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EDITORIAL

SIRT1 and stem cells: In the forefront with cardiovascular disease, neurodegeneration and cancer

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Abstract

Cardiovascular disease, nervous system disorders, and cancer in association with other diseases such as diabetes mellitus result in greater than sixty percent of the global annual deaths. These noncommunicable diseases also affect at least one-third of the population in low and middle-income countries and lead to hypertension, elevated cholesterol, malignancy, and neurodegenerative disorders such as Alzheimer's disease and stroke. With the climbing lifespan of the world's population, increased prevalence of these disorders is expected requiring the development of new therapeutic strategies against these disabling disease entities. Targeting stem cell proliferation for cardiac disease, vascular disorders, cancer, and neurodegenerative disorders is receiving great enthusiasm, especially those that focus upon SIRT1, a mammalian homologue of the yeast silent information regulator-2. Modulation of the cellular activity of SIRT1 can involve oversight by nicotinamide/nicotinic acid mononucleotide adenylyltransferase, mammalian forkhead transcription factors, mechanistic of rapamycin pathways, and cysteine-rich protein 61, connective tissue growth factor, and nephroblastoma over-expressed gene family members that can impact cytoprotective outcomes. Ultimately, the ability of SIRT1 to control the programmed cell death pathways of apoptosis and autophagy can determine not only cardiac, vascular, and neuronal stem cell development and longevity, but also the onset of tumorigenesis and the resistance against chemotherapy. SIRT1 therefore has a critical role and holds exciting prospects for new therapeutic strategies that can offer reparative processes for cardiac, vascular, and nervous system degenerative disorders as well as targeted control of aberrant cell growth during cancer.

Key words: FoxO; Mechanistic of rapamycin; Apoptosis; Autophagy; Cardiovascular; Cysteine-rich protein 61, connective tissue growth factor, and nephroblastoma over-expressed gene; Neurodegeneration; Progenitor stem cells; SIRT1; Cancer

Core tip: SIRT1, a mammalian homologue of the yeast silent information regulator-2, holds exciting prospects for new therapeutic strategies that can offer reparative processes for cardiac, vascular, and nervous system degenerative disorders as well as targeted control of unchecked cell growth during cancer.

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THE IMPACT OF CARDIOVASCULAR DISEASE, CANCER, AND NEURODEGENERATIVE DISORDERS

Life expectancy is increasing in developed countries such as the United States and has been accompanied by a one percent decrease in the age-adjusted death rate from the years 2000 through 2011[1]. Yet, a number of disorders on a global scale continue to plague the population with increased morbidity and mortality from cardiovascular disease, disorders of the nervous system, and cancer. The World Health Organization reports that in 2008, greater than 60% of 57 million global deaths were primarily due to cardiovascular diseases, diabetes, cancer, and respiratory disorders[2]. Almost 80% of these noncommunicable diseases (NCDs) occur in low and middle-income countries. These NCDs affect approximately 30% of the population under 60 in low and middle-income countries. In contrast, in high-income countries, 13% of the population under 60 is affected. Hypertension and elevated cholesterol are significant risk factors for cardiovascular disease with hypertension alone contributing to approximately 13% of all deaths[3]. Disorders such as hypertension and elevated cholesterol also contribute to acute neurodegenerative disease such as stroke, the fourth leading cause of death[4,5]. With the increasing lifespan of the world's population and advancing age, it is expected that the incidence of neurodegenerative disorders also will grow. As an example, ten percent of the global population over the age of 65 is now affected with the sporadic form of Alzheimer's disease, but this is expected to increase significantly[6-8]. Continued development of new therapeutic strategies directed against the NCDs of cardiovascular disease, neurodegeneration, and cancer are necessary to increase our armamentarium against the complexity of these disease entities.

