Translating cell survival and cell longevity into treatment strategies with SIRT1

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Abstract

The sirtuin SIRT1, a class III NAD^+-dependent protein histone deacetylase, is present throughout the body that involves cells of the central nervous system, immune system, cardiovascular system, and the musculoskeletal system. SIRT1 has broad biological effects that affect cellular metabolism as well as cellular survival and longevity that can impact both acute and chronic disease processes that involve neurodegenerative disease, diabetes mellitus, cardiovascular disease, and cancer. Given the intricate relationship SIRT1 holds with a host of signal transduction pathways ranging from transcription factors, such as forkhead, to cytokines and growth factors, such as erythropoietin, it becomes critical to elucidate the cellular pathways of SIRT1 to safely and effectively develop and translate novel avenues of treatment for multiple disease entities.

Keywords

Cell Injury and Oxidative Stress

Oxidative stress is the result of the cellular release of reactive oxygen species, such as oxygen free radicals and other chemical entities that lead to cell injury in the body. Excessive amounts of oxygen free radicals can be generated during the reduction of oxygen and lead to cell injury. Reactive oxygen species (ROS) include superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide (NO), and peroxynitrite [1–8]. During normal physiological conditions, reactive oxygen species are released at low levels and are scavenged by endogenous antioxidant systems that include superoxide dismutase (SOD), glutathione peroxidase, catalase, and small molecule substances such as vitamins C and E [9–11]. Additional anti-oxidant pathways may block oxidative injury as well as affect tumor growth such as vitamin D_3 [12, 13] and the amide form of niacin or vitamin B_3, nicotinamide [4, 14–22].

Oxidative stress is involved in the pathology of a broad range of disease processes that involve metabolic disorders and diabetes mellitus (DM) [23–29], loss of cognition [30–34],

myocardial disease [5, 28, 35–37], psychiatric disorders [32, 38, 39], nervous system injury [40–44], vascular disease [28, 34, 45–52], and hepatic disease [7, 53, 54]. In cells, oxygen free radicals can result in cellular membrane lipid peroxidation and protein oxidation leading to the disruption of cellular integrity [7].

Loss of cellular integrity can occur through a variety of mechanisms that include both apoptosis and autophagy. Apoptosis and autophagy occur in multiple cells including ocular cells [55, 56], non-neuronal cells [9, 57–61], neurons [42, 43, 61–67], vascular cells [46, 48, 49, 68–70], cancer cells [14, 71–76], and inflammatory cells [77–81]. In regards to programmed cell death with apoptosis, this process consists of both the early exposure of membrane phosphatidylserine (PS) residues and the later destruction of genomic DNA [5, 57, 82]. Apoptotic membrane PS exposure is present during conditions such as oxidant stress [5, 57, 82] and β-amyloid (Aβ) exposure [41, 83]. Membrane PS exposure can function to identify cells for the phagocytosis, alter vascular endothelial cell function[15, 19, 84–86], and influence inflammatory cell activation and proliferation [58, 59, 80, 81, 83, 87, 88].

The SIRT1 Pathway

Sirtuins, class III NAD$^+$-dependent protein histone deacetylases, are the mammalian homologues of Sir2 of the yeast silent information regulator-2 (Sir2). Sirtuins transfer the acetyl residue from the acetyllysine residue of histone to the ADP-ribose moiety of NAD+, resulting in the production of nicotinamide, 2′-O-acetyl ADP ribose, and deacetylated proteins. Seven mammalian homologues of Sir2, SIRT1 through SIRT7, have been identified. SIRT1 was the first to be identified. SIRT1 uses NAD$^+$ as substrate. Yet, the level of NAD$^+$ also can control the deacetylating activity of SIRT1. In the salvage pathway of NAD$^+$ synthesis, nicotinamide phosphoribosyltransferase (NAMPT) catalyzes the conversion of nicotinamide to nicotinamide mononucleotide, which is then converted to NAD$^+$ by nicotinamide/nicotinic acid mononucleotide adenylyl-transferase (NMNAT). NAMPT functions as the rate-limiting enzyme in mammalian NAD$^+$ biosynthesis pathway. Increased NAMPT activity raises the total cellular NAD level and subsequent transcriptional regulatory activity of SIRT1 [89]. In addition, NMNAT can regulate the deacetylating activity SIRT1 at its target gene promoters [89, 90].

