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Review

Sirtuins in vascular diseases: Emerging roles and therapeutic potential

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ABSTRACT

Silent information regulator-2 (Sir-2) proteins, or sirtuins, are a highly conserved protein family of histone deacetylases that promote longevity by mediating many of the beneficial effects of calorie restriction which extends life span and reduces the incidence of cancer, cardiovascular disease (CVD), and diabetes. Here, we review the role of sirtuins (SIRT1-7) in vascular homeostasis and diseases by providing an update on the latest knowledge about their roles in endothelial damage and vascular repair mechanisms. Among all sirtuins, in the light of the numerous functions reported on SIRT1 in the vascular system, herein we discuss its roles not only in the control of endothelial cells (EC) functionality but also in other cell types beyond EC, including endothelial progenitor cells (EPC), smooth muscle cells (SMC), and immune cells. Furthermore, we also provide an update on the growing field of compounds under clinical evaluation for the modulation of SIRT1 which, at the state of the art, represents the most promising target for the development of novel drugs against CVD, especially when concomitant with type 2 diabetes.

1. Introduction

The structural and functional changes of the vasculature are strictly linked to vascular aging processes and other risk factors for cardiovascular diseases (CVD), such as hypercholesterolemia, hypertension, smoking, and diabetes. Specifically, the complex phenomenon of vascular dysfunction involves aging-related deterioration of the vasculature and secondary stresses, such as metabolic disorders, altered nitric oxide (NO) pathway, and increased inflammation and oxidative stress [1–5]. Particularly, the reduction of NO bioavailability caused by its diminished synthesis and/or by its augmented scavenging due to oxidative stress, along with the increased platelet aggregation, cytokines production, and adhesion molecule and chemokine expression, are the main intracellular events leading to endothelial dysfunction and vascular damage [1–5].

The epigenetic changes of histone and non-histone protein deacetylation catalyzed by sirtuins, or silent information regulator 2 (Sir2) proteins, take part to the mechanisms regulating vascular dysfunction related to aging, CVD and, most of all, vascular complications during diabetes [1,6–9]. Beyond controversy about the influence of Sir2 on lifespan extension in *C. elegans* and *Drosophila melanogaster* [10–12], the first evidence showing the connection between sirtuins and aging is the observations that overexpression of the sirtuin member Sir2 was able to extend lifespan in yeast, *C. elegans*, and in *D. melanogaster* [13]. Sirtuins, firstly described as modulators of energy metabolism, DNA repair, and oxidative stress responses [13] are known to exert protective effects against age-related diseases such as CVD, cancer, diabetes, and neurodegenerative diseases [13–15].

Mammals hold seven members of the sirtuin family, from SIRT1, the most extensively characterized for its role in aging, to SIRT7, all possessing a common highly conserved catalytic domain and nicotinamide adenine dinucleotide (NAD^+)-binding site. They have different subcellular localization, tissue specificity, activity, and targets [16].

Abbreviations: ACE, angiotensin converting enzyme; AICAR, 5-amino-4-imidazole-carboxamide riboside; AMPK, AMP-activated protein kinase; Ang II, angiotensin II; ApoE, apolipoprotein E; AT1R, angiotensin II type 1 receptor; ATM, ataxia telangiectasia mutated; ATP, adenosine triphosphate; CaMKKβ, Ca2+/calmodulin-dependent protein kinase β; COPD, chronic obstructive pulmonary disease; CSE, cigarette smoke extract; CVD, cardiovascular disease; DDAH2, dimethylarginine dimethylaminohydrolase; DDR, DNA damage response; EC, endothelial cells; ELAV, embryonic lethal abnormal vision; eNOs, endothelial nitric oxide; EPC, endothelial progenitor cells; FGFR 21, fibroblast growth factor 21; FOXO, forkheadbox O transcription factor; GHD, glutamate dehydrogenase; HIF, hypoxia-inducible factor; HUVEC, human umbilical vein endothelial cells; ICAM-1, intercellular adhesion molecule-1; IGC, intensive glycemic control; IL, interleukin; KDR, kinase-domain insert containing receptor; LDL, low density lipoprotein; LKB1, serine/threonine kinase B1; MCP-1, monocyte chemoattractant protein-1; MnSOD, manganese superoxide dismutase; NAD^+, nicotinamide adenine dinucleotide; NAM, nicotinamide; NAMPT, nicotinamide phosphoribosyltransferase; NBS1, repair protein Nijmegen Breakage Syndrome-1; NF-κB, Nuclear factor-kappaB; NO, nitric oxide; PAI, plasminogen activator inhibitor; PCI, percutaneous coronary intervention; PDH, pyruvate dehydrogenase complex; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPAR-α, peroxisome proliferator-activated receptor alfa; RFX5, regulatory factor for X-box; ROS, reactive oxygen species; Sir2, silent information regulator 2; SIRT, sirtuin; SIN-1, 3-morpholinosydnonimine; SMC, smooth muscle cells; SNP, single nucleotide polymorphisms; STEMI, ST-segment elevation myocardial infarction; TIMP3, tissue inhibitor of metalloproteinase 3; TNF-α, tumor necrosis factor-α; UCP, uncoupling protein; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor

