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Harnessing the Power of SIRT1 and Non-coding RNAs in Vascular Disease

Kenneth Maiese[1,*]

[1]Cellular and Molecular Signaling, Newark, New Jersey 07101

Abstract

Noncommunicable diseases (NCDs) contribute to a significant amount of disability and death in the world. Of these disorders, vascular disease is ranked high, falls within the five leading causes of death, and impacts multiple other disease entities such as those of the cardiac system, nervous system, and metabolic disease. Targeting the silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1) pathway and the modulation of micro ribonucleic acids (miRNAs) may hold great promise for the development of novel strategies for the treatment of vascular disease since each of these pathways are highly relevant to cardiac and nervous system disorders as well as to metabolic dysfunction. SIRT1 is vital in determining the course of stem cell development and the survival, metabolism, and life span of differentiated cells that are overseen by both autophagy and apoptosis. SIRT1 interfaces with a number of pathways that involve forkhead transcription factors, mechanistic of rapamycin (mTOR), AMP activated protein kinase (AMPK) and Wnt1 inducible signaling pathway protein 1 (WISP1) such that the level of activity of SIRT1 can become a critical determinant for biological and clinical outcomes. The essential fine control of SIRT1 is directly tied to the world of non-coding RNAs that ultimately oversee SIRT1 activity to either extend or end cellular survival. Future studies that can further elucidate the crosstalk between SIRT1 and non-coding RNAs should serve well our ability to harness the power of SIRT1 and non-coding RNAs for the treatment of vascular disorders.

Keywords

aging; apoptosis; autophagy; biomarker; cardiovascular disease; CCN4; cyclin-dependent kinase 2 (CDK2); cyclin-dependent kinase inhibitor 1 (p21); cell cycle; circular RNA; diabetes mellitus; endothelial cells; forkhead transcription factors; FoxO; metabolism; microRNA; non-coding RNA; oxidative stress; programmed cell death; senescence; SIRT1; stem cells; transcription factors; WISP1; Wnt signaling

The Global Presence of Vascular Disease

Noncommunicable diseases (NCDs) contribute to a significant amount of deaths across the globe. At least sixty percent of the fifty-seven million global deaths result from NCDs and almost eighty percent of these NCDs occur in low and middle-income countries (1). In

[*]Correspondence to: Kenneth Maiese, MD, Cellular and Molecular Signaling, USA. wntin75@yahoo.com.

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regards to the leading causes of NCDs, vascular disorders rank high and fall within the five leading causes of death that include cardiac disease, cancer, chronic lower respiratory disease, stroke, and traumatic accidents (2). Interestingly, vascular disorders not only affect cardiac disease, but also disorders of the nervous system. Hypertension and elevated serum lipids are significant risk factors for stroke, a disorder that affects approximately fifteen million individuals every year and leads to an annual cost of seventy-five billion dollars in the United States (3–7). Other NCDs such as diabetes mellitus (DM) also can lead to neurodegenerative disease (8–11). DM is increasing in incidence throughout the world. Approximately 350 million individuals currently have DM and an additional eight million individuals are believed to suffer from metabolic disorders and are currently undiagnosed (12, 13). Although DM can affect any system of the body, DM significantly impacts vascular disease resulting in platelet dysfunction (14, 15), atherosclerosis (9, 16, 17), endothelial cell senescence (18, 19), injury to endothelial cells (20–27), endothelial progenitor cell dysfunction (27–30), impaired angiogenesis (31–33), and cardiovascular disease (24, 34–38).

SIRT1 as a Target for Vascular Disease

The extent of vascular disease in the population is immense. Coupled to the progression of vascular disease in the world is the increasing age of the global population. Life expectancy is approaching eighty years of age for all individuals and is accompanied by a one percent decrease in the age-adjusted death rate from the years 2000 through 2011 (39). In addition, the number of individuals over the age of sixty-five also has doubled during the past fifty years (40). As a result, new avenues of investigation to develop novel therapies against vascular disease are required to stem this tide of vascular disease. One such avenue involves the silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1) that is under such consideration for the development of new treatments against vascular disease (29, 35, 41–47).

