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Protective effects and mechanisms of sirtuins in the nervous system

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Abstract

Silent information regulator two proteins (sirtuins or SIRTs) are a group of histone deacetylases whose activities are dependent on and regulated by nicotinamide adenine dinucleotide (NAD^+). They suppress genome-wide transcription, yet upregulate a select set of proteins related to energy metabolism and pro-survival mechanisms, and therefore play a key role in the longevity effects elicited by calorie restriction. Recently, a neuroprotective effect of sirtuins has been reported for both acute and chronic neurological diseases. The focus of this review is to summarize the latest progress regarding the protective effects of sirtuins, with a focus on SIRT1. We first introduce the distribution of sirtuins in the brain and how their expression and activity are regulated. We then highlight their protective effects against common neurological disorders, such as cerebral ischemia, axonal injury, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis. Finally, we analyze the mechanisms underlying sirtuin-mediated neuroprotection, centering on their non-histone substrates such as DNA repair enzymes, protein kinases, transcription factors, and coactivators. Collectively, the information compiled here will serve as a comprehensive reference for the actions of sirtuins in the nervous system to date, and will hopefully help to design further experimental research and expand sirtuins as therapeutic targets in the future.

Keywords

SIRT1; deacetylation; cell death; cerebral ischemia; neurodegenerative disease; neuroprotection

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1. Introduction

1.1 Histone deacetylases

Proteins undergo many posttranslational modifications to alter their function. One such modification is that certain proteins are acetylated on their lysine residues, a reaction mediated by acetyltransferases (Mellert and McMahon, 2009). Removal of these acetyl groups is facilitated by another family of enzymes--deacetylases (Mellert and McMahon, 2009; Yang and Seto, 2007). The prototypical proteins that exemplify the effects of acetylation are histones, as acetylated histones are unbound to DNA and allow transcription, while deacetylated histones bind tightly to DNA and restrict transcription (for a more detailed description see Section 5.1).

There are four classes of deacetylases in mammals; among them, class III is unique because its members require nicotinamide adenine dinucleotide (NAD^+) for catalysis. Therefore, they are also known as the NAD^+-dependent class III histone deacetylases (Imai *et al*., 2000; Mellert and McMahon, 2009; Yang and Seto, 2007). More commonly, they are referred to as silent information regulator two proteins (sirtuins or SIRTs), named after their yeast homologue, silent information regulator 2 (sir2) (Afshar and Murnane, 1999). To date, seven sirtuins have been identified, and they are known as sirtuin 1 (SIRT1) through SIRT 7 (Figure 1) (Michan and Sinclair, 2007). Structurally, they share significant sequence homology, and they all contain a conserved catalytic domain and a NAD^+-binding domain (Finnin *et al*., 2001; Sherman *et al*., 1999; Yamamoto *et al*., 2007).

1.2 SIRT1 mediates longevity under calorie restriction

SIRT1 is the best-characterized sirtuin among the seven. It contains 747 amino acids in human, with a predicted molecular weight of 81 kDa and a measured one of 120 kDa. In addition to histones, SIRT1 also deacetylates a number of non-histone substrates, such as p53 (Luo *et al*., 2001) and peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α) (Nemoto *et al*., 2005). SIRT1 is drawing even more attention since it is considered to be one of the determining factors in lifespan elongation induced by calorie restriction, a phenomenon observed in phylogenetically diverse organisms including yeast, worm, fruit fly and mouse (Howitz *et al*., 2003; Kaeberlein *et al*., 1999; Rogina and Helfand, 2004; Tissenbaum and Guarente, 2001). Its beneficial roles are further supported by the findings that putative SIRT1-activating compounds, such as resveratrol, also promote longevity in several species, including yeast (Howitz *et al*., 2003), worm, (Wood *et al*., 2004) and mouse (Baur *et al*., 2006), making it an anti-aging target.

The longevity effects of SIRT1 rely on its enzymatic activity of deacetylation on histone and non-histone substrates. While the deacetylation of histones leads to their interaction with DNA and consequent gene silencing (Braunstein *et al*., 1993; Dali-Youcef *et al*., 2007; Sauve *et al*., 2006), the deacetylation of non-histone proteins has a wide range of biological effects, including metabolic adjustment, survival promotion, and autophagy (Brooks and Gu, 2009; Campisi, 2005; Dali-Youcef *et al*., 2007; Madeo *et al*., 2010). For example, SIRT1 inhibits p53 (Luo *et al*., 2001), reducing its pro-apoptotic effect. It also inhibits nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) (Yeung *et al*., 2004), reducing its pro-inflammatory effects. In contrast, SIRT1 activates a transcriptional coactivator, PGC-1α (Nemoto *et al*., 2005), leading to increased glucose levels, insulin sensitivity, and mitochondrial biogenesis. These effects, along with others, collectively contribute to the longevity effect of calorie restriction.