SIRT1 is expressed in the brain, heart, liver, pancreas, skeletal muscle, spleen, and adipose tissues [91–93]. At the cellular level, SIRT1 is present in the nucleus and cytoplasm with primary expression in the nucleus. SIRT1 and agents that affect its activity play a significant role in multiple biological processes that include oxidative stress, metabolism, cellular proliferation, and genomic stability [94]. SIRT1 has been demonstrated to regulate cellular protection against oxidative stress in many disease states that involve aging, neurodegeneration, metabolic disorders, cancer, and cardiovascular disease [47, 48, 79, 95–102] (Figure 1).

Cytoprotection by SIRT1

SIRT1 can offer protection in multiple cell types during oxidative stress as either a down-stream mediator of cell protection or through the modulation of specific cellular pathways. Treatment with the cytokine and growth factor erythropoietin (EPO) offers one example of the ability of SIRT1 to function as a mediator of cellular protection during oxidative stress. EPO is a 30.4 kDa glycoprotein with almost half of its molecular weight derived from carbohydrates that can vary among species [103, 104]. EPO has four glycosylated chains that include three *N*-linked and one *O*-linked acidic oligosaccharide side chains. The *N*-linked glycosylation sites occur at the positions 24, 38, and 83 of aspartyl residues, while the *O*-linked glycosylation site is at Serine[126] [54, 105]. Although the Food and Drug

Administration has approved EPO for the treatment of anemia, a number of investigations have shown that EPO is not only important for erythropoiesis, but also has a significant role in other organ systems such as the brain, heart, and vascular system [10, 36, 84, 106–113]. In the nervous system, EPO production and secretion occurs in the hippocampus, internal capsule, cortex, midbrain, cerebral endothelial cells, and astrocytes. Other organs as secretory tissues for EPO include endothelial cells, myoblasts, insulin-producing cells, and cardiac tissue [5, 110, 113–116].

As a cytoprotectant, EPO can increase cell survival during hypoxia [61, 84, 117–121], free radical injury [63, 117, 122–124], infection [125–127], cardiovascular injury [48, 52, 69, 84, 121, 122, 128–136], amyloid exposure [32, 137–139], and diabetic complications [25, 69, 128, 130, 140, 141]. In addition, EPO modulates both the activity and proliferation of non-neuronal and inflammatory cells [120, 142–144].

In regards to SIRT1, recent work has shown that EPO increases endogenous SIRT1 activity in endothelial cells and fosters the subcellular trafficking of SIRT1 to the nucleus which is necessary for EPO to foster vascular protection [48]. Downstream from SIRT1, activation of protein kinase B (Akt1) is required. Activation of Akt1 results in cellular protection [16, 18, 42, 45–47, 64, 73, 78, 128, 143, 145–153] and SIRT1 has been associated with enhanced activity of Akt [47, 48, 93, 154, 155].

In addition, SIRT1 employs Akt1 to modulate the phosphorylation and subcellular trafficking of the forkhead transcription factor FoxO3a [48]. Mammalian forkhead transcription factors of the O class (FoxO1, FoxO3, FoxO4, and FoxO6) are involved in cell metabolism, insulin sensitivity, aging, fertility, and oxidative stress [29, 75, 156–165] and have been tied to the modulatory effects of EPO [48, 68, 128, 166–168]. Phosphorylation of FoxOs results in their retention in the cytoplasm and inhibition of their transcription activity [20, 169]. Acetylation of FoxOs can also modulate their transcriptional activity through facilitating their phosphorylation and nuclear translocation [81, 83, 170]. Nuclear localization of FoxO occurs through deacetylation [171] and is inhibited by phosphorylation.

SIRT1 controls the nuclear shuttling and transcriptional activity of forkhead transcription factors. During oxidative stress, FoxOs translocate to the nucleus, interact with SIRT1, and result in the deacetylation of FoxOs. Dependent upon the post-translational changes on FoxOs, SIRT1 can inhibit FoxO activity and protect cells from oxidative stress [47, 48] or increase the activity of FoxOs to lead to gene activation [75, 159, 163]. With some forkhead family members such as FoxO4, SIRT1 can bind to FOXO4, catalyze deacetylation in an NAD-dependent manner, and increase FoxO4 transactivation activity [172].