SIRT1, a member of the sirtuin family, is a histone deacetylase that transfers acetyl groups from ε-N-acetyl lysine amino acids on the histones of DNA to control transcription (29, 48–51). Seven identified mammalian homologues of Sir2 exist that include SIRT1 through SIRT7 that control post-translational changes of proteins and oversee cellular proliferation, survival, and senescence. In regards to SIRT1, it is dependent upon nicotinamide adenine dinucleotide (NAD^+) as substrate (48, 52–54). Nicotinamide phosphoribosyltransferase (NAMPT) catalyzes the conversion of nicotinamide to nicotinamide mononucleotide through the salvage pathway of NAD^+ synthesis (55–57). Nicotinamide mononucleotide is then converted to NAD^+ by enzymes in the nicotinamide/nicotinic acid mononucleotide adenylyltransferase (NMNAT) family.

The level of SIRT1 activity is believed to be an important factor in determining cell survival and protection against toxic insults. NAMPT is a rate-limiting enzyme in mammalian NAD^+ biosynthesis pathway such that elevated levels of NAMPT activity increase cellular NAD^+ levels and the activity of SIRT1 transcription. Other factors also can influence SIRT1 activity. NMNAT can modulate the deacetylating activity of SIRT1. Mammalian forkhead transcription factors (58, 59) also can bind to the SIRT1 promoter region that contains a

cluster of five insulin-responsive core repeat motifs (IRS-1) and a forkhead-like consensus-binding site (FKHD-L). This allows forkhead transcription factors, such as FoxO1, to increase SIRT1 expression (60). AMP activated protein kinase (AMPK) is another mechanism for the control of SIRT1 activity (61–67). AMPK is a member of the mechanistic of rapamycin (mTOR) pathway that phosphorylates tuberous sclerosis protein 2 (TSC2) and inhibits the activity of mTORC1 (67, 68). AMPK increases the activity of NAMPT (51). This process catalyzes the conversion of nicotinamide to nicotinamide mononucleotide (69), increases NAD^+ levels (69), decreases levels of nicotinamide (70), an inhibitor of SIRT1 (69, 71–73), and leads to SIRT1 transcription (13, 48, 74). As a result of increasing the intracellular NAD^+/NADH ratio, AMPK leads to deacetylation of the SIRT1 targets peroxisome proliferator-activated receptor-gamma coactivator 1 (PGC-1α) and forkhead transcription factors that include FoxO1 (37) and FoxO3a (75). Crosstalk between SIRT1 and AMPK also occurs (74). Resveratrol, a SIRT1 activator, has been demonstrated to activate AMPK (76).

At times, reduced SIRT1 activity may be required to promote cellular survival involving trophic factors such as as insulin growth factor-1 (77). However, insufficient SIRT1 activity may have a detrimental affect upon vascular cell survival (23, 78, 79) and block protection against cardiovascular disease (53, 80–82). Overall, SIRT1 controls multiple cellular functions that are involved with modulation of vascular survival and senescence (18, 83, 84), control of vascular tone through the transient receptor potential cation channel A1 (TRPA1) (85), development of atherosclerosis (80, 86–89), extension of lifespan (42, 73, 90, 91), alterations in cellular metabolism (10, 31, 57, 92–96), enhancement of neuronal survival and cognition (46, 59, 92, 97), and protection against oxidative stress (58, 81, 94, 98–103).

SIRT1, Stem Cells, Autophagy, and Apoptosis

SIRT1 can have a protective effective over stem cell development and maturation. Through pathways of autophagy (104, 105), SIRT1 can control stem cell survival by modulating autophagic flux (106). SIRT1 has a role in autophagic flux by promoting autophagy in mitochondria (107) that may be required to maintain a healthy pool of mitochondria (108). SIRT1 is required to initiate autophagy and transition muscle stem cells from a quiescence state to an active state (109). SIRT1 also inhibits apoptotic cell injury in endothelial progenitor cells during oxidative stress through the induction of autophagy (110). In endothelial cells exposed to oxidized low density lipoproteins that can lead to atherosclerosis, SIRT1 activity is increased in conjunction with AMPK that leads to autophagy and promotes cellular protection (86). SIRT1 activation of autophagy also involves the inhibition of other pathways such as the mechanistic target of rapamycin (mTOR) (33, 101, 111, 112). SIRT1 can have an inverse relationship with mTOR in embryonic stem cells (57, 113). SIRT1 inhibits mTOR pathways to promote autophagy and preserve the integrity of embryonic stem cells during oxidant stress (101) as well as to promote neuronal growth (114).

