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SIRTIIN REGULATION IN AGING AND INJURY

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Abstract

Sirtuins or Sir2 family of proteins are a class of NAD⁺ dependent protein deacetylases which are evolutionarily conserved from bacteria to humans. Some sirtuins also exhibit mono-ADP ribosyl transferase, demalonylation and desuccinylation activities. Originally identified in the yeast, these proteins regulate key cellular processes like cell cycle, apoptosis, metabolic regulation and inflammation. Humans encode seven sirtuin isoforms SIRT1-SIRT7 with varying intracellular distribution. Apart from their classic role as histone deacetylases regulating transcription, a number of cytoplasmic and mitochondrial targets of sirtuins have also been identified. Sirtuins have been implicated in longevity and accumulating evidences indicate their role in a spectrum of diseases like cancer, diabetes, obesity and neurodegenerative diseases. A number of studies have reported profound changes in SIRT1 expression and activity linked to mitochondrial functional alterations following hypoxic-ischemic conditions and following reoxygenation injury. The SIRT1 mediated deacetylation of targets such as PGC-1 α , FOXO3, p53 and NF- κ b has profound effect on mitochondrial function, apoptosis and inflammation. These biological processes and functions are critical in life-span determination and outcome following injury. Aging is reported to be characterized by declining SIRT1 activity and its increased expression or activation demonstrated prolonged life-span in lower forms of animals. A pseudohypoxic state due to declining NAD⁺ has also been implicated in aging. In this review we provide an overview of studies on the role of sirtuins in aging and injury.

Keywords

SIRT1; mitochondria; ischemia/reperfusion; hypoxia

Introduction

Protein acetylation is a post translational modification that regulates key cellular functions including DNA recognition, protein–protein interaction, catalytic activity and protein stability [1–3]. The protein acetylation and deacetylation at N-epsilon lysine residues are catalyzed by histone acetyltransferases (HATs) and histone deacetylases (HDACs) respectively [4]. There are four classes of HDACs, Classes I–IV, based on phylogenetic

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analysis of all HDAC-related proteins [5]. Sirtuins are classified as Class III HDACs that are homologous to yeast transcriptional repressor, Sir2 [4]. The major functional difference between sirtuins and other HDACs is that sirtuins catalyze deacetylation of substrate proteins in a reaction that consumes NAD^+ . These protein modifying enzymes play significant roles in diverse cellular processes like apoptosis [6, 7], mitochondrial biogenesis [8], lipid metabolism [9], fatty acid oxidation [9, 10], cellular stress response [11–14], insulin secretion [15], aging [16–19] and inflammation [20].

Biochemistry of sirtuins

Sir2 (silent information regulator2) was the first sirtuin identified, from studies on mating type regulation in yeast *Saccharomyces cerevisiae* [21, 22]. The first evidences of the enzymatic activity of sirtuins came from studies on Sir2. Using ^{32}P -labelled NAD^+ it was shown that human ortholog of yeast Sir2 can transfer ^{32}P from NAD^+ to bovine serum albumin, suggesting their role in mono ADP ribosylation of proteins [23]. The observed enzymatic activity of Sir2 was found to be critical for the transcriptional repression at the silent mating-type loci, telomeric DNA regions, and the rDNA repeats [24]. The role of sirtuins as histone deacetylases was better characterized following molecular analysis of lysine residues of specific histone subunits [25–27]. Imai et al analyzed the product formed from Sir2 reaction by HPLC and mass spectrometry, and together with supporting data from mutational studies on conserved residues of the core domain of Sir2 concluded that NAD^+ dependent deacetylase activity rather than ADP-ribosyltransferase activity account for Sir2 functions in vivo [25]. The histone deacetylation by Sir2 is coupled to NAD breakdown resulting in the formation of deacetylated protein, nicotinamide (NAM) and O-acetyl-ADP-ribose (OAADPr) [28]. The deacetylation reaction catalyzed by Sir2 is represented in Figure 1. The absolute requirement of NAD^+ in the reaction, unlike the reactions catalyzed by other known protein deacetylases, makes their chemistry complex and energetically more demanding. However the benefit of this seemingly expensive reaction is its intricate regulation in multiple ways including by its own reaction products. The catalytic activity of Sir2 function is regulated by dynamic changes in cellular NAD^+ concentration or the NAD^+/NADH ratio [29, 30]. Cellular levels of nicotinamide phosphoribosyltransferase (Nampt), the rate-limiting enzyme for NAD^+ synthesis varies during different pathophysiological conditions and hence affect sirtuin activity [31]. NAM is a potent inhibitor of sirtuin-mediated deacetylation [32]. PNC1 (pyrazinamidase/nicotinamidase 1), which encodes an enzyme that deamidates nicotinamide, converts NAM to nicotinic acid by a salvage pathway and regulates NAM accumulation [33]. Therefore both PNC1 and NAM can modulate Sir2 activity in the cells. In addition, OAADPr, another product of Sir2 mediated deacetylation, is also increasingly recognized as an important metabolic by-product [34, 35]. OAADPr was found to regulate gene silencing by facilitating the assembly and loading of the Sir2-4 silencing complex onto nucleosomes [36, 37]. Moreover, it is also a substrate for deacetylation by cellular macrodomain proteins like human MacroD1, human MacroD2, Escherichia coli YmdB, and the sirtuin-linked MacroD-like protein from *Staphylococcus aureus* [38]. Therefore the deacetylation catalyzed by Sir2 serves critical functions in cellular homeostasis.

Sir2 gene family is highly conserved from bacteria to humans suggesting a common mechanism of gene silencing across the phylogenetic domains [39]. The bacterial and archaeal sirtuins play important roles in regulating transcription and cellular processes. For instance bacterial sirtuin CobB is an enzyme involved in propionate catabolism and cobalamin biosynthesis [40]. It deacetylates and activates acetyl-CoA synthetase in an NAD-dependent manner [41] and regulates *E. coli* chemotaxis by deacetylating CheY [42]. These findings suggest that both eukaryotes and prokaryotes carry out lysine acetylation as a common regulatory mechanism [41]. Studies also suggest a role for protein acetylation and deacetylation in bacterial stress response systems [43]. The archaeal sir2 homolog from *Sulfolobus solfataricus* P2 has both NAD-dependent deacetylase and mono-ADP-ribosyl transferase activities and regulate the binding of DNA binding protein alba [44].