Multiple FoxO family members may participate in the protective effects of SIRT1. Modulation by SIRT1 over FoxO function occurs via NAD-dependent deacetylation in response to oxidative stress. SIRT1 also can target FoxOs such as FoxO1 to bind and deacetylate FoxO1 at residues that are acetylated by cAMP-response element-binding protein [173]. Studies with over-expression of SIRT1 demonstrate protection of cardiomyocytes from oxidative stress through a FoxO1-dependent pathway [174]. It should be noted that SIRT1 can enhance expression of FoxO targets that are involved in stress resistance, such as manganese superoxide dismutase (MnSOD) and Gadd45, but diminishes the expression of pro-apoptotic FoxO targets (Fas ligand and Bim), suggesting that SIRT1 may modulate the balance between stress resistance and cell death within cells [159, 163]. Deacetylation of FoxOs by SIRT1 also can regulate autophagy. SIRT1 mediated deacetylation of FoxO1 has been associated with increases in autophagic flux which may be required to maintain cardiac function during glucose deprivation and starvation [175]. FoxO1 also increases the expression of Rab7, a small GTP-binding protein that mediates

late autophagosome-lysosome fusion, which is both necessary and sufficient for mediating FoxO1-induced increases in autophagic process [175].

FoxOs also exert a positive feedback mechanism regulating SIRT1 expression. FoxO1 can directly bind to the SIRT1 promoter region containing a cluster of five putative FoxO1 core binding repeat motifs (IRS-1) and a forkhead-like consensus-binding site (FKHD-L). This leads to a FoxO1 modulating SIRT1 transcription and leads to an increase in the expression of SIRT1 [176]. FoxO3a also can regulate the expression of SIRT1 by binding to two p53 binding sites within the SIRT1 promoter to foster SIRT1 transcription during acute nutrient withdrawal [177].

It is interesting to note that SIRT1 may, at times, influence cancer growth. SIRT1 has been found to negatively regulate the tumor suppressor gene p53 through an NAD dependent deacetylating mechanism and therefore, SIRT1 has been considered as a tumorigenic factor [178]. A nuclear protein active regulator of SIRT1 (AROS) also can enhance SIRT1-mediated deacetylation of p53 both *in vitro* and *in vivo* models and prevents p53-mediated transcriptional activity [179]. Hypermethylated in Cancer 1 (HIC1) and deleted in breast cancer 1 (DBC1) have been identified as negative regulators of SIRT1 [180]. HIC1, a transcriptional repressor, binds to the SIRT1 promoter and represses its transcription. Loss of HIC1 increases SIRT1 expression in normal or cancer cells, resulting in the deacetylation and inactivation of p53 and enhanced tumorigenesis [181]. However, other studies suggest, such as in BRCA1-associated breast cancer, that SIRT1 may stem cancer cell progression [182].

FoxOs may be tied to the modulatory role of SIRT1 during tumorigenesis. FoxO proteins promote apoptotic cell death and cell cycle progression [76, 183]. FoxO3a and FoxO4 can promote cell cycle arrest in mouse myoblastic cell lines through modulation of growth-arrest and DNA-damage-response protein 45 [74, 160]. The transcription factor E2F1 that controls the induction of the cell cycle can increase the endogenous expression of FoxO1 and FoxO3a to lead to cell cycle arrest [184]. However, loss of FoxO3a activity in association with c-myc, p27, and nuclear factor-κB (NF-κB) can result in cell cycle induction and malignant transformation of mouse cells in the presence of oncogene activation [159, 185]. SIRT1 may oversee FoxO transcription pathways to enhance anti-tumor activity. For example, resveratrol can block the phosphorylation of FKHRL1 leading to increased activity and enhancement of TRAIL pathways to block tumor growth in prostate cancer [71]. In addition, SIRT1 can interact with E2F1 during cell cycle regulation and apoptosis [186]. As an important regulator in response to DNA damage induced stress, E2F1 can positively regulate SIRT1 expression at the transcriptional level. SIRT1 binds to E2F1 and deacetylates E2F1, resulting in the inhibition of E2F1 transcriptional activity [186].

It should be emphasized that the relationship between SIRT1 and forkhead transcription factors is not entirely clear. In some cell systems, such as in renal cells, the presence of FoxO3a may be necessary for SIRT1 to exert protection and maintain cell longevity during oxidative stress [187]. SIRT1 also may be dependent upon other forkhead transcription factors, such as FoxO1, to regulate the transcription of SIRT1 [176]. Under such circumstances, enhanced SIRT1 expression during increased FoxO1 activity may negate the protective ability of SIRT1 in the presence of active FoxO1 and ultimately lead to the demise of cells. In other scenarios, SIRT1 with combined FoxO activity may offer inhibition of cell cycle progression that can limit apoptosis and be beneficial in cardiac or neurodegenerative disorders [188, 189], but in the setting of tumorigenesis, loss of cell cycle regulation could spell disaster for a patient [75, 183].

