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Sirtuins, cell senescence, and vascular aging

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Abstract

The sirtuin (SIRT) family constitute a class of proteins with NAD⁺-dependent deacetylase or ADP-ribosyltransferase activity. Seven SIRT family members have been identified in mammals, from SIRT1, the best studied for its role in vascular aging, to SIRT7. SIRT1 and SIRT2 are localized both in the nucleus and cytoplasm. SIRT3, SIRT4, and SIRT5 are mitochondrial, while SIRT6 and SIRT7 are nuclear. Extensive studies have clearly revealed that SIRT proteins regulate diverse cell functions and responses to stressors. Vascular aging involves the aging process (senescence) of endothelial and vascular smooth muscle cells. Two types of cell senescence have been identified: (1) replicative senescence with telomere attrition and (2) stress-induced premature senescence without telomere involvement. Both types of senescence induce vascular cell growth arrest and loss of vascular homeostasis, contributing to the initiation and progression of cardiovascular diseases. Previous mechanistic studies have revealed in detail that SIRT1, SIRT3, and SIRT6 demonstrate protective functions against vascular aging, while definite vascular function of other SIRT proteins is under investigation. Thus, direct SIRT modulation and NAD⁺ stimulation of SIRT are promising candidates for cardiovascular disease therapy. A small number of pilot studies have been conducted to assess SIRT modulation in humans. These clinical studies have not yet provided convincing evidence that SIRT proteins alleviate morbidity and mortality in patients with cardiovascular diseases. The outcomes of multiple ongoing clinical trials are awaited to define the efficacy of SIRT modulators and SIRT activators in cardiovascular diseases, along with the potential adverse effects of chronic SIRT modulation.

1. Introduction

1.1 Sirtuins

Sirtuin (SIRT), or silent information regulator 2 (Sir2) proteins, are a class of proteins that possess nicotinamide adenine dinucleotide (NAD⁺)-dependent deacetylase activity or ADP-ribosyltransferase activity. In mammals, seven SIRT proteins have been identified, from SIRT1, the best studied for its role in vascular aging, to SIRT7. They have different tissue

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Disclosures

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and sub-cellular localization¹: SIRT1 and SIRT2 are expressed both in the nucleus and cytoplasm. SIRT3, SIRT4, and SIRT5 are mitochondrial, while SIRT6 and SIRT7 are localized in the nucleus. This implies SIRT proteins have variety of cellular functions. Initial studies identified that Sir2 protein contributes to extending lifespan in yeasts, flies, and worms, providing the first evidence that SIRT has an anti-aging effect^{2, 3}. However, an effect of SIRT proteins on longevity is unclear in mammals. In mice, over-expression of SIRT1, the closest mammalian homologue of Sir2, did not change lifespan while SIRT6 expression level positively affected longevity^{4–6}. Furthermore, no genetic association was detected between *Sirt1* polymorphisms and lifespan in humans⁷. Instead, extensive studies have clearly revealed that SIRT proteins regulate diverse cell functions and responses to stressors and that SIRT proteins protect against age-related diseases (cardiovascular diseases, diabetes, neurodegenerative diseases, cancer)⁸.

1.2 Vascular cell senescence

Vascular aging is composed of the aging process (senescence) of endothelial cells as well as vascular smooth muscle cells (VSMCs). There are two types of cell senescence, replicative senescence and stress induced premature senescence (SIPS). Most cells including endothelial cells and VSMCs in culture stop to proliferate after a limited number of doublings (i.e. Hayflick limit⁹), which determines a lifespan of each cell type and usually requires weeks or months of passaging in culture. Cessation of cell division induces cell growth arrest, which is termed replicative senescence and is a consequence of telomere attrition¹⁰. Some stresses such as oxidative stress and DNA damage elicit quite similar cell growth arrest within just a few days, referred to as SIPS¹⁰. Interestingly, telomere shortening is not essential for SIPS^{11, 12}. It is well documented that two types of senescence of endothelial cells and VSMCs are involved in the process of cardiovascular diseases^{13–15}. Senescent cells alter their morphology and gene expression pattern, which impair essential cellular function^{10, 16}. These alterations induce a dysfunctional vascular phenotype that enhances inflammation, thrombosis, and atherosclerosis with impairment of vasorelaxation, angiogenesis, and vascular regeneration, all of which contribute to development and progress of cardiovascular diseases. In this review, we describe how SIRT proteins function in the process of vascular aging and diseases. Subsequently, we review the capacity of SIRT modulators to treat cardiovascular diseases in patients.