Crystal structures of bacterial, yeast and mammalian sirtuins have been elucidated and reveal a highly conserved core domain made of a larger region with Rossmann-fold structure and a smaller variable region with zinc ribbon motif [45–47]. The sirtuins also contain N- and C-terminal extensions outside the catalytic core which are not conserved [47]. Prokaryotes generally contain one or two sirtuin genes whereas eukaryotes encode multiple isoforms. Yeasts contain the founding member Sir2 and four homologs of Sir2 (HST1-4). Mammalian sirtuin system is composed of seven genes; SIRT1 to SIRT7 among which SIRT1 has the highest sequence similarity to yeast Sir2 [48]. Sirtuins from a diverse number of organisms were phylogenetically analyzed and organized in to 5 major classes (I, II, III, IV and U) [48]. Class 1 comprises 5 yeast sirtuins (Sir2 and HST proteins) and human sirtuins SIRT1, SIRT2 and SIRT3. Class II has mammalian SIRT4 and sirtuins from other eukaryotes and bacteria. Class III has mammalian SIRT5 as well as bacterial and archaeal sirtuins. Most bacterial sirtuins belong to Class III. Class IV includes mammalian SIRT6 and 7. Class U contains sirtuins from gram positive bacteria and *Thermotoga maritima*.

An Overview of Mammalian Sirtuins

Mammalian sirtuins differ in their subcellular localization and function. SIRT1, SIRT6 and SIRT7 are mainly nuclear proteins with distinct subnuclear compartmentalization [49]. SIRT3, SIRT4 and SIRT5 are localized to mitochondria whereas SIRT2 is predominantly cytoplasmic [49]. While SIRT1-3 have strong deacetylase activity, SIRT4-7 are reported to have weak or no detectable deacetylase activity [50, 51] [52]; SIRT4 has predominantly ADP ribosyl transferase activity [53]. Table 1 represents the different mammalian sirtuins, their localization, and intracellular targets.

SIRT1

SIRT1, the mammalian ortholog of yeast Sir2, is the most studied mammalian sirtuin. SIRT1 plays important roles in embryonic development [149, 150] and skeletal muscle differentiation [151]. It has diverse functions in the cells ranging from chromatin modification and epigenetics to roles in metabolic pathways, inflammation and stress response (Figure 2) [152]. It interacts with and deacetylates histones and a number of non-histone substrates. SIRT1 preferentially deacetylates specific residues in histone subunits like the lysine 16 of histone 4 (H4K16), lysine 9 of histone 3 (H3K9), lysine 56 of histone 3 (H3K56) [153] and lysine 26 of histone 1 to promote heterochromatin formation and

transcriptional silencing [54, 55]. The non-histone protein substrates of SIRT1 include but not limited to tumor suppressor p53, nuclear factor- κ B (NF- κ B), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), fork-head box protein O (FOXO) transcription factors, liver X receptor (LXR), PARP, Ku70 and hypoxia-inducible factor (HIF)-1 α [154] [11, 58], [60], [61], [65] [70, 85, 155]). SIRT1 plays a predominant role in regulating apoptosis through deacetylating p53 and inhibiting p53 dependent transcription during cellular stress [56, 150, 156]. It also controls inflammation through regulating NF- κ B signaling by deacetylating the p65 subunit of the complex thereby inhibiting NF- κ B signaling. On the contrary, NF- κ B signaling diminishes SIRT1 activity by modulating expression of miR-34a, IFN γ , and reactive oxygen species [57]. miR-34a, a tumor suppressor, has been reported to bind directly to 3'-UTR of SIRT1 thereby repressing its expression and enhancing p53 mediated apoptosis [157]. It has been also known that miR-34a is a transcriptional target of p53 [157, 158]. Furthermore, Kim et al demonstrated that p53 is influenced in miR-34a-mediated repression of SIRT1 in cisplatin-induced cytotoxicity [159]. The antagonistic crosstalk between SIRT1 and NF- κ B signaling is apparent in many inflammatory diseases and aging [160–163]. Moreover, inflammation associated increase in nitric oxide (NO) production results in S-Nitrosylation and inhibition of SIRT1 activity which further heightens the inflammatory response through increased acetylation of p65 [164]. In addition, SIRT1 has demonstrated role as a tumor suppressor in rodent studies which likely involves its ability to deacetylate and inhibit beta-catenin transcriptional activity [165, 166].

SIRT1 plays a major role in metabolic regulation and PGC-1 α deacetylation is one of the important events in this process. Hepatic SIRT1 has been suggested to play an important role in glucose and lipid metabolism in during fasting [167]. SIRT1 has a vital role in maintaining lipid homeostasis through PPAR α mediated beta-oxidation of fatty acids in the liver [9] and mobilization of fat from white adipocytes during fasting [168]. In addition, SIRT1 controls mitochondrial biogenesis through regulating PGC-1 α pathway [59]. SIRT1 negatively regulates the expression and phosphorylation of signal transducer and activator of transcription 3 (STAT3) and STAT3 mediated cellular respiration [169]. A noteworthy aspect of SIRT1 mediated metabolic control is its regulation by AMPK which is also known as the cellular fuel gauge. AMPK activation has been reported to enhance SIRT1 activity by increasing NAD⁺ levels resulting in deacetylation of SIRT1 targets [170]. Conversely, SIRT1 activation is reported to induce AMPK activation by deacetylation of AMPK upstream kinase, LKB1 [74]. Adipokines like adiponectin have been shown to stimulate AMPK-SIRT1-PGC-1 α pathway and increase mitochondrial content in myocytes [74]. Another key feature of SIRT1 is its positive regulation on insulin secretion in pancreatic β cells by repressing uncoupling protein2 (UCP2) gene [171]. The SIRT1 localization and/or enzymatic activity is subjected to regulation by post-translational modifications like phosphorylation [172], SUMOylation [173], S-nitrosylation [164] and carbonylation [174]. The pleiotropic roles of SIRT1 in the cells make it an important intracellular marker protein in aging as well as different diseases like cardiovascular diseases, diabetes, cancer, neurodegenerative diseases and other conditions in health and disease (Figure 3) [152].

SIRT2

SIRT2 is the mammalian ortholog of yeast Hst2 and is predominantly cytoplasmic. It deacetylates α -tubulin [98]. SIRT2 protein levels often fluctuate during cell cycle, with a marked increase in expression and phosphorylation during the mitotic and G2/M transition phase playing a role in mitotic exit during cell cycle [175]. A characteristic feature of SIRT2 is its migration to the nucleus during G2/M transition to modulate chromatin condensation by histone H4 deacetylation [96]. SIRT2 can also deacetylate FOXO1 and promote FOXO1 binding to PPAR γ resulting in the suppression of PPAR γ activity and hence adipocyte differentiation [99]. It also deacetylates FOXO3A to promote expression of antioxidant and pro-apoptotic molecules under cellular stress [100]. A recent study suggests that cells sense extracellular oxidative stimuli to decrease acetylation of a key enzyme in the pentose phosphate pathway, glucose-6-phosphate dehydrogenase, in a SIRT2-dependent manner [108]. SIRT2 has been implicated in a number of diseases like cancer and neurodegenerative disorders like Parkinson's and Huntington's disease [176].