These metabolic changes and cytoprotective endorsements are generally considered to happen in non-neural organs, such as the liver, pancreas, muscle, and fat tissues (Brooks and Gu, 2009; Imai and Guarente, 2010). However, recent studies suggest that the hypothalamus

may also contribute to the longevity effects of SIRT1 and calorie restriction via coordination of neurobehavioral and neuro-endocrinal changes including body temperature, appetite, and overall physical activity (Dietrich *et al*., 2010; Satoh *et al*., 2010). SIRT1 is abundantly expressed in several regions in the hypothalamus of mice, especially in the arcuate, paraventricular, ventro- and dorsomedial nuclei; and calorie restriction increases SIRT1 levels in the hypothalamus, which increases body temperature, food intake, and physical activity (Dietrich *et al*., 2010; Ramadori *et al*., 2008; Satoh *et al*., 2010). SIRT1 appears to be required for the aforementioned behavioral changes, as the changes are prevented if SIRT1 is knocked out or inhibited (Chen *et al*., 2005a; Satoh *et al*., 2010).

In addition to the hypothalamus, SIRT1 is also expressed in other regions of the brain, including the cortex, striatum and hippocampus (Ramadori *et al*., 2008). Shortly after this finding, a neuroprotective role of sirtuins, especially SIRT1, has been delineated (Morris *et al*., 2011; Tang, 2009). Hence, in this article, we intend to summarize recent progress on the neural benefits of the sirtuins. First, we briefly review how the sirtuins are regulated in terms of their expression and activity. Next, we look at their distribution in the brain and examine their neuroprotective effects against neurological disorders. Finally, we highlight the neuroprotective mechanisms of the sirtuins, with a focus on SIRT1.

2. Regulation of SIRT1 expression and activity

2.1 Transcriptional regulation of SIRT1 expression

2.1.1 Upregulation—Expression of SIRT1 is regulated at the transcriptional level. The basal level of SIRT1 is regulated by the transcription factor E2F transcription factor 1 (E2F1), through binding to the SIRT1 promoter at a consensus site (Wang *et al*., 2006). Calorie restriction and cellular stresses increase the transcriptional activity of E2F1 and upregulate the level of SIRT1. For instance, DNA damage and oxidative stress stabilize and activate E2F1, leading to increased SIRT1 transcription (Wang *et al*., 2006). Forkhead box proteins (FOXO) belong to another group of transcription factors that upregulate SIRT1. FOXO1 binds to several consensus sites within the SIRT1 promoter and enables its transcription (Xiong *et al*., 2011). FOXO3a is another SIRT1 regulator, and starvation in mammal cells activates FOXO3a and consequently augments SIRT1 expression, indicating an important role of these proteins in nutrient-sensing signaling (Nemoto *et al*., 2004).

Feedback mechanisms exist between SIRT1 and E2F1 and FOXO1. In a negative manner, SIRT1 can deacetylate E2F1 and inhibit its transcriptional activity, and therefore maintain SIRT1 protein level homeostasis (Wang *et al*., 2006). In contrast, SIRT1 deacetylates FOXO1 and increases its transcriptional activity, forming a positive feedback loop (Xiong *et al*., 2011). These feedback loops may play important roles in the fine regulation of SIRT1 expression.

Additionally, SIRT1 is upregulated by a nuclear receptor, a human homologue of the *Drosophila* tailless gene (TLX). It was recently reported that TLX binds the TLX-activating element on the promoter of mammalian SIRT1, and upregulates SIRT1 expression (Iwahara *et al*., 2009). Knockdown of TLX with siRNA reduces the level of SIRT1 (Iwahara *et al*., 2009).

2.1.2 Downregulation—Alternatively, SIRT1 is downregulated under certain conditions. Hypermethylated in cancer 1 (HIC1) is a transcriptional repressor, with SIRT1 as one of its targets (Chen *et al*., 2005c). HIC1 binds SIRT1, forming a transcriptional repression complex through its N-terminus. This complex directly binds to the SIRT1 promoter, consequently represses the transcriptional activity of the SIRT1gene, and thereby inhibits SIRT1-mediated p53 inactivation (Chen *et al*., 2005c). A recent study showed that PPARγ

binds the promoter of SIRT1 and inhibits its expression (Han *et al*., 2010). There are two p53 binding sites (−178bp and −168bp) within the promoter of the SIRT1 gene, and their interaction normally represses the transcription of SIRT1 (Nemoto *et al*., 2004). In the absence of nutrients, FOXO3a physically binds p53 and inhibits the suppressive activity of p53 on SIRT1, resulting in increased transcription of SIRT1 (Nemoto *et al*., 2004; Zschoernig and Mahlknecht, 2008).