In addition, the relationship between SIRT1 and forkhead transcription factors represents a fine balance to promote both cell protection with cellular longevity. Activation of SIRT1 can increase lifespan in higher organisms such as Drosophila while also protecting neurons from oxidant stress [95, 190]. In regards to cellular protection, SIRT1 may rely upon the regulation of FoxO transcription factors such as to protect against inflammation [79], to promote cardiac function during starvation [156, 175], to protect against cardiac ischemia [35], and to maintain vessel integrity during oxidative stress [47, 48]. Furthermore, an increase in FoxO3a and SIRT1 activity can occur in the heart during exercise [191], suggesting that physical activity may be beneficial for the cardiovascular system through SIRT1 and FoxO proteins.

In addition to Akt and FoxOs, cytoprotection by SIRT1 may be controlled by other means. In many experimental paradigms, resveratrol (*trans*-3,5,4′-trihydroxystibene), a naturally occurring phytoalexin polyphenol in the grape and red wine, is used to increase SIRT1 activity. At the cellular level, SIRT1 is expressed in both the cytoplasm and the nucleus. During events that incite apoptosis, SIRT1 translocates from the cytoplasm to the nucleus to prevent apoptosis. Resveratrol enhances SIRT1 translocation to the nucleus to protect cells from oxidative stress [47, 48]. Prevention of SIRT1 nuclear translocation abolishes protection by SIRT1 and resveratrol, suggesting that translocation of SIRT1 to the nucleus is necessary as well to protect against cellular injury [20, 47, 48]. Resveratrol treatment increases SIRT1 activity and prevents apoptotic injury during models of experimental diabetes with elevated glucose [47, 48], amyloid toxicity [192], cardiac disease [193], metabolic disorders [97, 98], and cerebral global ischemia [194]. SIRT1 has been shown to protect cells against oxidative stress by increasing the activity of catalase [187]. SIRT1 over-expression enhances the tolerance against free radical toxicity in neuronal cells [42, 95]. SIRT1 can block p53-induced apoptosis [179] through p53 deacetylation and induction of manganese superoxide dismutase (MnSOD) [195, 196]. Nuclear factor-κB (NF-κB) has been identified as another transcription factor that may play a significant role with SIRT1 in the protection against oxidative stress [81, 137, 197, 198]. Once activated, NF-κB is translocated to the cell nucleus and activates several anti-apoptotic genes, such as the inhibitors of apoptotic protein (IAPs), Gadd45β, and Bcl-x_L to prevent apoptosis against oxidative stress [81, 137, 143, 147, 199]. Yet, it should be recognized that NF-κB at times also can lead to pro-inflammatory gene induction that promote inflammation, cell death, and tumorigenesis [33, 81, 198, 200, 201]. SIRT1 has been shown to interact with and deacetylate the RelA/p65 subunit of NF-κB and inhibit its transcriptional activity [202]. In addition, use of resveratrol potentiates chromatin-associated SIRT1 protein on the cIAP-2 promoter region and inhibits NF-κB regulated gene expression. This leads to an increase in the sensitization of cells to tumor necrosis factor-α-induced apoptosis [202]. In regards to feedback pathways, HuR, a RNA binding protein, regulates the stability of many target mRNAs and can bind the 3′ non-translated region of the mRNA of SIRT1, leading to the stabilization of the SIRT1 mRNA and up-regulation of SIRT1 expression [203]. During oxidative stress, HuR is phosphorylated, resulting in the dissociation of the HuR-SIRT1 mRNA complex and subsequent SIRT1 mRNA decay

SIRT1 and Clinical Disorders

Disorders of Metabolism

Diabetes mellitus (DM) has become a significant health concern throughout the world [5, 25, 26, 204]. By the year 2030, it is predicted that more than 360 million individuals will be afflicted with DM and its debilitating conditions [10, 27]. Insulin resistance and the complications of DM can be the result of cellular oxidative stress [24, 25]. Hyperglycemia leads to increased production of reactive oxygen species (ROS) in endothelial cells, liver cells, and pancreatic β-cells [24-26]. As a result, patients with DM can develop immune

dysfunction [205], cognitive disorders [205, 206], hepatic dysfunction [207], renal disease [208], hematological disease [209], neurodegenerative disorders [5, 24, 204], and cardiovascular disease [23, 28, 114, 115, 210].