SIRT3

SIRT3 is an NAD⁺ dependent deacetylase predominantly located in the mitochondrial matrix. Inactive SIRT3 has been shown to be converted to an active form in the matrix following its cleavage by mitochondrial matrix processing peptidase [177]. It is highly expressed in tissues rich in mitochondria [178] and has a role in brown adipose tissue thermogenesis [179]. Another group reported the presence of enzymatically active full length SIRT3 in the nucleus which gets transported to the mitochondria under conditions of cellular stress [180]. However a later study by Cooper et al demonstrated an exclusive mitochondrial localization of human SIRT3 [180]. Consistent with its localization in mitochondria, loss of SIRT3 in a mouse model markedly elevated mitochondrial lysine acetylation [178]. SIRT3 loss resulted in a reduction in basal ATP levels in multiple organs, hyperacetylation of complex I components and reduction in complex I activity [181]. The first SIRT3 substrate identified was mitochondrial enzyme acetyl-CoA synthetase 2, the deacetylation of which leads to its activation [182]. SIRT3 acts as a stress responsive protein in the cardiomyocytes by deacetylating Ku70 and promoting its interaction with proapoptotic protein Bax thereby preventing Bax translocation to the mitochondria [117]. Another SIRT3 interacting partner is mitochondrial complex I protein NDUF9 [181]. Two critical targets of SIRT3 deacetylation are mitochondrial superoxide dismutase (SOD2) and isocitrate dehydrogenase 2 (IDH2), the enhanced activity of these redox enzymes prevents accumulation of toxic ROS. By regulating ROS production, SIRT3 suppresses the hypoxia inducible factor 1 α (HIF-1 α) transcriptional activity and hence may act as a tumor suppressor [183]. SIRT3 has been reported to promote mitochondrial fatty acid oxidation by deacetylating long-chain acyl coenzyme A dehydrogenase, key enzyme involved in the oxidation of long-chain substrates [10]. A recent study suggests that a natural polyphenolic, Honokiol, blocks and reverses cardiac hypertrophy in mice by activating mitochondrial SIRT3 [184]. Taken together, it may be concluded that SIRT3 plays a significant role in maintaining mitochondrial homeostasis.

SIRT4

SIRT4 is an NAD⁺ dependent ADP-ribosyl transferase localized to the mitochondria. Insulin secretion in pancreatic β cells is subjected to modulation by SIRT4 as secretion of insulin granules is triggered by local increase in ATP concentration by enzymes like glutamate dehydrogenase (GDH) that undergoes inhibition by SIRT4 ADP-ribosylation [53]. Another notable function of SIRT4 is its regulatory control over glutamine metabolism to facilitate DNA damage responses and to prevent tumorigenesis [185]. Consistently, mTORC1 pathway which is activated in proliferating tumor cells downregulates SIRT4 expression [186]. Its deacetylase activity is reported to regulate hepatic lipid homeostasis [134]. SIRT4 was recently shown to possess lipoamidase function that inhibits the activity of pyruvate dehydrogenase, an enzyme that links glycolysis to citric acid cycle [135]. Together, these studies highlight a major role for SIRT4 in regulating cellular metabolism and preventing tumorigenesis.

SIRT5

Mitochondrial SIRT5 is an NAD⁺ dependent protein lysine demalonylase, desuccinylase [52] and a deglutarylase [187]. It plays a pivotal role in ammonia detoxification by deacetylating carbamoyl phosphate synthetase 1 (CPS1), the rate limiting step in urea cycle [136]. In fact SIRT5 knockout mice had higher ammonia levels in blood during fasting or with a high protein diet [136]. CPS1 is also a target of desuccinylation [52] and deglutarylation by SIRT5 [187]. Other key targets of SIRT5 include SOD1 [137] and mitochondrial urate oxidase [138]. A recent study has reported its role in desuccinylating a key fatty acid oxidizing enzyme and promoting fatty acid oxidation [139]. Although loss of SIRT5 leads to hypersuccinylation of several metabolic pathway components [188], it is considered a dispensable isoform in terms of regulating metabolism [189].

SIRT6

SIRT6 is localized to nucleus and its enzymatic activities include deacetylation of histones, ADP ribosylase and lysine deacylase [190]. SIRT6 mediated lysine deacylation of tumour necrosis factor- α (TNF- α) promotes its secretion from macrophages [140]. SIRT6 is reported to have a crucial role in maintaining genomic stability and repairing DNA damages by different mechanisms [190]. It has a profound effect on glucose metabolism by suppressing the expression of HIF-1 α and other glycolytic genes [191]. Hence a loss of SIRT6 resulted in severe hypoglycemia due to increased glucose uptake in muscle and fat tissues. It also exerts control over hepatic gluconeogenesis by regulating PGC-1 α acetylation in an indirect manner through modifying the activity of acetyltransferase GCN5 [143]. Additionally, SIRT6 is involved in lipid metabolism by negatively regulating triglyceride synthesis [192]. Like SIRT1, SIRT6 expression is correlated with longevity; its expression decreased with age in human dermal fibroblasts [193] and overexpression in male mice increased its life span [18]. SIRT6 function has also been implicated in several different types of cancers [190]. Collectively, these studies reveal major roles for SIRT6 in metabolism and aging.

SIRT7

SIRT7 has been shown to be expressed in the nucleolus where it interacts with histones and RNA polymerase I to positively regulate ribosomal gene (rDNA) transcription [194]. It is phosphorylated during mitosis when the rDNA transcription is repressed and undergoes dephosphorylation and conformational changes to resume rDNA transcription at the exit from mitosis [195]. It is also proposed to play a key role in connecting the chromatin remodeling complexes to RNA Pol I machinery during transcription [196]. Initially an anti-proliferative role for SIRT7 was described in a mouse model and murine cell lines [197]. In stark contrast, it was shown to deacetylate and repress transcription of genes linked to tumor suppression, thus maintaining oncogenic transformation [145]. The oncogenic potential of SIRT7 was further demonstrated in human hepatocarcinomas [198] and human colorectal cancer [199]. Other notable functions of SIRT7 include its role in ribosome biogenesis and protein synthesis [200], inhibition of hypoxia-inducible factor HIF-1 α and HIF-2 α [201], cofactor for transcriptional repression by Myc [202] and hepatic lipid metabolism [203]. A recent study reported its positive influence on mitochondrial homeostasis by regulating acetylation of GABP β 1, a master regulator of nuclear-encoded mitochondrial genes [147]. SIRT7 is considered a potential target for cancer therapy and studies continue to unravel novel roles for SIRT7.

Role of Sirtuins in Aging

The role of sirtuins in extending organism life span has been a topic of great interest among aging researchers. The functional relevance of sirtuins in mitochondrial bioenergetics and oxidative stress coupled with the observation that some of the sirtuins prolonged life prompted extensive studies on sirtuin family of proteins in aging biology. Though most of the studies on sirtuins were focused towards elucidating the functional role of SIRT1, other members of this family are also being studied to understand their role in aging, health and disease [204].