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SIRT1 is localized both in the nucleus and cytosol and the signal from nucleus to cytosol occurs following specific conditions [17]. SIRT2 is cytosolic but also nuclear in certain phase of the cell cycle [18]. SIRT3, SIRT4 and SIRT5 are mitochondrial [19], while SIRT6 and SIRT7 are nuclear and nucleolar, respectively [20,21]. As for the catalytic activities, SIRT1, SIRT2, SIRT3, SIRT5 SIRT6 and SIRT7 act as deacetylase enzymes using NAD^+ to cleave acetyl groups from ε-acetyl lysine residues of target proteins in a reaction that generates nicotinamide (NAM), 2′-O-acetyl-ADP-ribose, and deacetylated substrates [22] (Fig. 1).

SIRT4, as well as SIRT6, acts as a mono-ADP-ribosyltransferase, in a reaction where the ADP-ribosyl moiety of NAD^+ is transferred to a substrate protein [19,23]. It has been demonstrated that SIRT4 acts as lipoamidase that regulates the pyruvate dehydrogenase complex (PDH) and, importantly, its catalytic efficiency for lipoyl- and biotinyl–lysine modifications is superior to its deacetylation activity [24]. As for SIRT6, this deacetylase can locate at the endoplasmic reticulum and controls protein lysine fatty acylation [25]. Indeed, as revealed by crystal structure, SIRT6 possesses a large hydrophobic pocket able to accommodate long chain fatty acyl groups and efficiently remove them from lysine residues [25]. Beside the deacetylase activity, SIRT5 also shows demalonylase and desuccinylase activity [26] (Fig. 1).

Sirtuin chromatin-associated functions are also exerted through the modulation of epigenetic information by direct deacetylation of specific histone acetylation marks [27]. Among mammalian sirtuins, SIRT1 and SIRT6 are the most functionally important deacetylase of histone (H) 3 acetylated (Ac) on lysine (K) 9 (H3K9Ac). SIRT1 deacetylation of H3K9Ac and H4K16Ac is directly associated with its capacity to coordinate the formation of constitutive and facultative heterochromatin [27]. Other histone substrates of SIRT1 are H1K27Ac, H3K9Ac, H3K14Ac, H3K18Ac, H3K56Ac, H4K12Ac, and 6 H4K6Ac. SIRT6 H3K9Ac deacetylase activity is important for modulating telomere structure and DNA repair of double-strand breaks [27].

Given the array of potentially beneficial effects of sirtuin modulation on cardiovascular health, the interest in developing specific modulators is keeping increasing [28–30]. Indeed, although the role of SIRT1 on longevity *per se* is not fully convincing because transgenic mice overexpressing SIRT1 did not show to live longer than controls, to date, the efficacy of SIRT1 in protecting mice against age-associated diseases unveils an important role in improving health span and preventing CVD [14,31]. At vascular level, given that all seven sirtuins are expressed in vascular endothelial cells (EC), SIRT1 is the only member of the sirtuin family shown to uniquely regulate EC physiology by promoting vasodilatory and regenerative functions of the vascular wall through the modulation of endothelial nitric oxide synthase (eNOS) activity, forkhead box O1 (FOXO1), p53, and angiotensin II (Ang II) type 1 receptor (AT1R) [28,32,33].

