its effect on the SIRT1/eNOS axis. A new PARP1 inhibitor (poly[ADP-ribose] polymerase 1) AG-690/11026014 demonstrated protective effects on Ang II-induced cardiac muscle remodeling by restoring SIRT1 activity in cardiac tissue [47].

Among natural nutrients that can modulate SIRT1 and SIRT6, ergothioneine has been shown to prevent high glucose-induced endothelial aging by modulating SIRT1/p66shc (one of the isoforms of SHC1 protein) and SIRT6/NF-*k*B [48]. Finally, the recently identified SIRT6 inhibitor, compound 1 (2,4-dioxo-N-(4- (pyridin-3-yloxy)phenyl)-1,2,3,4-tetrahydroquinazoline-6-sulfonamide), tested in a mouse model of type 2 diabetes reduced levels of insulin, triglycerides, and plasma cholesterol, and improved glycemic control by increasing the expression of GLUT (glucose transporter) 1 and GLUT4 in muscles and increased the activity of the glycolytic pathway [49].

Conclusions and Future Focus Areas

Studying the role of SIRT1 and SIRT6 signaling pathways in protection against CVD became relevant over the past couple of years. The beneficial effects of these compounds on inflammation, vascular aging, control of glucose homeostasis, atherosclerosis, and cardiac diseases are now intensively analyzed, and new targets are constantly being discovered within the complex structures [50]. In this regard, summarizing the achievements in the study of the role of SIRT1 and SIRT6 signals in protection against CVD, we can conclude that they are associated with the establishment of:

- dependence of SIRT1 and SIRT6 activity on the cellular redox state. This fact indicates that antioxidant compounds have a strong potential to protect against CVD, which compounds have an effect on the SIRT1/FOXO axis, SIRT1/NF-*k*B axis, SIRT1/p66Shc axis and SIRT6/NF*k*B axis;
- antiatherogenic role of SIRT6 *in vivo*, which makes this sirtuin a potentially new target in the prevention of atherosclerosis;
- effectiveness of SIRT1 synthetic activators with good tolerance and bioavailability in individuals who overcome the limit of low bioavailability of resveratrol;
- overlapping of regulatory mechanisms including transcription factors and miRs such as NF-*k*B and miR-34a, which indicates a regulatory interaction between these sirtuins.

Overall, regarding the mechanisms controlled by these sirtuins, recently obtained data linking SIRT6 with the development of atherosclerotic plaques and their vulnerability by NF-*k*B/NKG2D (natural-killer group 2 member D) indicate that the control of inflammatory pathways in CVD is very important, especially for SIRT1 and SIRT6. At the same time, equally important are cell mechanisms that influence intracellular glutathione levels under conditions of oxidative stress, which appears to be critical for controlling both SIRT1 and SIRT6.

Although these sirtuins control the mechanisms responsible for genome longevity and stability, and this fact makes them attractive in terms of their roles in the context of age-related diseases, the interactions between SIRT1 and SIRT6 signals clearly demonstrate the need to understand the set of their molecular targets in order to achieve highly specific and selective modulation at cardiovascular level. As demonstrated in this review, the discussion of both SIRT1 and SIRT6 signaling pathways in the protection against CVD, as well as the presence of common molecular targets, suggests that these sirtuins can act synergistically.

The complete discovery of the whole set of SIRT1 and SIRT6 signaling pathways, including their possible

associations with the cell mechanisms of vascular aging and CVD, remains a key challenge in this area, along with a deeper understanding of the redox regulation of these sirtuins. In this regard, the prospects for future research will be associated with the expected mapping of the epigenome in human diseases, which will allow the identification of epigenetic targets specific to a particular disease or disease stage. As for today, using dietary antioxidant compounds, as well as a healthy lifestyle with moderate exercise and calorie restriction, can be important for controlling the conditions of cellular oxidative stress that cause vascular aging and cardiovascular disease.

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