THE SIRT1 PATHWAY

In this arsenal directed against cardiovascular disease, neurodegenerative disorders, and cancer, multiple therapeutic strategies are being advanced that involve novel stem cell applications. Targeting stem cell proliferation is being considered for cardiac disease[9], vascular disorders[10,11], cancer[12,13], and neurodegenerative disease[14-16]. However, it is the investigation of stem cells that focus upon sirtuins, mammalian homologues of the yeast silent information regulator-2 (Sir2), that are proving to be extremely exciting.

Sirtuins are histone deacetylases that transfer acetyl groups from ε-N-acetyl lysine amino acids on the histones of DNA to regulate transcription[17-19]. This family of histone deacetylases also mediates post-translational changes of proteins involved with cellular proliferation, survival, and senescence[20-23]. There are seven identified mammalian homologues of Sir2 that include SIRT1 through SIRT7. Of these, SIRT1 has been tied to the modulation of multiple cellular functions that include protection against oxidative stress[24-28], development of atherosclerosis[29,30], modulation of vascular survival and senescence[17,20,21,31,32], proliferation of cancer cells[33-36], changes in diabetic cellular metabolism[33-36], control of vascular tone through the transient receptor potential cation channel A1[37], promotion of neuronal survival and cognitive function[21,38-41], and the extension of lifespan[25,42,43]. Furthermore, SIRT1 appears to be necessary for efficient post-reprogramming of telomere elongation, the maintenance of pluripotency, and the modulation of differentiation in induced pluripotent stem cells[44]. In differentiated cells, SIRT1 also controls telomere length and maintenance[45].

SIRT1 is dependent upon NAD^+ as substrate[17,38,46,47]. Through the salvage pathway of NAD^+ synthesis, nicotinamide phosphoribosyltransferase (NAMPT) catalyzes the conversion of nicotinamide to nicotinamide mononucleotide[48]. Nicotinamide mononucleotide is subsequently converted to NAD^+ by enzymes in the nicotinamide/nicotinic acid mononucleotide adenylyltransferase (NMNAT) family. NAMPT is a rate-limiting enzyme in mammalian NAD^+ biosynthesis pathway. Elevated levels of NAMPT activity increase cellular NAD levels as well as the activity of SIRT1 transcription.

The level of SIRT1 activity and its modulation in these cellular processes is considered to be an important factor in determining cell survival and protection against toxic insults. Insufficient SIRT1 activity can have a detrimental affect upon vascular cell survival[22,23,49], protection against cardiovascular disease[31], and prevention of neuronal injury[28,50,51]. Yet, a reduction in SIRT1 activity also may be required to promote cellular survival in systems involving trophic factors such as as insulin growth factor-1[52].

Several biological systems can control the activity of SIRT1 (Figure 1). For example, NMNAT can modulate the deacetylating activity of SIRT1. In addition, mammalian forkhead transcription factors[53] can bind to the SIRT1 promoter region that contains a cluster of five putative core binding repeat motifs (IRS-1) and a forkhead-like consensus-binding site (FKHD-L). As a result, forkhead transcription factors such as FoxO1 can govern SIRT1 transcription and increase SIRT1 expression[54]. AMP activated protein kinase (AMPK) represents another pathway for the control of SIRT1 activity. AMPK is a member of the mechanistic