Over the recent years, in addition to SIRT1, the function of other sirtuins in vascular physiology has been investigated and some of them are likely to have roles in the normal and diseased blood vessels. Among these, recent advances have been made on the role of SIRT3, a

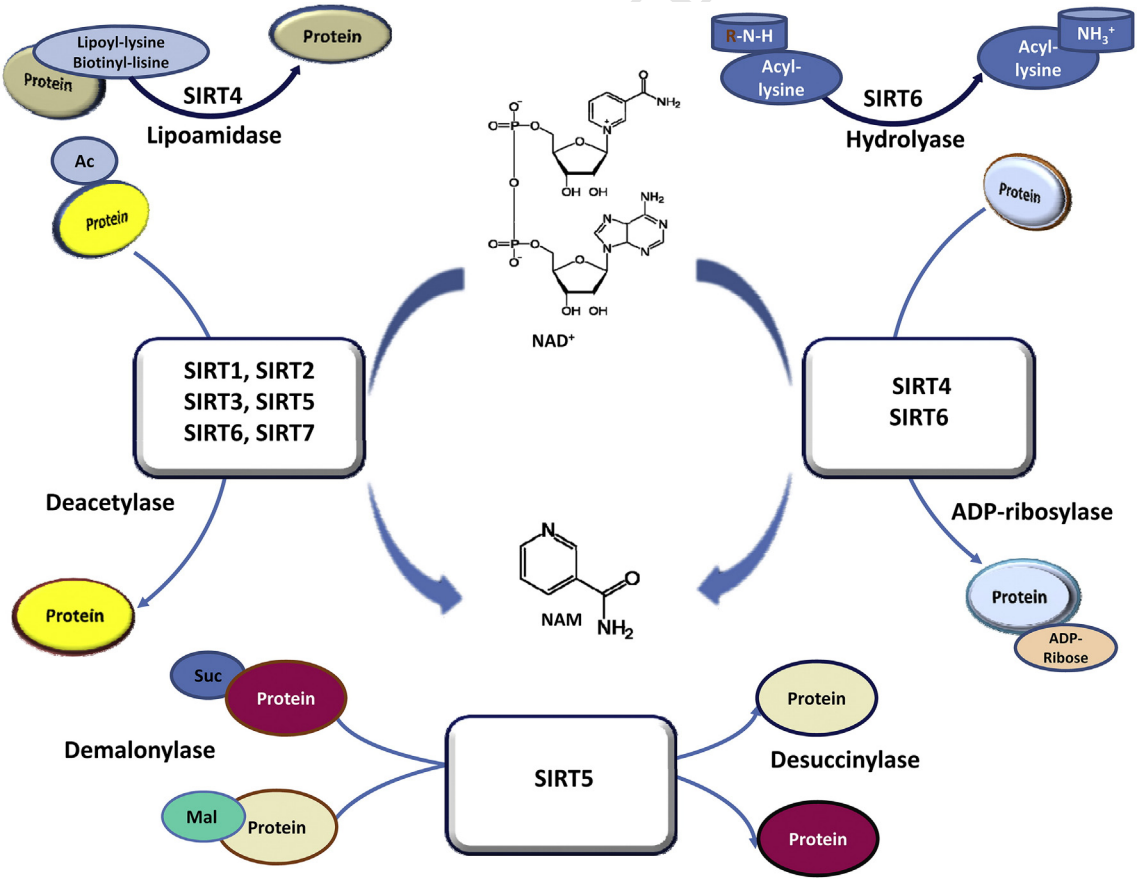

Fig. 1. Enzymatic activities of sirtuins. The seven sirtuins are categorized into four classes, class I (SIRT1, SIRT2, and SIRT3), class II (SIRT4), class III (SIRT5), and class IV (SIRT6 and SIRT7). Mammalian sirtuins have primarily two different NAD^+-consuming activities. SIRT1, SIRT2, SIRT3, SIRT5 SIRT6 and SIRT7 act as deacetylase enzymes using NAD^+ to cleave acetyl groups from ε-acetyl lysine residues of target proteins in a reaction that generates NAM and 2′-O-acetyl-ADP-ribose. SIRT4 and SIRT6 act as a mono-ADP-ribosyltransferase, in a reaction where the ADP-ribosyl moiety of NAD^+ is transferred to a substrate protein. SIRT6 has both enzymatic activities and, also, efficiently removes long chain fatty acyl groups from lysine residues. Moreover, SIRT4 acts as a cellular lipoamidase and SIRT5 acts as demalonylase and desuccinylase, by removing malonyl (Mal) or succinyl moiety (Suc) from target proteins. NAD^+, nicotinamide adenine dinucleotide; NAM, nicotinamide; ADP: adenosine diphosphate.

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