SIRT1 activity has been associated with insulin sensitivity. SIRT1 expression is decreased in the pancreas and liver in rats on high fat diets and may be associated with insulin resistance [211]. In insulin resistance cells, SIRT1 protein is significantly decreased and the reduction of SIRT1 levels in gastrocnemius muscle in mice results in the impairment of glucose tolerance [212]. Gene deletion or inhibition of SIRT1 impairs the insulin signaling by interfering with insulin stimulated insulin receptor phosphorylation and glycogen synthase [212]. Over-expression of SIRT1 in the liver serves to attenuate hepatic steatosis and improves insulin sensitivity, resulting in improved glucose homeostasis [98]. The ability of SIRT1 to improve insulin sensitivity may occur through several factors such as modulation of fat mobilization [213], gluconeogenesis [214], and inflammation [215]. SIRT1 also can function as a positive modulator of insulin signaling in insulin-sensitive organs and activate the insulin downstream target Akt through phosphotidylinositide 3-kinase (PI 3-K) [97]. SIRT1 can stimulate glucose-dependent insulin secretion from pancreatic β cells via repressing the uncoupling protein (UCP) gene UCP2 [216]. The SIRT1 activator resveratrol also promotes glucose stimulated insulin secretion in insulinoma INS-1E cells and human islets that is dependent on active SIRT1 [102].

SIRT1 not only has a role with insulin sensitivity, but also can affect fat metabolism and obesity. In obese mice, SIRT1 expression is low in adipose tissue and loss of SIRT1 in white adipose cells results in the impairment of fatty acid mobilization. Over-expression of SIRT1 in adipose tissue suppresses the transcriptional activity of PPAR-γ to inhibit adipogenesis and activation of lipolysis during fasting [213]. Resveratrol application can mimic calorie restriction to prevent obesity as a result of a high calorie diet in mice [217]. SIRT1 has been shown to be expressed in anorexigenic pro-opiomelanocortin (POMC) neurons and orexigenic agouti-related peptide (AgRP) neurons in the arcuate nucleus of the hypothalamus and regulate food intake and cellular metabolism [218]. For example, over-expression of SIRT1 in the hypothalamus prevents FoxO1 from promoting hyperphagia and body weight gain [218]. However, lack of SIRT1 in POMC neurons leads to obesity due to reduced energy expenditure [100].

SIRT1 may regulate insulin sensitivity and metabolism through the phosphorylation of AMP-activated protein kinase (AMPK). SIRT1 controls AMPK through the AMPK kinase, serine-threonine liver kinase B1 (LKB1). Over-expression of SIRT1 results in the deacetylation of LKB1, leading to its translocation from the nucleus to the cytoplasm, where LKB1 activates AMPK [219]. AMPK, in turn, can mediate the activation of SIRT1. Activation of AMPK occurs during decreased energy with a subsequent increase in the AMP/ATP ratio and can function to promote insulin sensitivity, fatty acid oxidation, and mitochondrial biogenesis. These events can lead to the generation of ATP and reduction in oxidative stress [29].

AMPK mediated impairment of muscle differentiation during glucose restriction and peroxisome proliferators-activated receptor-γ coactivator (PGC)-1α mediated gene expression is also SIRT1 dependent. AMPK is not believed to directly activate SIRT1, but may enhance SIRT1 activity. AMPK activation enhances SIRT1 activity either by increasing cellular $NAD^+/NADH$ ratio, resulting in the deacetylation and modulation of the activity of downstream SIRT1 targets that include the PGC-1α, FoxO1, and FoxO3a [220] or by up-regulating nicotinamide phosphoribosyltransferase (NAMPT) during glucose restriction, leading to increased NAD^+ and decreased nicotinamide, an inhibitor of SIRT1 [221]. Resveratrol also has been demonstrated to activate AMPK through SIRT1 dependent

or independent mechanisms [220, 222]. Resveratrol increases AMPK phosphorylation to protect cells against elevated glucose concentration, improve insulin sensitivity, and stimulate glucose transport. Increased AMPK activation reduces myocardial infarct size in both non-diabetic and diabetic rat hearts following ischemia/reperfusion, which may be mediated through the inhibition of mitochondrial permeability transition pore opening in cardiomyocytes [28]. Mice expressing dominant negative AMPK or loss of AMPK have glucose uptake inhibition and increased infarct volume following cardiac ischemia [223].

SIRT1 also controls insulin sensitivity through targeting protein tyrosine phosphatase (PTP). In the PTP family, PTP1B down-regulates insulin signal transduction via targeting the insulin receptor. PTP1B deficiency or inhibition leads to improved insulin sensitivity and glycemic control. Lowering the PTP1B level in the liver decreases blood glucose in diabetic mice. SIRT1 over-expression or SIRT1 activation can reduce both the PTP1B mRNA and protein levels during insulin-resistance. In contrast, an increase in PTP1B expression prevents SIRT1 mediated glucose uptake and insulin receptor phosphorylation in response to insulin stimulation, suggesting that SIRT1 improves insulin sensitivity through the repression of PTP1B [212].