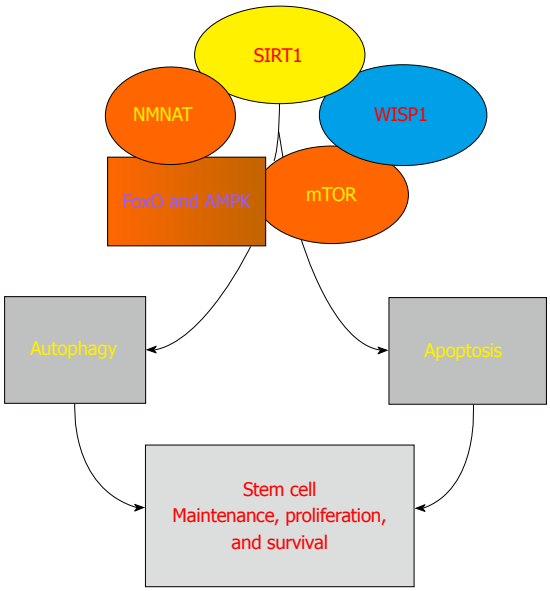

Figure 1 Schematic of SIRT1 pathways that can influence stem cell maintenance, proliferation, and survival. Several pathways can control SIRT1. For example, NMNAT can modulate the deacetylating activity of SIRT1, FoxO1 can govern SIRT1 transcription and increase SIRT1 expression, and AMPK can increase the cellular NAD^+/NADH ratio leading to the deacetylation of downstream SIRT1 targets. SIRT1 subsequently can depress mTOR pathways and promote autophagy to preserve stem cell integrity during oxidant stress as well as promote neuronal growth. In addition, SIRT1 is necessary to initiate autophagy and transition cells from a quiescence state to an active state. WISP1 increases SIRT1 activity to protect cells from oxidative stress and apoptotic injury and blocks SIRT1 caspase degradation. NMNAT: Nicotinamide/nicotinic acid mononucleotide adenylyltransferase; mTOR: Mechanistic of rapamycin; AMPK: AMP activated protein kinase.

of rapamycin (mTOR) pathway that phosphorylates tuberous sclerosis protein 2 and inhibits the activity of mTORC1[55,56]. AMPK can increase the cellular NAD^+/NADH ratio leading to the deacetylation of downstream SIRT1 targets that include the peroxisome proliferator-activated receptor-gamma coactivator 1 α, FoxO1, and FoxO3a[57]. AMPK also can increase NAMPT during glucose restriction that results in increased NAD^+ and decreased levels of nicotinamide[58], an inhibitor of SIRT1[59]. Resveratrol, a SIRT1 activator, also has been shown to activate AMPK through SIRT1 dependent or independent mechanisms[57,60].

STEM CELLS, SIRT1, APOPTOSIS, AND AUTOPHAGY

The impact of SIRT1 on cellular function is intimately associated with programmed cell death pathways that involve apoptosis and autophagy[61-63]. Apoptosis leads to DNA degradation and caspase activation through an early phase that involves the loss of plasma membrane lipid phosphatidylserine (PS) asymmetry and a later phase that results in genomic DNA degradation[64]. During the early phase of apoptosis, prevention of membrane PS externalization in injured cells is necessary to block the loss of functional cells that may be removed by activated inflammatory cells[56]. SIRT1 activation limits external membrane PS exposure during the early phases of apoptosis in mature cells[22,23,65,66]. In endothelial progenitor cells, SIRT1 activity can counteract the "pro-apoptotic" effects of tumor necrosis factor-α (TNF-α)[67]. During exposure to TNF-α, SIRT1 also has been shown to protect skeletal myoblast survival[68]. Loss of SIRT1 activity in human mesenchymal stem cells yields a reduction of proliferation rate with increased apoptosis[69]. During aging in the mouse auditory system, loss of SIRT1 in cochlear neurons and in the auditory cortex is associated with hearing loss[70]. In addition, endothelial progenitor cell dysfunction with apoptotic cell death that can occur in smokers and chronic obstructive disease patients has been associated with the loss of SIRT1 expression[71].

Stem cell survival with SIRT1 can be reliant upon forkhead transcription factors and mTOR (Figure 1). Although several studies involving differentiated cells support the premise that down-regulation of forkhead transcription factors by SIRT1 activation can protect against apoptotic cell death especially during oxidant stress[22,23,65,72,73], other studies in embryonic stem cells suggest that SIRT1 down-regulation can lead to the acetylation/phosphorylation of forkhead transcription factor pathways such as FoxO1, and in association with phosphatase and tensin homolog (PTEN) and c-Jun N-terminal kinase (JNK), block oxidant stress induced apoptosis[74]. However, in embryonic stem cells, the presence of SIRT1 also can be protective and appears to have an inverse relationship with mTOR[35]. SIRT1 can depress mTOR mediated pathways as well as promote autophagy to preserve the integrity of embryonic stem cells during oxidant stress[75]. SIRT1 can foster inhibition of mTOR signaling to promote neuronal growth[76]. In addition, during high glucose exposure to mesangial cells, the loss of SIRT1 activity is necessary for mTOR to arrest mesangial cell senescence[77].