2.2 Post-transcriptional regulation of SIRT1 expression

2.2.1 MicroRNAs—In addition to transcriptional control, the post-transcriptional regulation of SIRT1mRNA is another major determinant of SIRT1 protein expression (Cheadle *et al*., 2005). These procedures are governed by specific RNA binding proteins or microRNAs (miRs), leading to either stabilization or degradation of the mRNA. MicroRNAs refer to a group of short RNAs with an average length of 22 nucleotides (Bartel, 2009; Lee and Kemper, 2010). They cause gene silencing by binding to complementary sequences on their target mRNAs, leading to the degradation of mRNAs (Bartel, 2009; Lee and Kemper, 2010). To date, several microRNAs have been identified that reduce SIRT1 expression, including miR-9 (Saunders *et al*., 2010), miR-34a (Lee and Kemper, 2010; Yamakuchi *et al*., 2008), miR-132 (Strum *et al*., 2009), miR-181 (Saunders *et al*., 2010) and miR-199 (Rane *et al*., 2009; Saunders *et al*., 2010), miR-217 (Menghini *et al*., 2009), demonstrating an additional means to regulate SIRT1 expression at the post-transcriptional level.

2.2.2 RNA-binding proteins—An example of RNA binding proteins is the Hu family of RNA-binding protein (HuR). Under physiological conditions, HuR associates with the 3′ untranslated region of the SIRT1 mRNA. This interaction leads to increased stability of SIRT1 mRNA, promoting the translation of SIRT1 (Abdelmohsen *et al*., 2007; Brennan and Steitz, 2001). However, the complex between HuR and SIRT1 mRNA is disrupted by DNA damage and oxidative stress, leading to the instability of SIRT1 mRNA (Brennan and Steitz, 2001). These insults also lead to the activation of a serine/threonine kinase, the cell cycle checkpoint kinase 2 (CHK2), which then phosphorylates HuR at Ser88, Ser100, and Thr118. When hyperphosphorylated, HuR loses its binding ability to SIRT1 mRNA, setting the mRNA free to be degraded (Abdelmohsen *et al*., 2007; Zschoernig and Mahlknecht, 2008).

2.3 The regulation of SIRT1 activity via protein-protein interactions

It is well established that protein-protein interaction, or complex formation, is a key regulatory mechanism for the activity of histone deacetylases (Table 2), including sirtuins (Sengupta and Seto, 2004). Thus far, two regulatory proteins have been found that alter SIRT1 activity by forming complexes with SIRT1 in response to cellular stresses (Sengupta and Seto, 2004; Zschoernig and Mahlknecht, 2008). Active regulator of SIRT1 (AROS) is a recently identified nuclear protein that directly interacts with SIRT1 and increases the deacetylating activity of SIRT1 on p53 following DNA damage, inhibiting p53-mediated transcription of pro-apoptotic genes (Kim *et al*., 2007b). In contrast, deleted in breast cancer-1 (DBC1), another nuclear protein, functions as a negative regulator of SIRT1 (Chini *et al*., 2010; Kim *et al*., 2008; Zhao *et al*., 2008). DBC1 directly forms a complex with SIRT1 via the interaction of a leucine zipper motif and the deacetylase domain of SIRT1. This interaction consequently inhibits the enzymatic activity of SIRT1 on p53 (Kim *et al*., 2008; Zhao *et al*., 2008). DBC-1 interacts only with SIRT1 of the sirtuin family, implying that the underlying regulatory mechanism is highly specific (Chini *et al*., 2010). However, the molecular mechanisms underlying SIRT1 activation by AROS and SIRT1 inhibition by DBC-1 are not completely understood.

2.4 Regulation of SIRT1 activity by post-translational modification

2.4.1 Sumoylation—As seen in other enzymes, SIRT1 enzymatic activity is also altered by post-translational modification (Table 2) (Chung *et al*., 2010; Tang, 2009). The most common post-translational modifications for SIRT1 are sumoylation and phosphorylation. The small ubiquitin-like modifiers (SUMO) are a group of proteins that are covalently attached to lysine residues of targeting proteins via a process called sumoylation. Distinct from the degradation function of ubiquitination, sumoylation exerts a regulatory function on its target proteins, and those regulations include subcellular translocation and altered enzymatic activity of the target proteins (Verger *et al*., 2003; Zschoernig and Mahlknecht, 2008). SIRT1 is one target of sumoylation (Yang *et al*., 2007b). Sumoylation of Lys734 significantly increases the enzymatic activity of SIRT1, and the abrogation of sumoylation by site-directed mutagenesis impairs its deacetylase activity on p53 and histones. The desumoylation of SIRT1 occurs after genotoxic stresses, leading to increased cell death (Yang *et al*., 2007b; Zschoernig and Mahlknecht, 2008). These results suggest that the sumoylation and desumoylation of SIRT1can function as a molecular switch to regulate SIRT1 activity in response to cellular stresses.