The initial results on the effect of Sir2 on life-span in yeast was further extrapolated into other model organisms like *Drosophila*, *Caenorhabditis elegans* and rodents [16, 18, 205, 206]. In yeast, Sir2 mutation shortened lifespan owing to accumulation of toxic extrachromosomal rDNA circles (ERC) whereas Sir2 overexpression extended life span by silencing HM loci and inhibiting ERC formation [205]. Sir2 was found to mediate the life span extension in yeast induced by caloric restriction [207] by increasing mitochondrial oxidation and respiration [208]. Life span may be extended by limiting activity of glucose-sensing cyclic-AMP-dependent kinase (PKA) which requires Sir2 and NAD [208]. Studies have also uncovered the role of nicotinamide clearance by PNC1 in regulating longevity by CR in yeast [33, 209]. Aging is reported to decrease tissue levels of NAD resulting in declined SIRT1 activity and decreased NAD⁺/NADH leading to increased ROS formation in mitochondria [210]. Another theory is the suppression of target of rapamycin (TOR) signaling pathway by CR [211] which leads to inhibition of ribosome biogenesis and relocalization of the transcription factors Msn2p and Msn4p from the cytoplasm to the nucleus thereby increasing expression of PNC1 [212].

Consistent with a role for Sir2, its activator resveratrol was found to mimic CR induced longevity in the yeast [2] and sirtuin activating compounds (STACs) delayed aging in metazoans [213]. However the involvement of Sir2 or other homologs [214] in CR induced longevity has also been questioned in some studies [215–217]. For instance, CR was reported to enhance longevity in yeast cells lacking Sir2, implying a Sir2 independent mechanism [215]. Conforming to this observation, Sir2 homolog Hst2 was shown to mediate SIR2-independent life-span extension by CR [214]. Contrary to the above, another report precludes the involvement of any Sir2 family members in lifespan extension by CR [216]. Another study reports absence of a role for Sir2 in chronological aging (long term survival of non-dividing cells) in yeast unlike its role in replicative aging [218]. Increased Sir2 gene content also extended life span in *Caenorhabditis elegans* [16] and *Drosophila* [206]. In *C. elegans*, Sir2.1 activated DAF-16 [219], a forkhead transcription factor, that mediates life span regulation by insulin/IGF-1 signaling pathway [220]. Activating autophagy is one of the underlying mechanisms suggested to be behind life span extension benefits of Sir2 [221]. In *Drosophila*, overexpression of Sir2 in adult fat body but not in muscle promoted longevity indicating tissue specific effects of Sir2 expression [222, 223]. In humans, SIRT1 expression and activity are abrogated in aged arteries suggesting its role in vascular aging [224]. SRT1720, a small molecule activator of SIRT1, improved health and life span of mice, further suggesting the role of SIRT1 [225]. Interestingly a positive correlation exists between mitotic activity and SIRT1 levels in mammalian tissues [226]. The anti-aging effect of SIRT1 likely involves p53, as SIRT1 was found to antagonize promyelocytic leukemia protein (PML) induced acetylation of p53 and cellular senescence in primary mouse embryo fibroblasts [227]. Another plausible mechanism is through repressing PPAR γ thereby attenuating adipogenesis and promoting fat mobilization in white adipocytes [168].

SIRT2 is reportedly elevated in the white adipose tissue and kidney of caloric restricted mice where it deacetylates FOXO transcription factors and increases expression of FOXO target genes, p27(Kip1), manganese superoxide dismutase and Bim [100]. Cohen and colleagues recently showed that SIRT6 overexpression in male mice extended life span compared to wild type mice and this was associated with lower serum levels of insulin-like growth factor 1 (IGF1) [18]. They also had observed an increased SIRT6 levels following caloric restriction in rats [228]. Accumulating evidences also suggest a role for SIRT3 in age related pathologies [229, 230]. Interestingly both mammalian SIRT3 and bacterial CobB regulate acetyl-CoA synthetase through its deacetylation suggesting an evolutionary conservation of the mechanism. Although sirtuins possess anti-aging functions from yeast to mammals, the underlying mechanisms have also evolved to meet the complexity of higher order species. In yeast, sirtuins mainly act through suppressing genomic instability (recombination mainly at the ribosomal DNA locus) where as in mammals they affect multiple pathways to regulate aging.

Aging has been described to be characterized by declining NAD⁺, delinking PGC-1 α/β from mitochondrial control and the emergence of a pseudo-hypoxic state [210, 231]. Further, the pseudo-hypoxic state was compared to Warburg reprogramming and was suggested to be reflected in SIRT1 deficiency which may be restored with NAD⁺ augmentation. This has

parallels to injury conditions manifested by hypoxia and nutrient deprivation in downstream tissues and therefore SIRT1 mediated metabolic regulation in tissue injury and repair draws attention for investigations.

Role of Sirtuins in Tissue Injury and Repair

Sirtuins are key physiological modulators controlling a number of critical metabolic pathways and functions including cell death and repair. These physiological regulations occur by virtue of their direct enzymatic action on target proteins as well as due to alterations in the level of metabolites related to the reaction. Though not all sirtuins are robust deacetylases, the network of proteins that include PGC-1 α , SIRT1 and AMPK are considered to be a critical part of the energy sensing network in cells [232]. SIRT1 and AMPK act as metabolic sensors by their ability to deacetylate and phosphorylate, respectively, the mitochondrial biogenesis factor PGC-1 α . Therefore the actions of SIRT1 are closely linked to enhancement of mitochondrial function and biogenesis and mitigation of redox injury making this protein an attractive target in molecular therapeutics [233]. It is further substantiated by the observation that following cellular stress SIRT1 activity is altered and modulation of the activity and or expression of SIRT1 following cellular injury is important in restoring cellular homeostasis, repair and death.

Sirtuins and cardiac injury

Several studies, including that from our lab, have demonstrated the importance of sirtuins in improving organ function and survival following tissue injury [234–236]. In post myocardial infarction (MI) patients, ischemia/reperfusion (I/R) injury remains the major cause for cardiac remodeling and heart failure [237]. Therefore methods to prevent I/R injury become instrumental in reducing mortality in post MI patients. Numerous studies have been reported on the role of sirtuins, specifically SIRT1, in managing I/R injury [234, 238, 239].

I/R injury was associated with a reduction in SIRT1 mRNA and protein [234]. Using transgenic mice with cardiac specific over expression of SIRT1, Hsu *et al* clearly demonstrated a significant reduction in myocardial infarction area and a greater recovery after reperfusion of isolated hearts, compared to wild type. Conversely, cardiac specific knockdown of SIRT1 resulted in increased size of myocardial infarction/area. The observed effects of SIRT1 overexpression is attributed to suppression of oxidative stress and apoptosis by FOXO1 mediated upregulation of antioxidant molecules like manganese superoxide dismutase and down regulation of proapoptotic molecules [234]. One of the prominent changes that occurs during cardiac hypertrophy is the shift in myosin isoform from α - to β -myosin heavy chain (MHC) [240]. Interestingly, fructose feeding was shown to have a protective effect on the heart following I/R injury by inducing cardiac α -MHC expression. Fructose feeding also stimulated cardiac NAD⁺ and SIRT1 levels and these effects were mimicked by resveratrol [241]. The role of SIRT1 in α -MHC expression was further confirmed by cardiac specific overexpression studies. It is interesting to note that both a direct agonist of SIRT1 (resveratrol) and its indirect activation by NAD⁺ levels could cause similar physiological effects in tested animals. However the mechanism of SIRT1 mediated induction of α -MHC expression is still unclear.