It is important to note that during apoptotic cell injury with the induction of caspase activity, SIRT1 is susceptible to degradation by caspases. Although SIRT1 degradation also may be mediated by apoptotic pathways associated with p38[78] and JNK1[79], loss of SIRT1 activity can be the result of caspase degradation of the SIRT1 protein[80] that can then accelerate further activation of caspases[80,81]. In some systems that involve the cysteine-rich protein 61, connective tissue growth factor, and nephroblastoma over-expressed gene (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)[12], the CCN member WISP1 increases SIRT1 activity to protect cells from oxidative stress and apoptotic injury[28] (Figure 1). WISP1 also prevents SIRT1 degradation and oversees forkhead transcription activity with SIRT1 similar to other

cytoprotective pathways[20,73,82] to block FoxO3a activity and prevent caspase activation that would otherwise lead to the degradation of SIRT1[28,83-85].

In contrast to apoptosis, autophagy promotes tissue remodeling by recycling cytoplasmic components and eliminating no longer useful organelles[62]. Macroautophagy is the classification of autophagy most commonly described[86]. It involves the sequestration of cytoplasmic proteins into autophagosomes that fuse with lysosomes for degradation and are eventually recycled. In most cases, SIRT1 activation with the induction of autophagy appears to be vital to promote cell survival in mature cells. In differentiated chondrocytes during oxidant stress, knockdown of the forkhead transcription factors FoxO1 and FoxO3 result in cell death with decreased SIRT1 activity and reduced autophagic related proteins, suggesting that SIRT1 with the activation of autophagy is necessary for cellular protection[24]. SIRT1 also plays a role in autophagic flux and promoting autophagy in mitochondria[87] that may be required to maintain a healthy pool of mitochondria[88]. In endothelial cells exposed to oxidized low density lipoproteins that can lead to atherosclerosis, SIRT1 up-regulation in conjunction with AMPK results in autophagy that is necessary for cellular protection[89]. In models of cognitive loss with chronic intermittent hypoxia hypercapnia exposure, SIRT1 activation is able to block apoptotic cell injury, up-regulate autophagy, and improve cognitive performance[90]. However, in pulmonary models of oxidant stress such as the exposure to cigarette smoke in bronchial epithelial cells, SIRT1 has been shown to prevent cell injury through the inhibition of of autophagy[91,92]. In regards to stem cells and the autophagic pathway, stem cells rely upon SIRT1 to modulate autophagic flux[93]. In muscle stem cells, SIRT1 is necessary to initiate autophagy and transition muscle stem cells from a quiescence state to an active state[94]. In endothelial progenitor cells, SIRT1 blocks apoptotic cell injury during oxidative stress through the induction of autophagy[95].

STEM CELLS, SIRT1, AND THE CARDIOVASCULAR SYSTEM

In the cardiovascular system, SIRT1 expression can affect not only the survival of stem cells, but also the ability of stem cells to differentiate and the efficacy of these cells for therapeutic applications. Increased SIRT1 expression can improve the survival of cardiomyoblasts[96] and prevent senescence and impaired differentiation in endothelial progenitor cells[97]. In regards to treatment efficacy, mesenchymal stem cells that are subjected to SIRT1 over-expression exhibit increased blood vessel density in the area of cardiac infarcts, reduced cardiac remodeling, and improved cardiac performance in rodent models[98], factors that may be associated with cardiac stem migration that is vital to tissue repair[99]. SIRT1 also can limit expression of aged mesenchymal stem cell phenotypes[98]. Loss of SIRT1 in circulating endothelial progenitor cells that can occur during tobacco exposure or chronic obstructive pulmonary disease may lead to increased senescence and apoptotic cell death that presents increased risk for vascular disease or cardiac disease[71]. SIRT1 also may improve the function of aged stem cells that are senescent. Aged mesenchymal stem cells that were exposed to pre-conditioning with glucose depletion exhibited increased expression of SIRT1 in addition to other proliferative entities such as growth factors and resulted in increased cardiac performance[100].