2. Roles of SIRT proteins in vascular aging

2.1 SIRT1

Among SIRT family, SIRT1 is the best-studied and currently considered to be the most important factor involved in vascular homeostasis and diseases. SIRT1 modulates variety of molecular signaling pathways essential for vascular function at multiple types of vascular cells (Fig. 1).

2.1.1 SIRT1 in endothelial cells—SIRT1 is highly expressed in endothelial cells where it is shuttling between the nucleus and cytoplasm^{17, 18}. The first study connecting SIRT1 to endothelial cells reported that SIRT1 expression is positively regulated by endothelial nitric oxide synthase (eNOS)¹⁹. Following studies revealed that SIRT1 deacetylates and activates

eNOS in the cytoplasm²⁰, indicating that SIRT1 and eNOS are mutually regulated by a positive feedback loop. It is well known that eNOS generates nitric oxide (NO), a gaseous signaling molecule, that exerts vascular relaxation, inhibition of VSMC proliferation, antithrombotic and anti-oxidant effects. In mice, aging lowers endothelial expression of SIRT1, eNOS activity, and endothelial dependent vasorelaxation, while endothelial SIRT1 over-expression exhibits opposite effects^{21, 22}, implying SIRT1 counteracts vascular aging. SIRT1 deacetylates and inactivates p53, by which SIRT1 antagonizes replicative senescence and SIPS^{23–27}. In endothelial cells, SIRT1 blocks H₂O₂ induced SIPS via p53 deacetylation²⁷. In addition to p53, endothelial SIRT1 has been shown to negatively regulate forkhead box O1 (FOXO1)¹⁷, Notch intracellular domain²⁸, and plasminogen activator inhibitor-1 (PAI-1)²⁹, all of which impair angiogenesis and induce senescence of endothelial cells^{29–31}. Separately, SIRT1 prevents expression of endothelial adhesion molecules such as intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 by suppression of NF- κ B³², where SIRT1 deacetylates and inhibits RelA/p65 subunit of NF- κ B³³. Consequently, SIRT1 inhibits monocyte binding to endothelial cells, as well as monocyte transmigration into the arterial wall, indicating anti-inflammatory effects in endothelial cells. Endothelial NF- κ B inhibition by SIRT1 also prevents arterial thrombosis triggered by coagulation factor III³⁴, suggesting that SIRT1 is involved in the pathogenesis of ischemic heart disease. Emerging evidence identifies that multiple endogenous regulators deplete SIRT1 to induce replicative senescence and SIPS in endothelial cells. In endothelial cells, oxidative stress causes lysosomal membrane dysfunction and permeabilization that trigger the leakage of lysosomal proteases, cathepsins, resulting in cleavage and degradation of SIRT1 by cathepsins³⁵. MicroRNA (miR)-34a and miR-217 are identified to induce endothelial senescence via SIRT1 inhibition *in vitro*^{30, 36}. Inflammation-activated caspase-1 cleaves endothelial SIRT1^{37, 38}. Angiotensin II also represses SIRT1 through p38 mediated cytoplasmic sequestration of SIRT1³⁹ while cyclin-dependent kinase (CDK)-5 inhibits SIRT1 nuclear retention by SIRT1 phosphorylation and induce endothelial senescence⁴⁰. However, it is poorly understood whether these endogenous SIRT1 inhibitors also regulate other SIRT proteins. Multiple studies addressed roles of SIRT1 in endothelial cells *in vivo* using endothelial SIRT1 inactive mice, where SIRT1 loses its deacetylase activity by deletion of exon 4⁴¹. These mutant mice have impaired angiogenesis in the non-damaged retina, in the hind-limb ischemic models, and in the nephrotoxic and cardiac hypertrophy models (Fig. 2)^{17, 42, 43}. Moreover, these mice show premature endothelial senescence and impaired endothelial dependent vasorelaxation under basal conditions⁴². In the kidney of the young mutant mice, tissue fibrosis was detected at low level even without injury and it was robustly enhanced in response to chronic nephrotoxic stress due to suppression of matrix metalloproteinase-14 (MMP-14) that is up-regulated by SIRT1^{17, 42}. Endothelial SIRT1 dysfunction causes MMP-14 down-regulation, which in turn increases a collagen cross-linking enzyme, transglutaminase-2 that is normally cleaved by MMP-14⁴². These findings indicate that endothelial SIRT1 counteracts endothelial senescence and subsequent tissue fibrosis. In terms of cardiac injury, mutant mice have aggravated cardiac diastolic dysfunction and cardiac capillary rarefaction during aging, as well as pressure overload⁴³. One intriguing study using transgenic mice with heart specific SIRT1 over-expression reported that moderate SIRT1 over-expression attenuates aging-related cardiac dysfunction and hypertrophy, whereas high SIRT1 over-expression aggravates them⁴⁴. This study