Ischemic preconditioning (IPC) is effective in limiting cardiac damage occurring during prolonged occlusion and reperfusion [237]. Nadtochiy et al studied the role of SIRT1 in cardioprotective effects of acute IPC using SIRT1 deficient and SIRT1 overexpressing mice. Consistent with a role for SIRT1, IPC induced cytosolic lysine deacetylation in wild type hearts whereas SIRT1 deficient hearts had more cytosolic lysine acetylation and were refractive to preconditioning. Conforming to these results, SIRT1 overexpressing mice exhibited decreased cytosolic acetylation and endogenous protection against I/R injury [238]. Both IPC induced lysine deacetylation and cardiac protection was inhibited by SIRT1 inhibitor splitomycin [238]. Nicotinamide phosphoribosyltransferase (Nampt), a key enzyme in the salvage pathway of NAD synthesis, is a critical regulator of energy status and survival in cardiac myocytes [242]. Nampt was found to play a crucial role in mediating the protective effect of IPC against ischemia and reperfusion, which was also mimicked by exogenous nicotinamide mononucleotide (NMN), a product of Nampt in the NAD⁺ salvage pathway. On the other hand, Nampt can be secreted from cardiomyocytes to act as a proinflammatory cytokine. The exogenous Nampt was found to be a positive regulator of cardiac hypertrophy and adverse ventricular remodeling [243]. Therefore, although intracellular Nampt is essential to the cardiac myocyte survival, exogenous Nampt could be detrimental demanding fine balance between its synthesis and secretion. Interestingly, the cardiac protection conferred by IPC deteriorates with age [244]. The lack of ischemic tolerance in aged hearts is mainly accounted for by a reduced SIRT1 expression and activity although one study has ruled out the role of SIRT1 [244].

Caloric restriction (CR) was previously shown to increase longevity in yeast and other species [207, 245, 246]. Shinumura et al studied the effects of short-term [247] and long-term caloric restriction [248] on ischemic tolerance and ischemic preconditioning (IPC) in aged rats. Short-term CR improved left ventricular function in both young and aged rats which was associated with an increase in AMPK phosphorylation [247]. Long term caloric restriction also improved recovery of left ventricular function and reduced infarct size after ischemia-reperfusion. However these changes were not associated with any changes in expression of myocardial total or phosphorylated AMPK. Strikingly, long-term CR induced cardiac protection was associated with nitric oxide-dependent increase in nuclear SIRT1 content [248]. CR mediated protection against I/R injury was associated with Nampt upregulation whereas the protective effect was abrogated in SIRT1^{-/-} mice, suggesting a Nampt-SIRT1 axis [249]. Analysis of the molecular changes underlying CR induced cardioprotection revealed an overall reduction in acetylated mitochondrial proteins with CR. Consistent with a role for sirtuins, deacetylation of specific proteins of the electron transport chain was observed, which preserves mitochondrial integrity by preventing accumulation of toxic ROS [250]. Deacetylation of mitochondrial proteins also implies an involvement of mitochondrial sirtuins apart from nuclear/cytoplasmic sirtuins like SIRT1.

Studies from our laboratory using a hemorrhagic shock model showed that when 60% of the blood volume was removed from rats and subjected to a prolonged shock phase, there was a significant decline in SIRT1 and PGC-1 α protein levels in the heart at two hours following resuscitation [235]. It is unclear whether this is the effect of oxidative stress associated with resuscitation or initiated by the hypoxic/ischemic condition due to hemorrhagic shock. However, administration of resveratrol, a SIRT1 activator and antioxidant, along with

resuscitation fluid proved to be beneficial in improving left ventricular function and cardiac contractility, and prolonged lifespan in the absence of resuscitation [235, 251]. Furthermore, hemorrhagic shock induced a shift in the metabolic process towards glycolysis, consistent with a mitochondrial functional decline which was restored by resveratrol administration [252]. Other investigators have also observed the beneficial effect of resveratrol following hemorrhagic shock, though methodologies varied [253–255]. Resveratrol pretreatment was also effective in reducing IR-induced arrhythmias and mortality in rats [80]. Resveratrol was protective against myocardial injury in a rat model of autoimmune myocarditis [81]. The SIRT1 activator resveratrol has been extensively used in aging and injury conditions and at least part of the health effect of resveratrol is likely through activation of SIRT1.

SIRT1 exerts its beneficial effects at both transcriptional level and posttranslational levels. At the transcriptional level, it affects the expression of many antioxidant genes and apoptotic molecules by stimulating the transcriptional activity of FOXO1 [234]. Rui-Hong Wang et al found that hepatic SIRT1 deficiency in mice can impair mTorc2/Akt signaling leading to oxidative damage and insulin resistance [256]. At the post-translational level, SIRT1 influences acetylation and activity of a number of proteins. Likewise the regulation of SIRT1 exists at multiple levels. Aldehyde mediated carbonyl stress is considered as yet another factor contributing to increased susceptibility of aging heart to I/R injury [174]. Carbonyl modification of SIRT1 during aging impairs its activity and causes myocardial ischemic intolerance which could be restored by cardiac aldehyde dehydrogenase activation [174]. Therefore more studies are required to address the posttranslational changes in SIRT1 and other sirtuins that may affect their compartmentalization and function inside the cells. In cardiac myocytes SIRT1 expression is regulated by microRNA, miR199a. miR199a itself is markedly down regulated during cardiac ischemia which favors rapid accumulation of HIF-1 α by preventing its degradation [257].

Several endogenous and exogenous molecules have been shown to exercise cardio protective effects through SIRT1 regulation. For example locally acting insulin-like growth factor-1 isoform has been shown to protect cardiomyocytes from oxidative/hypertrophic stress through SIRT1 activation [258]. SIRT1 induction by resveratrol is reported to have a modulatory effect on mitogen-activated protein kinase (MAPK) pathway which is commonly upregulated under stress [259]. Likewise sildenafil, a phosphodiesterase-5 inhibitor improves I/R injury and a concomitant SIRT1 activation was observed [260]. Cardiomyocyte apoptosis is a characteristic feature of heart failure. Silibinin, a plant flavonoid was found to ameliorate β -adrenergic agonist isoproterenol-induced injury in cultured rat neonatal cardiac myocytes through mechanisms including but not limited to upregulation of SIRT1 [261]. However, in one study it has been shown that constitutive SIRT1 overexpression resulted in impaired cardiac mitochondria and cardiac dysfunction in response to pressure overload [262].