SIRT1 in association with PPAR-γ plays an important role during adipogenesis. PPAR-α increases free fatty acid uptake and decreases lipolysis. Under nutrient restriction, SIRT1 protein binds to and represses genes controlled by the fat regulator PPAR-γ. SIRT1 inhibits PPAR-γ and silencing mediator of retinoid and thyroid hormone receptors, resulting in the mobilization of fatty acids from white adipocytes upon fasting [213]. PPAR-γ also may directly interact with SIRT1 and form a negative feedback to regulate SIRT1 activity [224].

SIRT1 plays a role during hepatic glucose output and lipid homeostasis. SIRT1 regulates the activity of PGC-1α via deacetylation and it can interact with PGC-1α in the liver to induce gluconeogenic genes and hepatic glucose output. PGC-1α is a member of a family of transcriptional coactivators that includes PGC-1α, PGC-1β and PGC-1 related coactivator (PRC). PGC-1α interacts with transcription factors to activate transcription and increases the expression of genes that regulate mitochondrial functions and fatty acid oxidation [225]. As a result, enhanced PGC-1α activity may function to protect against some metabolic diseases and improve mitochondrial biogenesis. SIRT1 also can control the ability of PGC-1α to repress glycolytic genes in response to fasting and pyruvate [214]. Hepatic SIRT1 interacts with PPAR-α through activating PGC-1α to mediate lipid homeostasis. For example, SIRT1 deletion in the liver results in the loss of PGC-1α activity and the impairment of fatty acid oxidation, predisposing to develop hepatic steatosis when fed with a high-fat diet [215].

Disorders of Aging and Nervous System Injury

When one considers the role of SIRT1 in clinical disorders and especially those impacting the nervous system, it is important to differentiate whether a treatment strategy not only can influence cell survival, but also influence cell longevity [226–228]. Recent work suggests that acute cellular protection by SIRT1 is closely linked to the ability of SIRT1 to extend cell longevity. SIRT1 can promote increased lifespan in higher organisms above yeast and metazoans while also increasing the protection of neuronal cells during oxidant stress exposure [95, 190]. SIRT1 during both acute injury and aging processes may be necessary for DNA repair to block apoptotic cell death [14]. Furthermore, in clinical studies of aging in patients with Alzheimer's disease, loss of SIRT1 has been associated with the increased accumulation of β-amyloid and tau [229]. In the vascular system, increased SIRT1 activity is necessary to block endothelial cell death, extend cellular lifespan, and decrease endothelial senescence in models of both DM and oxidative stress [47, 48, 154]. Moderate over-expression of SIRT1 in cardiac cells can lessen age-dependent increases in cardiac hypertrophy and reduce the expression of senescence markers [174].

Given these properties of SIRT1 especially for the nervous system, SIRT1 may be critical for the protection of neurons during both acute and chronic injuries. Application of resveratrol protects neuronal cells against oxidative stress that is dependent on SIRT1 activation [192]. Resveratrol also can mimic the benefits of ischemic preconditioning in the brain to reduce ischemic brain injury [230]. Furthermore, loss of SIRT1 activity during application of the SIRT1 inhibitor sirtinol abolishes neuroprotection by resveratrol [95, 190]. Treatment with resveratrol reduces brain infarct volume, decreases neurological deficits, and increases regional brain blood flow after cerebral ischemia [231]. Additional work suggests that resveratrol also protects neurons during both transient focal and global cerebral ischemia via the reduction oxygen free radicals and the prevention of lipid peroxidation [194].

In regards to chronic neurodegenerative diseases, such as Alzheimer's disease (AD), SIRT1 also may have a vital role. SIRT1 is believed to be necessary in maintaining normal learning, memory, and synaptic plasticity [99]. In patients with AD with progressive cognitive impairment, a decrease in SIRT1 is present in the parietal cortex in conjunction with an associated accumulation of amyloid-beta (Aβ) and tau protein [229]. In animal models of AD, application of SIRT1 and resveratrol reduces neurodegeneration in the hippocampus and prevents learning impairment [232]. Over-expression of SIRT1 in a mouse model of AD reduces the accumulation of Aβ, while gene silencing of SIRT1 in the brain results in an increased production of Aβ [96]. Resveratrol also has been reported to protect neuronal cells against Aβ during oxidative stress [192]. Activation of SIRT1 also reduces Aβ cell toxicity and decreases NF-κB transcriptional activity, suggesting that SIRT1 may promotes cellular protection against Aβ through inhibiting NF-κB transcriptional activity [199].