suggested that high levels of SIRT1 consume and deplete NAD⁺, leading to ATP deficiency and subsequent cell death, because NAD⁺ is required for mitochondrial respiration⁴⁴. Collectively, endothelial SIRT1 is a multifunctional protein protecting vessels against vascular aging, vascular injury, and tissue damage.

2.1.2 SIRT1 in vascular smooth muscle cells—A study using human samples reported that aging-related SIRT1 loss in VSMCs causes impaired stress responses and increased senescence⁴⁵. VSMC specific SIRT1 over-expression inhibits proliferation and migration of VSMCs, hypertension, neointima formation post-arterial injury, resulting in resistance to atherosclerosis^{46, 47}. Another study using VSMC specific Sirt1 inactive mice showed that SIRT1 protects against DNA damage, medial degeneration, premature senescence of VSMCs, and atherosclerosis⁴⁸. Nicotinamide phosphoribosyltransferase (NAMPT) is a key enzyme that contributes to the availability of NAD⁺ for SIRT proteins⁴⁹. A marked decline in NAMPT activity precedes VSMC replicative senescence, while NAMPT over-expression in aging VSMCs confers resistance to oxidative stress and delays their senescence via enhanced deacetylation of p53 by SIRT1⁴⁹. Overall, SIRT1 protects against VSMCs senescence.

2.1.3 SIRT1 in monocytes/macrophages—Foam cells are lipid-loaded macrophages derived from circulating monocytes. After transmigration into the arterial intima, these invading pro-inflammatory macrophages differentiate into foam cells upon massive uptake of oxidized low-density lipoprotein (LDL), causing atherosclerosis⁵⁰. In macrophages, SIRT1 inhibits NF- κ B via deacetylation of RelA/p65 subunit and suppresses expression of pro-inflammatory molecules such as tumor necrosis factor- α and interleukin (IL)-1 β ⁵¹. In addition, SIRT1 reduces the uptake of oxidized LDL via inhibition of NF- κ B and prevents foam cell formation as well as atherosclerosis in mice⁵². Further, macrophage SIRT1 enhances the cholesterol efflux from macrophages to high-density lipoprotein (HDL), preventing excessive cholesterol accumulation in macrophages⁵³. Thus, macrophage SIRT1 antagonizes vascular inflammation, atherosclerosis, and indirectly prevents vascular aging.

2.2 SIRT2

Global loss of SIRT2 in mice demonstrated no abnormality under the basal condition except tumorigenesis due to accelerated mitosis⁵⁴. However, *Sirt2* deficient mice showed marked protection from ischemic heart injury by blocking cardiomyocyte necrosis⁵⁵. SIRT2 deacetylates receptor-interacting protein (RIP)-1, facilitating cellular necrosis⁵⁵. Consistent with this, in culture, pharmacological inhibition of SIRT2 prevents endothelial cells from H₂O₂-induced cell death⁵⁶, suggesting that SIRT2 aggravates cardiovascular diseases. Although SIRT2 was reported to increase longevity in mice⁵⁷, further study is required to determine roles of SIRT2 in vascular aging.