Other sirtuins are also gaining prominence with respect to their roles in managing the detrimental effects of hypoxic/ischemic and reperfusion injury. One of the mitochondrial sirtuins, SIRT4 was shown to play a protective role in hypoxia induced apoptosis in H9c2 cardiomyoblast cells [263]. Similarly, another mitochondrial sirtuin, SIRT5 undergoes marked downregulation in cardiomyocytes upon oxidative stress [264]. Both SIRT4 and

SIRT5 knockdown significantly increased apoptosis in cardiomyocytes [263, 264]. The mitochondrial sirtuin, SIRT3 is increasingly recognized as an important molecule in preserving mitochondrial integrity and improving cardiac function. Case studies on post MI patients indicate that exercise training exerts beneficial effects on improving cardiac functions [265, 266]. Jiang et al studied the molecular basis of cardioprotection by aerobic interval training (AIT) exercise in rat models. They found increased mitochondrial biogenesis in AIT rats accompanied by AMPK phosphorylation and increased SIRT3 levels [267]. A recent report shows the protective effect of resveratrol in combating oxidative stress by upregulating SIRT3 expression in the mitochondria of human vascular endothelial cells [268]. Flavanoids like rhamnetin also exhibit cyto protective effects against oxidative stress in H9c2 cardiomyoblasts by SIRT3 and SIRT4 induction [269]. Consistent with these observations, SIRT3 deficient hearts were less tolerant to I/R injury with greater infarct size [270]. This decline in function is attributed to inhibition of enzymatic activities of SIRT3 targets Cx1 and Mn SOD. SIRT3 knockdown in H9C3 cardiac cells made them more vulnerable to oxidative damage [270]. Together these results suggest that SIRT3 may be an important component of damage control in I/R and other forms of injury and demand more attention. SIRT7 is yet another sirtuin with a profound effect on preventing apoptosis and inflammatory cardiomyopathy; the observed effects likely mediated through its effect on p53 deacetylation [148].

Sirtuins and Neuronal injury

The neuroprotective effects of SIRT1 have been demonstrated in different models of traumatic brain injury, ischemic injury and in a number of neurodegenerative disorders. Ischemic brain damage often leads to fatal outcomes unless managed in a narrow window of time [271, 272]. Therefore studies to identify novel strategies to manage ischemic damage would have important clinical implications [273] [274]. Like in hearts, ischemic preconditioning is found to be an effective strategy in protecting neurons from lethal ischemia. An *in vitro* model of cerebral ischemia using hippocampal slice cultures subjected to oxygen-glucose deprivation (OGD) is a useful alternative to *in vivo* ischemia [275]. Initial studies by Raval and colleagues using this *in vitro* model confirmed neuroprotective action of SIRT1 agonist resveratrol in cerebral ischemia [272, 276]. Both IPC and resveratrol preconditioning induced neuroprotection were accompanied by SIRT1 activation and concomitant reduction in uncoupling protein 2 levels [239]. Ischemic brain injury leads to brain cell apoptosis by poly(ADP-ribose)polymerase (PARP) activation which depletes intracellular NAD⁺ [277]. NAD⁺ replenishment could reduce ischemic injury by OGD in *in vitro* cultures of primary neurons [278] and also in rat model of focal ischemia [279]. The positive effects of NAD⁺ repletion is mimicked by overexpression of Nampt. Nampt overexpression induced neuroprotection was dependent on SIRT1 mediated LKB1 deacetylation and AMPK activation [74]. A later study also showed the involvement of autophagy in the neuroprotection conferred by Nampt in cerebral ischemia. Overexpression of Nampt enhanced autophagy in a SIRT1 dependent manner through TSC2-mTOR-S6K1 signaling pathway [280]. Analyzing the signaling pathways modulated by resveratrol in the ischemic brain concluded an increase in Akt and p38MAPK phosphorylation and a decrease in ERK1/2 phosphorylation. Additionally the expression of SIRT1, PGC-1 α and phosphorylation of cyclic AMP-response-element-binding protein were augmented with a

reduction in anti-apoptotic Bcl2 transcription [281]. A direct role for SIRT1 in stroke is evident from studies that show greater infarct size in SIRT1 knockout mice that underwent middle cerebral artery occlusion compared to wild type mice [282, 283]. The infarct volume was also affected by pharmacologic modulation of SIRT1; SIRT1 activator A3 decreased infarct volume whereas sirtinol increased the infarct volume. An increase in acetylation of p53 and NF κ B explains the exacerbated injury upon SIRT1 deletion [283]. Recent reports highlight the role of SIRT1 in preserving cerebral blood flow following cerebral hypoperfusion injury [284, 285]. These vasculoprotective effects of SIRT1 are likely mediated through its deacetylation of brain endothelial nitric oxide synthase. Traumatic brain injury (TBI) is another domain where SIRT1 action comes to the limelight. SIRT1 induction seen in TBI is crucial in preventing neuronal apoptosis and this protection is lost with SIRT1 inhibition [286]. Taken together these studies indicate an indispensable role for SIRT1 activation in reversing brain damage.

Several natural products and neuroprotective agents have been shown to act through SIRT1. For instance, SIRT1 up regulation is involved in the neuroprotective effects of 2,3,5,4'-tetrahydroxystilbene-2-O-beta-D-glucoside (TSG) [287] and icarin [288] against ischemic brain injury. Epigallocatechin-3-gallate, a component of tea polyphenols conferred protection in an *in vitro* model of neuronal cell injury by stimulating SIRT1 and PGC-1 α levels and suppressing ROS production [289]. SIRT1 is also augmented with vitamin E supplementation that alleviates oxidative damage following mild traumatic brain injury [290]. Adipokine leptin showed neuroprotection in permanent middle cerebral artery occlusion accompanied by increased SIRT1 expression [291]. Erythropoietin is yet another hormone which protects against brain injury by SIRT1 activation [292]. In fact SIRT1 behaves like a sensor that helps the cells adapt to environmental changes. Several dietary modifications which cause cellular oxidative imbalances have been linked with changes in SIRT1 levels. For example a high fat diet diminished SIRT1 expression in hippocampus and cerebral cortex which was reversed by vitamin E supplementation [293]. SIRT1 expression in hippocampus was reduced in mild traumatic brain injury and was restored by omega-3 fatty acids supplementation [294]. Similar to hearts, caloric restriction offers protection against ischemia-induced neurodegeneration. Rats subjected to short term food restriction displayed improved recovery in terms of spatial learning and memory following ischemia [295]. However the role of sirtuins in these protective effects is yet to be determined.

The SIRT1 protective effects are implicated in neurodegenerative diseases like Alzheimer's [296, 297], Parkinson's [298], Huntington's disease [299], Amyotrophic lateral sclerosis [300], Multiple sclerosis [301] and prion diseases [302]. Alzheimer's and Parkinson's are often associated with axonal degeneration which is an active process of self-destruction. Rapid Wallerian degeneration is observed in axons and their synapses distal to an injury whereas Wallerian degeneration slow (wlds) mice are protected from axonal degeneration [303]. Nicotinamide mononucleotide adenylyltransferase1 (Nmnat1) is a key enzyme involved in the NAD biosynthetic pathway in the nucleus. An increased Nmnat1 activity and SIRT1 activation is accounted for the axonal protection in wlds mice [274]. These studies clearly underscore a prominent role for SIRT1 in conferring neuroprotection. However

SIRT1 also sensitizes neurons to oxidative damage by deacetylating IRS-2 and reducing activation of the Ras/ERK1/2 pathway, hinting at a pro-aging role [304].