Apoptotic pathways with SIRT1 also play a role with stem cell survival (23, 42, 78, 103, 115, 116). For example, SIRT1 activation prevents external membrane phosphatidylserine (PS) exposure during the early phases of apoptosis in mature cells (23, 78, 117, 118). SIRT1

activity can counteract apoptosis initiated by tumor necrosis factor-α (TNF-α) in endothelial progenitor cells (84). During exposure to TNF-α, SIRT1 also has been shown to prevent skeletal myoblast injury (119). In the presence of decreased SIRT1 activity, human mesenchymal stem cells have been shown not to proliferate and succumb to apoptosis (83). Loss of SIRT1 expression in endothelial progenitor cells leads to apoptotic cell death that can occur in smokers and chronic obstructive disease patients (120).

During apoptosis, SIRT1 activity can be reduced by the degradation of caspases. Caspase degradation of the SIRT1 protein (121) also can accelerate further activation of caspases (121, 122). Other pathways such as p38 (123) and JNK1 (124) can degrade SIRT1 as well. Some pathways may protect SIRT1 against caspase degradation. The CCN family (defined by the first three members of the family that include Cysteine-rich protein 61, Connective tissue growth factor, and Nephroblastoma over-expressed gene) (125) member Wnt1 inducible signaling pathway protein 1 (WISP1) increases SIRT1 activity to protect cells from oxidative stress and apoptotic injury (126). WISP1 prevents SIRT1 caspase degradation and modulates forkhead transcription activity with SIRT1 to block FoxO3a activity and prevent caspase activation that would otherwise lead to the degradation of SIRT1 (126–129).

SIRT1, Non-Coding RNAs, and Stem Cell Proliferation

SIRT1 modulation of vascular disease as well as stem cell proliferation may be closely tied to the pathways of small non-coding ribonucleic acids (RNAs) that are termed microRNAs (miRNAs) (43, 49, 130, 131). MiRNAs oversee gene expression by silencing targeted messenger RNAs (mRNAs) translated by specific genes and are composed of 19–25 nucleotides. These small non-coding ribonucleic acids have an important role with SIRT1 to control stem cell development and differentiated cell survival. Under some conditions, increased SIRT1 activity is beneficial. Silencing of miR-195 in old mesenchymal stem cells promotes stem cell proliferation by increasing SIRT1 activity to restore anti-aging factors expression that include telomerase reverse transcriptase, the forkhead transcription factor FOXO1 (50), and protein kinase B (Akt) (131). Increased SIRT1 activity with loss of miR-204 promotes the proliferation of spermatogonial stem cells (132). Proliferation of stem cells also may require increased SIRT1 activity in combination with the inhibition or dysfunction of mTOR signaling that is controlled by miRNAs (133). However, it should be noted that a reduction in SIRT1 activity controlled by miRNAs may at times offer a benefit to stem cell populations. Neuronal differentiation can occur through miR-34a that leads to decreased SIRT1 expression and DNA-binding of p53 in mouse neural stem cells (134). Furthermore, miR-34a under other conditions that increase the SIRT1 and FoxO3a pathways can result in mitochondrial dysfunction and activation of intrinsic apoptotic pathways that are detrimental to mesenchymal stem cells (135).

Other non-coding RNAs also may have a critical role in vascular disease and be related to SIRT1 activity. For example, circular ribonucleic acids (circRNAs) are non-coding RNAs of approximately 100 nucleotides in length that were initially identified as being circular in nature (136–138). These non-coding RNAs have covalent bonds that maintain their circular structure. CircRNAs have both *cis* and *trans* regulation, regulate gene expression through the sponging of microRNAs (miRNAs) (139), can function as biomarkers, and oversee cellular

survival through programmed cell death involving apoptosis (104, 105). Circular antisense non-coding RNA in the INK4 locus (circANRIL) in vascular smooth muscle cells and macrophages can prevent exonuclease-mediated pre-ribosomal RNA processing, ribosome biogenesis, and proliferation of cells that may lead to atherosclerosis through the induction of apoptosis (140). CircRNA can function as an endogenous miR-223 sponge to inhibit cardiac hypertrophy and heart failure (141). Yet, circRNAs may not always be protective against apoptosis. Up-regulation of specific circRNAs may foster apoptotic cell injury during cell models of ischemia-reperfusion injury (142). In experimental models of myocardial infarction, the circRNA Cdr1as can increase cardiac infarct size and function as a sponge for “cytoprotective” miR-7a (143).