2.3 SIRT3

Mice lacking SIRT3 exhibit normal phenotype under the basal condition despite striking hyper-acetylation of mitochondrial proteins⁵⁸. By contrast, *Sirt3* null mice develop cardiac hypertrophy with interstitial fibrosis after various hypertrophic stimuli, because SIRT3 deacetylates and activates FOXO3 that increases transcription of antioxidant genes,

manganese superoxide dismutase and catalase, resulting in suppression of reactive oxygen species (ROS) generation in stimulated cells⁵⁹. In *Sirt3* null mice, ROS promotes Ras driven hypertrophic signaling pathway⁵⁹. In culture, hypoxia stimulates SIRT3 expression and SIRT3 dependent antioxidant signaling in endothelial cells, which preserves mitochondrial function as well as endothelial survival⁶⁰. SIRT3 protects endothelial cells in culture against H₂O₂- or angiotensin II-induced SIPS by deacetylation of FOXO3^{61, 62}. Moreover, SIRT3 deficiency induces proliferative phenotype of pulmonary artery smooth muscle cells with mitochondrial dysfunction, leading to vascular remodeling and pulmonary hypertension in rodents and patients⁶³. SIRT3 loss also facilitates the development of the metabolic syndrome, a cluster of risk factors for cardiovascular diseases. In mice, aging kidneys showed 50% of reduction of SIRT3 compared to young kidneys⁶⁴. In mice and humans, low expression of SIRT3 is detrimental for longevity^{65–67}. Overall, SIRT3 is protective against vascular aging in rodents and humans (Fig. 1).

2.4 SIRT4 and SIRT5

In addition to SIRT3, SIRT4 and SIRT5 localize to mitochondria. SIRT4 predominantly acts as an ADP-ribosyltransferase whereas SIRT5 operates as a desuccinylase and demalonylase with a weak deacetylase activity¹. Global *Sirt4* or *Sirt5* deficient mice developed normally and do not show any gross and vascular abnormality^{58, 68}, suggesting minor roles of these proteins in vascular homeostasis and aging. It was demonstrated in endothelial cells *in vitro* that SIRT4 over-expression inhibits NF- κ B nuclear translocation that triggers expression of IL-1 β , IL-6, and ICAM-1⁶⁹. Currently it is not fully elucidated whether SIRT4 and SIRT5 are protective against vascular aging.

2.5 SIRT6

SIRT6 is a chromatin-associated protein that stabilizes genomes and telomeres⁷⁰. Thus, SIRT6 prevents cells from premature senescence⁷⁰. *Sirt6* null mice show the premature aging phenotype whereas male, but not female, global *Sirt6* over-expressing mice show a longer lifespan with cardioprotection against hypoxia^{5, 6, 70, 71}. Endothelial cells highly express SIRT6 and deficiency of endothelial SIRT6 accelerates replicative senescence⁷². It is recently reported that SIRT6 negatively regulates the formation of unstable atherosclerotic plaques in diabetic patients⁷³. Additionally, SIRT6 suppresses cardiac hypertrophy and heart failure by controlling insulin-like growth factor (IGF)-Akt signaling at the level of chromatin through c-Jun, a stress-responsive transcription factor, and deacetylation of histone H3 at lysine 9 (H3K9)⁷⁴. By the transcriptional repression of Pcsk9 (proprotein convertase subtilisin/kexin type 9), SIRT6 prevents hepatic LDL receptor degradation and lowers plasma LDL-cholesterol level in mice⁷⁵, which may prevent the atherogenesis. Taken together, SIRT6 possesses the preventive effect on vascular aging (Fig. 1).

2.6 SIRT7

SIRT7 is the only SIRT protein localized predominantly in the nucleoli. Global *Sirt7* deficient mice have decreased longevity and develop cardiac hypertrophy with remarkable interstitial fibrosis⁷⁶. SIRT7 reduces myocardial apoptosis by efficient deacetylation of p53⁷⁶, indicating anti-aging effect of SIRT7. *Sirt7* null mice have impaired angiogenic responses after hind-limb ischemic injury⁷⁷. Silencing of *Sirt7* in endothelial cells also

compromises endothelial function⁷⁷. Although these results suggest that SIRT7 counteracts vascular aging by enhancing stress resistance, future investigation is necessary to confirm anti-vascular aging function of SIRT7.

3. SIRT modulators for cardiovascular disease therapy

Based on previous findings mentioned above, SIRT proteins predominantly possess protective roles against vascular aging and its resultant cardiovascular diseases in rodents and humans. However, there is paucity of data showing direct causal relationship between SIRT activity and cardiovascular morbidity and mortality in healthy and diseased population.