SIRT1 also may have a role during Parkinson's disease (PD), a disease closely linked to oxidative stress [31, 228, 233]. In mice, administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin and oxidant that mimics experimental PD, results in motor coordination impairment with resulting neuronal loss in the substantia nigra. Application of resveratrol significantly reduces MPTP-induced motor coordination impairment, hydroxyl radical formation, and neuronal loss [234]. In other experimental models of PD generated by 6-hydroxydopamine (6-OHDA), resveratrol was shown to increase the activity of antioxidant enzymes and lower dopamine loss in the substantia nigra [44].

Disorders of the Cardiovascular System

During cardiac ischemic/reperfusion injury, SIRT1 can be protective. Treatment with resveratrol during myocardial ischemia/reperfusion in rats can reduce rhythm disturbances, cardiac infarct size, and plasma levels of lactate dehydrogenase and creatine kinase [235]. Cell protection in the cardiovascular system may be determined by SIRT1 fostering protection against vascular inflammation and apoptosis [47, 48]. SIRT1 also has been demonstrated to promote the transcriptional activity of FoxO1 to up-regulate MnSOD, suppress oxidative stress in cardiomyocytes, reduce cardiac infarct volume, and improve functional recovery after ischemic/reperfusion in murine models [35]. SIRT1 also blocks myoblast injury from oxidative stress by enhancing the expression of MnSOD [195]. Activation of SIRT1 through resveratrol can assist cardiac recovery following global ischemia that may be tied to new vessel growth [236]. Loss of SIRT1 in endothelial cells leads to impairment of new blood vessel formation in ischemic tissues. The effect of SIRT1 on angiogenesis may be dependent through NF-κB and induction of nitric oxide synthase in endothelial cells [237]. Resveratrol also acts in animal models of cardiac infarction to increase the expression of vascular endothelial growth factor (VEGF) and its tyrosine kinase receptor Flk-1.

SIRT1 also may serve to block atherosclerosis [92]. High fat diets with the release of fatty acid anion and lipoprotein lipase products can activate vascular endothelial cells and impair the integrity of endothelium providing the foundation for atherosclerotic plaque [20, 238]. Injured endothelial cells also are known to lead to platelet activation and form vessel thrombi [1, 9, 228, 239]. SIRT1 can protect endothelial cells from oxidative stress and oxidized low-density lipoprotein induced apoptosis [47, 48, 240]. Over-expression of SIRT1 in human umbilical vein endothelial cells (HUVECs) prevents cell injury from oxidized low-debsity lipoproteins (LDLs). In endothelial cell-specific SIRT1 transgenic mice, impairment of vasorelaxation during high fat exposure was reversed with a reduction in atherosclerotic lesions [240], suggesting that SIRT1 improves endothelial function in the presence of atherosclerosis. Activation of SIRT1 also improves endothelium relaxation through up-regulating endothelial nitric oxide synthase (eNOS) expression and production of nitric oxide [241]. Activation of SIRT1 also can inhibit vascular smooth muscle cell (VSMC) hypertrophy, which can contribute to atherosclerosis. Over-expression of SIRT1 prevents angiotensin II induced VSMC hypertrophy. Treatment with resveratrol prevents oxidative stress induced human coronary smooth muscle cell proliferation through the inhibition of ERK activation [242]. SIRT1 in VSMCs also may regulate atherosclerosis through increased activity of tissue inhibitor of metalloproteinase 3 (TIMP3). TIMP3 is responsible for preventing metalloproteinase 3 to digest vascular intracellular matrix [92]. Down-regulation of TIMP3 has been tied to atherosclerosis in diabetic patients, since TIMP3 is significantly reduced in human carotid atherosclerotic plaques with decreased levels of SIRT1 [243]. In contrast, SIRT1 over-expression in VSMCs promotes TIMP3 expression and may, as a result, prevent atherosclerotic plaque [92, 243].