Apart from cardio and neuroprotective effects, sirtuins have to be shown to play important role in injuries to other organs. Renal specific overexpression of SIRT1 conferred considerable protection from cisplatin induced acute kidney injury (AKI). These protective effects of SIRT1 were mediated through a reversal of peroxisome number and function, mitochondrial function, attenuation of ROS and apoptosis [305]. Conforming to the above study, SIRT1^{-/-} mice were more susceptible to unilateral ureteral obstruction (UUO) model of kidney injury. The increased susceptibility to injury in SIRT1 deficient mice is attributed to diminished Cox2 expression and increased apoptosis and fibrosis. Opposite effects were observed with SIRT1 pharmacologic activation with resveratrol or SRT2183 [306]. Resveratrol also protected mouse proximal tubular cells from cisplatin induced renal injury through p53 deacetylation and apoptosis, further confirming the role of SIRT1 in p53 mediated apoptosis [307]. Not only does cisplatin increases acetylation of p53 but also induces acetylation of p65 subunit of NF-κB both of which accounts for the cytotoxic effects of cisplatin. Overexpression of SIRT1 in renal proximal tubule cells significantly attenuated the cytotoxic effects of cisplatin by NF-κB deacetylation [308]. Although, beneficial effects of resveratrol are well evident in diabetic nephropathy, it is also suggested to be independent of SIRT1 [309]. Resveratrol feeding in db/db mice significantly improved mitochondrial oxidative stress and associated pathologies but failed to enhance AMPK activation or SIRT1 expression in the kidney precluding a role for SIRT1 [309]. Since this study has not tested SIRT1 activity in the kidney, the role of SIRT1 in mediating resveratrol effects cannot be ruled out. In stark contrast another study clearly shows the involvement of AMPK-SIRT1-PGC1α axis in the salutary effects of resveratrol in diabetic nephropathy [310].

Sirtuin family of proteins are important physiological modulators and play critical roles in cellular homeostasis. Though SIRT1 is among the most studied sirtuins, the role of other sirtuins and small molecule modulators of sirtuins in cell survival, growth, proliferation and death is being investigated by many laboratories and the information gained will allow us to better understand the molecular processes in aging and injury. The profound effect of some of the sirtuins, such as SIRT1 and SIRT3, in regulating mitochondrial function and cellular energetics makes these proteins important players in determining outcome following cell, tissue and organ injury. Declining mitochondrial function is a hallmark of both aging and injury and therefore, further studies on the regulation of sirtuin family of proteins remain important.

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Highlights

Sirtuins are a family of evolutionary conserved proteins.

Sirtuin-mediated deacetylation of critical proteins modulate mitochondrial function.

Sirtuins play important functions in metabolism, immune response and longevity.

Sirtuins are also important in tissue injury and repair.

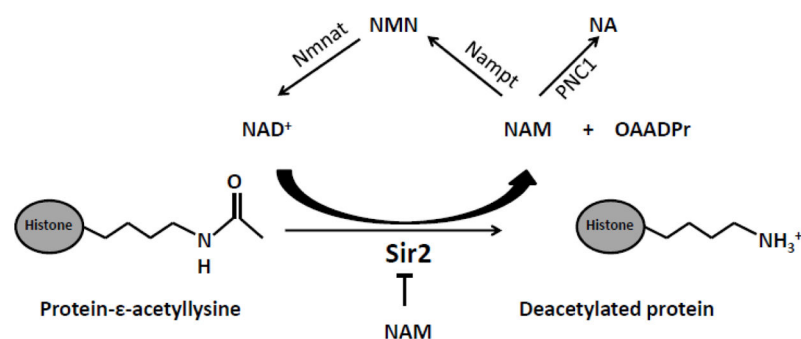


Figure 1. Protein Deacetylation by Sir2

Sir2 catalyzes the transfer of acetyl group from the protein to ADP-ribose moiety of NAD⁺ to form O-acetyl-ADP-ribose (OAADPr) and nicotinamide (NAM). Nicotinamide phosphoribosyltransferase (Nampt), the rate limiting enzyme in NAD biosynthetic pathway converts NAM to nicotinamide mononucleotide (NMN). NMN is then converted to NAD by nicotinamide mononucleotide adenylyltransferase (Nmnat). Another NAD salvage pathway component, Pnc1, converts NAM to nicotinic acid.

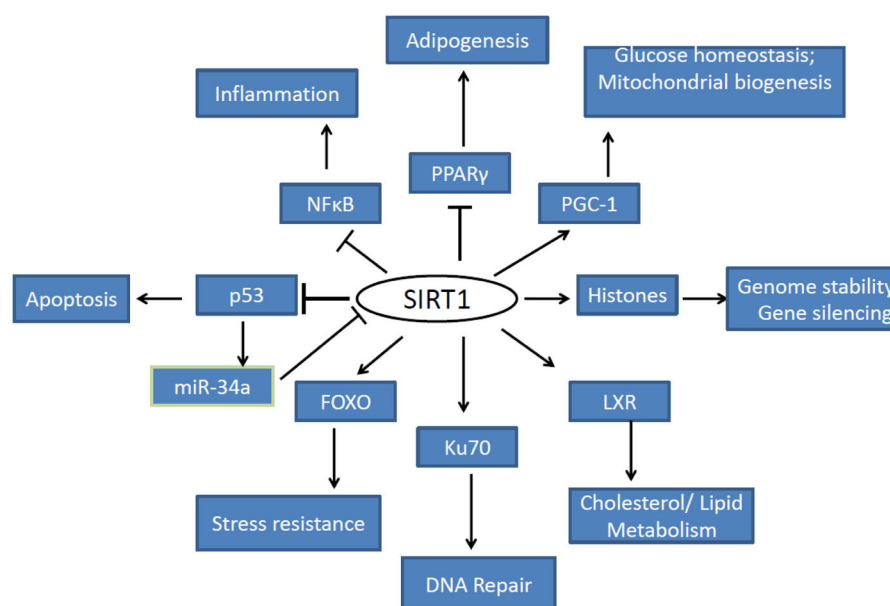


Figure 2. SIRT1 Regulation in Health and Disease

Increased SIRT1 activity results in deacetylation of histone and nonhistone substrates affecting multiple cellular processes.