Initial study of SIRT1 activation by resveratrol, a natural compound enriched in red wine, demonstrated protective effects of SIRT1 against diet induced-obesity and insulin resistance^{78, 79}, which gained the growing interest in developing more potent SIRT1 activators such as SRT1720 to treat diabetes and metabolic diseases^{80, 81}. Subsequently, these SIRT1 activators have been shown to antagonize vascular dysfunction, inflammation, and atherosclerosis in rodent models^{82–84}. However, the specificity of SIRT1 activators remains debatable. These activators including resveratrol could induce SIRT1 activation only when SIRT1 is conjugated with a non-physiological fluorescence substrate⁸⁵. Although one of physiological effects of SIRT1 activators may directly induce SIRT1 activation, these compounds may also activate SIRT1 through indirect mechanisms^{86, 87}. For instance, resveratrol increases SIRT1 activity via inhibition of phosphodiesterases⁸⁷ or activating AMP-dependent kinase⁸⁸. Growing evidence shows that pan-SIRT activators may be more promising than SIRT1 specific activators. As NAD⁺ is required for the activity of all SIRT proteins and NAD⁺ levels decline during aging⁸⁹, raising NAD⁺ levels would antagonize vascular aging. NAD⁺ levels could be increased either by giving NAD⁺ precursors^{89, 90}, inhibition of NAD⁺ consumption⁹¹, or enhancing NAMPT mediated NAD⁺ salvage from nicotinamide (NAM)^{49, 92}. To date, there have been a few clinical studies to evaluate the effect of SIRT modulators in humans. One pilot study demonstrated that the SIRT1 activator SRT2104 improves endothelial dysfunction and lowers serum LDL cholesterol in healthy smokers⁹³. Therefore, SIRT1 modulation could be a promising target to counteract vascular aging in human. Currently ongoing clinical trials are assessing efficacy of SIRT1 modulators, especially SIRT1 activators to treat vascular injury, endothelial dysfunction, type 2 diabetes, and coronary artery disease (for more details the reader is referred to other reviews^{94, 95}). However, no studies so far have shown convincing evidence that SIRT proteins counteract cardiovascular diseases in patients. On the contrary, carcinogenesis is suggested to be one of major side effects during SIRT modulation because, for example, SIRT1 could operate as either a tumor suppressor or an oncogenic factor depending on the context^{96, 97}. Future outcomes of these clinical trials are essential to evaluate the efficacy of SIRT modulators in cardiovascular diseases with particular emphasis on side effects of chronic SIRT modulation. Moreover, new study is required to assess whether vascular (or endothelial) selective SIRT modulators (currently unavailable) are better than global SIRT modulators to effectively treat patients with cardiovascular diseases.

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Summary

Sirtuin (SIRT) family with NAD⁺-dependent deacetylase activity or ADP-ribosyltransferase activity, consists seven SIRT proteins (SIRT1-7) in mammals. Vascular aging is composed of senescence of endothelial cells and vascular smooth muscle cells. These senescent cells lose their physiological function, resulting in cardiovascular diseases. SIRT proteins, especially SIRT1, demonstrate protective roles against vascular aging. Here we will review multiple functions of SIRT proteins during vascular aging and the clinical capacity of SIRT modulators to treat cardiovascular diseases.

Fig. 1.

Schematic of major roles and mechanisms of SIRT proteins in vascular senescence/aging. SIRT1, SIRT3, and SIRT6 demonstrate protective roles against vascular aging whereas exact vascular function of other SIRT proteins is still investigated. SIRT1 activity is negatively regulated by multiple endogenous factors (cathepsins, micro RNA-34a and 217, cyclin-dependent kinase-5, caspase-1, and angiotensin II). All SIRT proteins (SIRT1-7) generate nicotinamide (NAM) from NAD⁺, which is required for deacetylase activity or ADP-ribosyltransferase activity of SIRT proteins. Nicotinamide phosphoribosyltransferase (NAMPT) is the rate-limiting enzyme for NAD⁺ salvage synthesis from NAM. Arrows: positive regulation, ⊥: negative regulation.

Fig. 2.

Images of micro-vasculature in kidneys of wild type and endothelial SIRT1 inactive (Sirt1 mutant) mice with or without injury. Kidney capillary endothelial cells are visualized by immunofluorescence staining for CD31 (red). Tissue injury and endothelial SIRT1 inactivation synergistically contribute to vascular aging, resulting in impaired angiogenesis and loss of capillary. Note remarkable capillary loss in Sirt1 mutant kidney post-injury compared to wild type kidney without injury. Kidney tissue injury is induced by unilateral ureteral obstruction for 10 days. Blue represents nuclei. Scale bar: 50 μ m.