SIRT1 appears to play an important role during cardiac hypertrophy. Over-expression of SIRT1 in cardiac tissue has been shown to reduce cardiac hypertrophy, cellular apoptosis, cardiac dysfunction, and expression of senescence markers [174]. Yet, high expression of SIRT1 results in oxidative stress, apoptosis, and increased cardiac hypertrophy that may be associated with mitochondrial dysfunction and depletion of NAD^+ [174]. Treatment with resveratrol to increase SIRT1 activity prevents cardiac hypertrophy and cardiac cell dysfunction through the reduction of oxidative stress without lowering the blood pressure [37], can suppress pressure overload induced cardiac hypertrophy in rats [244], and can inhibit angiotensin II induced cardiomyocyte hypertrophy [245]. SIRT1 also prevents phenylephrine induced neonatal cardiomyocyte hypertrophy and inhibits phenylephrine-induced down-regulation of fatty acid oxidation genes. These observations with SIRT1 have been associated with the activation of peroxisome proliferators activated receptor-α (PPAR-α) [246]. The anti-hypertrophic effects of SIRT1 and resveratrol treatment also may function via AMP-activated protein kinase (AMPK) and the inhibition of Akt with subsequent suppression of protein synthesis and gene transcription [247].

Conclusions and Future Perspectives

SIRT1 offers new avenues of treatment against a number of disorders that can affect multiple systems of the body. Yet, it is vital to elucidate the biological pathways of SIRT1 that can determine cellular protection and cellular longevity. In this regard, the signal transduction pathways of SIRT1 must be carefully dissected to help determine the role of SIRT1 during a variety of disease process that may range from new vessel development to tumorigenesis. It is also important to recognize that current agents used to activate SIRT1 may be useful as investigational tools, but lack the precision to elucidate downstream mechanisms of SIRT1 as well as to lay the foundation for new drug development. As an example, resveratrol can increase SIRT1 activity in animal and cell models, but this agent is known to activate other pathways, such as the mammalian target of rapamycin (mTOR) and Akt1, that can cloud the ability to assess the direct role of SIRT1 [97, 233, 248, 249].

Overall, the exciting ability to develop novel therapeutic regimens with SIRT1 must always be countered by the clear appreciation of the multiple pathways govern by SIRT1 and the proper application of SIRT1 for particular disease entities to prevent any detrimental or unwanted outcomes.

Acknowledgments

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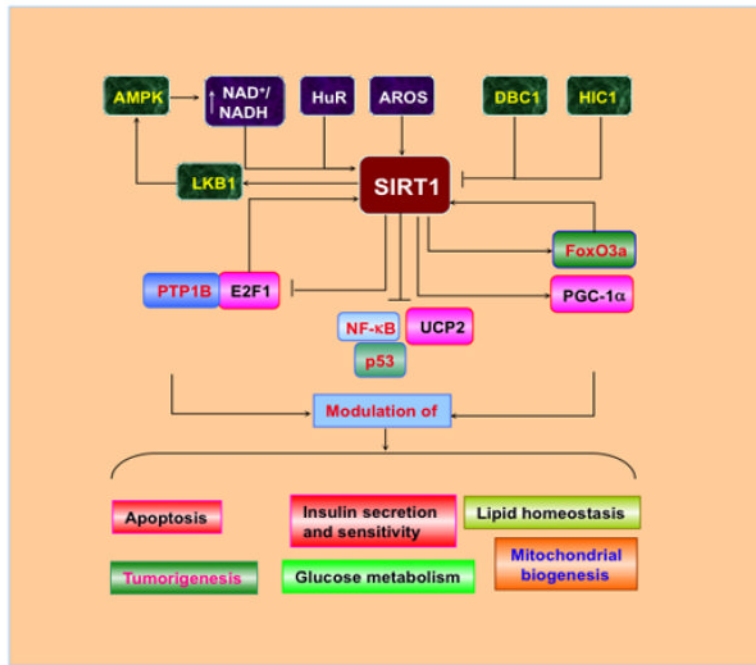
Figure 1.
Cell signaling pathways of SIRT1. The RNA binding protein HuR and a nuclear protein active regulator of SIRT1 (AROS) can promote SIRT1 activity. AMP activated protein kinase (AMPK) can activate SIRT1 through increasing the level of NAD$^+$/NADH ratio, but there exists a positive feedback, activated SIRT1 deacetylates the serine-threonine liver kinase B1 (LKB1) and subsequently activates AMPK. In contrast, hypermethylated in cancer 1 (HIC1) and deleted in breast cancer 1 (DBC1) negatively regulates the activity of SIRT1. Downstream of SIRT1 are the FoxO transcription factors, peroxisome proliferators-activated receptor-γ coactivator-1α (PGC-1α), protein tyrosine phosphatase 1B (PTP1B), p53, nuclear factor-κB (NF-κB), apoptotic transcription regulator E2F1, and the uncoupling protein gene UCP2. SIRT1 can, through modulating its multiple targets, regulate lipid metabolism, insulin secretion and sensitivity, mitochondrial function, and cell survival.