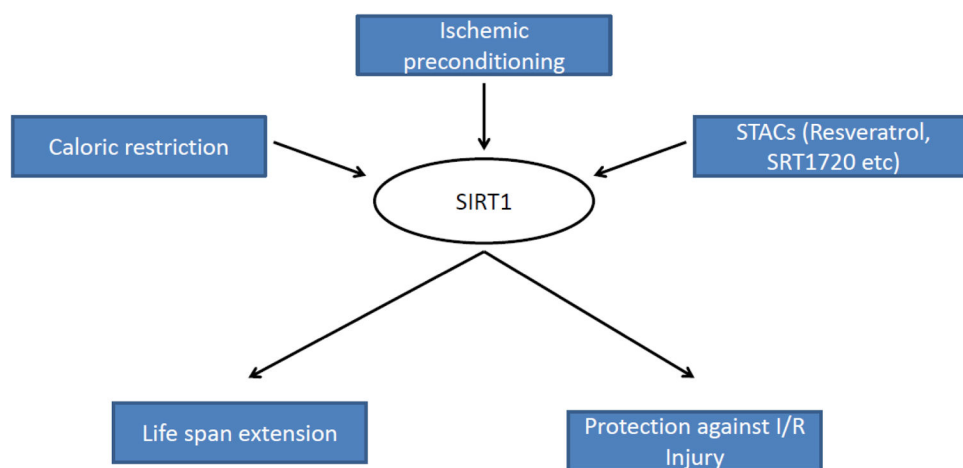


Figure 3. SIRT1 Modulation in Aging and Injury

SIRT1 expression and/or activity are upregulated with caloric restriction, ischemic preconditioning and STACS resulting in longevity and protection following injury.

Table 1

Sirtuin	Localization	Substrates	Enzymatic activity
SIRT1	Nuclear, cytoplasmic	Histone H1 [54], Histone H3[54], Histone H4 [55], p53 [56], NF- κ B [57], FOXO4 [58], PGC1 α [59], HIF1 α [60], HIF2 α [61], CTIP2 [62], Tat [63], p300 [64], LXR [65], FXR [66], eNOS [67], MEF2 [68], Notch1 [69], Ku70 [70], XPA[71], WRN [72], NBS1 [73], LKB1 [74], AceCS1 [75], HMGCS1 [76], c-Myc [77], androgen receptor [78], SUV39H1 [79], BMAL1 [80], PER2 [81], DNMT1 [82], hMOF [83], TIP60 [83], cortactin [84], PARP1 [85], SREBP-1C [64], SATB1 [86], RFX-5 [87], TDG [88], FOXA2 [89], IRF-1 [90], HMGB1 [91], PGAM1 [92], CRABP II [93], TopBP1 [94], PML [95].	Deacetylation
SIRT2	Nuclear, cytoplasmic	Histone H4 [96], Histone H3 [97], Tubulin [98], FOXO1 [99], FOXO3A [100], p53 [101], p300 [102], p65 [103], PEPCK1 [104], Par-3 [105], CDK9 [106], HIF1 α [107], G6PD [108], PGAM [109], ALDH1A1 [110], TUG [111], BubR1 [112], beta-secretase 1 [113].	Deacetylation, Demyristoylase
SIRT3	Mitochondrial	AceCS2 [75], HMGCS2 [114], LCAD [115], SDH [116], Ku70 [117], SOD2 [118], IDH2 [119], GDH [120], LKB1 [121], MRPL10 [122], LCAD [10], ATP synthase F1 [123], Cyclophilin D [124], OTC [125], ALDH2 [126], Skp2 [127], FOXO3 [128], PDH [129], OGG1 [130], OPA1 [131], Hsp10 [132], GOT2 [133], MDH [113], Aconitase 2 [113].	Deacetylation
SIRT4	Mitochondrial	GDH [53], MCD [134], PDH [135], Hsp60 [113], Stress-70 [113], Nnt [113].	ADP-Ribosylation, Deacetylation, Lipoamidase
SIRT5	Mitochondrial	Cytochrome C [120], CPS1 [136], SOD1 [137], Urate oxidase [138], PML [95], VLCAD [139], Prx-1 [113], HMGCS2 [113], Hsp70 [113], MCAD [113].	Deacetylation, Demalonylation, Desuccinylation, Deglutarylation
SIRT6	Nuclear	TNF α [140], Histone H3 [51], CtIP [141], PARP1 [142], GCN5 [143], KAP1 [144], GEN1 [113], Kup86 [113], p70 [113].	Deacetylation, ADP-ribosylation
SIRT7	Nucleolus	Histone H3 [145], PAF53 [146], GABP β 1 [147], p53 [148], MEF-2C [113], DNA-PK [113]	Deacetylation

Abbreviations: AceCS, acetyl-CoA Synthase; ALDH, aldehyde dehydrogenase; CDK9, cyclin-dependent kinase 9; CPS1, carbamoyl phosphate synthetase 1; CtIP, C-terminal binding protein; CTIP2, chicken ovalbumin upstream promoter transcription factor interacting protein 2; CRABP II, cellular retinoic acid binding protein II; DNA-PK, DNA-dependent protein kinase; DNMT1, DNA methyltransferase 1; eNOS, endothelial nitric oxide synthase; FOX, forkhead transcription factor; FXR, farnesoid X receptor; GABP β 1, GA binding protein 1; GCN5, General Control Non-repressed Protein 5; GDH, glutamate dehydrogenase; G6PD, glucose-6-phosphate dehydrogenase; GOT2, glutamate oxaloacetate transaminase 2; HMGB1, high-mobility group box 1; HMGCS, 3-hydroxy-3-methylglutaryl CoA synthase; hMOF, human ortholog of the Drosophila males-absent-on-the-first; Hsp10, heat shock protein 10; IDH2, isocitrate dehydrogenase 2; IRF-1, interferon regulatory factor 1; KAP1, KRAB-associated protein 1; LCAD, long-chain acyl coenzyme A dehydrogenase; LKB1, liver kinase B1; LXR, liver X receptor; MCAD, medium-chain acyl-CoA dehydrogenase; MCD, malonyl CoA decarboxylase; MDH, malate dehydrogenase; MEF2, myocyte enhancer factor 2; NBS, nijmegen breakage syndrome; Nnt, nicotinamide nucleotide transhydrogenase; OGG1, 8-oxoguanine-DNA glycosylase 1; OPA1, optic atrophy 1; PAF53, polymerase-associated factor 53; PARP1, poly(ADP-ribose) polymerase 1; PDH, pyruvate dehydrogenase; PEPCK1, phosphoenolpyruvate carboxykinase; PER2, period 2; PGAM, phosphoglycerate mutase; PML, Prx-1, peroxiredoxin 1; RFX-5, regulatory factor for X-box; SATB1, special AT-rich sequence-binding protein-1; Skp2, S-phase kinase associated protein 2; SOD2, superoxide dismutase 2; SUV39H1, suppressor of variegation 3-9 homolog 1; TDG, thymine DNA glycosylase; TIP60, HIV-1 TAT-interacting protein of 60 kDa; TopBP1, DNA topoisomerase 2-binding protein 1; XPA, xeroderma pigmentosum group A