In the cardiovascular system, circRNA generated from Foxo3 (circ-Foxo3) has been found to be expressed in aged patients that may be linked to processes of aging. Silencing circ-Foxo3 inhibits senescence in mouse embryonic fibroblasts and over-expression of circ-Foxo3 results in cell senescence (144). Circ-Foxo3 appears to block cell cycle progression by binding to the cell cycle proteins cyclin-dependent kinase 2 (CDK2) and cyclin-dependent kinase inhibitor 1 (p21) to prevent cellular proliferation (145). With advanced age, increased expression of circRNAs also has been demonstrated in the skeletal muscles of monkeys (146). Given the intimate association among SIRT1, forkhead transcription factors, lifespan extension, and aging, it is conceivable that SIRT1 may have a significant role in the vascular system with aging and circRNAs.

SIRT1, miRNAs, and Vascular Disease

In a number of recent experimental paradigms, miRNAs appear to significantly impact the ability of SIRT1 to control cell survival in the vascular and nervous system. In studies involving aging and the apoptotic loss of cochlear hair cells, high expression of miR-29b in aged C57BL/6 mice results in decreased expression of SIRT1 and mitochondrial dysfunction, suggesting a protective role for SIRT1 (147). Diabetic endothelial vascular dysfunction that occurs during hyperglycemia elevated free fatty acids can result from the up-regulation of miR-34a that depresses the expression of SIRT1. In rat glomerular mesangial cells, elevated glucose increases miR-217 that decreases SIRT1 expression as well to result in inflammation and fibrosis (148). During periods of hyperglycemia, angiogenesis is impaired as a result of suppressed SIRT1 expression and the up-regulation of miR-34a expression (31). The ill effects that can occur during DM also extend to the retinal microvasculature. Studies in rats demonstrate that an up-regulation of senescence-associated markers that include miR-34a depresses SIRT1 expression and accelerates aging and oxidative stress injury in the retinal vasculature (94). In additional studies, endothelial vascular dysfunction and oxidative stress are prevented with the maintenance of SIRT1 and the inhibition of miR-34a (95). Vascular miR-204 controlled by gut microbiome also impairs endothelial function by targeting SIRT1 and depressing its function (149).

Future Perspectives

Targeting the SIRT1 pathway and the modulation of miRNAs may hold great promise for the development of novel strategies for the treatment of vascular disease. Clearly, as a NCD,

cardiovascular disorders affect a large proportion of the global population as a leading cause of death and disability (29, 42, 150). In addition, vascular disorders not only impact the cardiac system, but also play a significant role in disease progression for other disease entities such as those that involve the nervous system and metabolic disease (36, 151–153). In its self, SIRT1 is critical in controlling cell development, survival, metabolism, life span, and programmed cell death with apoptosis and autophagy. SIRT1 also interfaces with a number of vital pathways that involve forkhead transcription factors, mTOR, AMPK and WISP1. Yet, it appears that the level of SIRT1 activity can be a vital determinant in both biological and clinical outcomes that requires careful analysis and targeting. The level of activity of SIRT1 can affect the balance of the programmed death pathways of apoptosis and autophagy that ultimately determine cell survival as well as alter the course of stem cell development, maintenance, and differentiation. For example, SIRT1 activity is required for neuronal cell protection (126, 154, 155) and vascular cell survival (23, 78, 79, 156). This necessary fine control of SIRT1 activity also translates into the world of miRNAs such that in several circumstances loss of SIRT1 activity that is controlled by high miRNA expression can be toxic to cell survival and stem cell maintenance. However, evidence exists that under other conditions, a reduction in SIRT1 activity by miRNAs is required in cases that can promote stem cell differentiation and stem cell survival (134, 135). Future work that can foster new insight into these challenges will be extremely conducive for the development of harnessing the power of SIRT1 and non-coding RNAs for the treatment of vascular disorders.

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