STEM CELLS, SIRT1, AND NEURODEGENERATION

In the nervous system, SIRT1 has been tied to the differentiation, maturation, and maintenance of neurons. Loss of SIRT1 expression with the concurrent induction of heat shock protein-70 promotes neural differentiation, maturation of embryonic cortical neurons[101], and the differentiation of human embryonic stem cells into motor neurons[102]. SIRT1 also is considered a negative regulator of subventricular zone and hippocampal neural precursors in murine animal models. Knockdown of SIRT1 does not eliminate neural precursor numbers or proliferation but increases the production of neurons in the subventricular zone and the hippocampus[103]. In the mouse cerebral cortex, repression of SIRT1 by the oncogene BCL6 leads to the conversion of neural stem cell/progenitor cells to become neurons[104]. Neural stem cell differentiation also can be controlled through alternate pathways that involve SIRT1. In mouse neural stem cells, neuronal differentiation can be driven through the microRNA miR-34a that leads to decreased SIRT1 expression and DNA-binding of p53[105]. Interestingly, in these studies, increased expression of SIRT1 enhanced the astrocytic subpopulation of cells[105].

STEM CELLS, SIRT1, AND CANCER

The cellular proliferative effects of SIRT1 also play a critical role in tumorigenesis. For example, SIRT1 activity can maintain acute myeloid leukemia stem cells and confer resistance against chemotherapy[106], stimulate endometrial cell tumor growth through lipogenesis[107], maintain neural stem cells and promote oncogenic transformation[108], and foster hepatocellular carcinoma[109]. As a result, SIRT1 and agents that modulate SIRT1 activity may represent new therapeutic strategies against tumorigenesis. For example, down-regulation of endoglin, a protein over-expressed in tumor associated endothelial cells, leads to apoptotic cell death, DNA damage, inhibition of several DNA repair genes including SIRT1, and enhanced chemotherapy sensitivity[110]. In addition, pathways linked to SIRT1

also may provide new strategies against cancer. Activation of p53 through SIRT1 inhibition can result in apoptotic cell death for quiescent leukemia stem cells in chronic myelogenous leukemia[111]. In breast cancer, estrogen receptor-α can lead to SIRT1 expression that activates pro-survival genes in breast cancer cells, such as catalase and glutathione peroxidase, and inhibits tumor suppressor genes, such as cyclin G2 (*CCNG2*) and *p53*. In these breast cancer cells, if SIRT1 is inhibited, estrogen receptor-induced breast cell growth is blocked through apoptotic cell death[112].

FUTURE CONSIDERATIONS

Cardiac disease, vascular disorders, neurodegenerative disease, and cancer lead to significant disability and death in the global population. Development of stem cell strategies for these disorders and the targeting of SIRT1 to drive stem cell viability and function holds great promise for the future. In the cardiovascular system, SIRT1 through stem cell proliferation can drive angiogenesis, improve cardiac performance following ischemic injury, limit cell senescence, and enhance the function of aged stem cells. In the nervous system, SIRT1 can be a negative modulator of neural precursors with the loss of SIRT1 leading to differentiation and maturation of embryonic stem cells in the nervous system. During tumorigenesis, SIRT1 foster the development of acute myeloid leukemia stem cells, promote oncogenic transformation of neural stem cells, and lead to hepatocellular cancer. Vital to the clinical outcomes controlled by SIRT1 is its level of activity overseen by pathways that include NMNAT, mammalian forkhead transcription factors, mTOR, and CCN family members such as WISP1 that determine cell survival through apoptosis and autophagy. Future work that can target SIRT1 and navigate stem cell proliferation under required conditions to either cellular proliferation or cellular death can open new avenues for the treatment of cardiovascular disorders, neurodegenerative disease, and cancer.

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