2.4.2 Phosphorylation

2.4.2.1 Increasing SIRT1 activity: Reversible phosphorylation of proteins is the most common post-translational modification that functions as a ‘molecular switch’ in the concerted control of biological systems (Figure 2). There are at least 13 candidate sites for phosphorylation in SIRT1 (Sasaki *et al*., 2008), including Ser27 and Ser47 in its N-terminus (Beausoleil *et al*., 2004; Beausoleil *et al*., 2006). Indeed, Nasrin and co-workers reported that c-jun N-terminal kinase 1 (JNK1) phosphorylates these two serine residues plus Thr530 of SIRT1 (Nasrin *et al*., 2009). The phosphorylation of SIRT1 occurs under oxidative stress and increases the nuclear translocation and enzymatic activity of SIRT1 specifically toward histone H3 but not p53 (Nasrin *et al*., 2009), suggesting this interaction may play a role in a stress-protective pathway.

The cell cycle checkpoint kinases (CHKs) are a group of kinases that also phosphorylate SIRT1. CHK1 is responsible for phosphorylation of Thr530 and Thr540 of SIRT1 to increase its activity; accordingly, dephosphorylation of SIRT1 results in decreased enzymatic activity (Sasaki *et al*., 2008).

Another family of protein kinases, the dual specificity tyrosine phosphorylation-regulated kinases (DYRKs), is also reported to phosphorylate SIRT1. DYRKs are important in the embryonic development of brain, with a special role in the pathogenesis of Down’s syndrome (Guo *et al*., 2010; Tejedor and Hammerle, 2011). One of their roles is to regulate apoptosis. Among its seven members, DYRK1A and DYRK3 inhibit apoptosis in various cell types, whereas DYRK2 induces apoptosis via activating p53 (Guo *et al*., 2010; Taira *et al*., 2007). Two of their members, namely the pro-survival DYRK1a and DYRK3, directly phosphorylate SIRT1 at its Thr522 and activate it, leading to increased p53 deacetylation (Guo *et al*., 2010).

The kinase identified most recently to increase SIRT1 activity is casein kinase II (CK2), a eukaryotic protein kinase with more than 100 substrates. CK2 is recruited to SIRT1 after cellular stresses and phosphorylates multiple conserved serine and threonine residues of SIRT1, including Ser154, 649, 651 and 683 (Kang *et al*., 2009), as well as Ser659 and Ser661 (Zschoernig and Mahlknecht, 2009) (Figure 2). Phosphorylation of SIRT1 by CK2 increases its substrate-binding affinity and deacetylation rate, especially in regard to p53 (Kang *et al*., 2009; Sasaki *et al*., 2008; Zschoernig and Mahlknecht, 2009).

2.4.2.2 Decreasing SIRT1 activity: Phosphorylation does not ubiquitously amplify the activity of SIRT1. Mammalian sterile 20-like kinase 1 (MST1) is a serine/threonine kinase, and the overexpression of MST1 induces apoptosis via activation of p53 (Lin *et al*., 2002; Yuan *et al*., 2011). A recent study showed that SIRT1 is phosphorylated by MST1 at its C-terminus (aa 489-747) after induced DNA damage, leading to reduced activity of SIRT1 and increased acetylation of p53, and ultimately causing cell death (Yuan *et al*., 2011) (Figure 2). Taken together, these results show that SIRT1 is phosphorylated at multiple sites by several protein kinases; which, together with sumoylation, play important roles in SIRT1 functional regulation.

2.5 Pharmacological regulation of SIRT1 activity

Several chemical compounds have been shown to inhibit the deacetylase activity of the sirtuin family. Inhibition of SIRT1 by splitomicin is observed in multiple systems, including budding yeast (Bedalov *et al*., 2001), mammalian cells (Nadtochiy *et al*.), and mice (Breitenstein *et al*., 2010). Sirtinol is another frequently used SIRT1 inhibitor that is effective both *in vitro* and *in vivo* (Grozinger *et al*., 2001; Ota *et al*., 2006; Shindler *et al*., 2010). Recent studies show that a series of indoles (Napper *et al*., 2005) are potent and selective inhibitors of SIRT1. Indeed, one of the most potent and specific inhibitors for SIRT1 is the indole EX-527 (Solomon *et al*., 2006),

SIRT1 is also activated by several small-molecule compounds. Most of these activators are polyphenols (Chung *et al*., 2010), including resveratrol (Baur *et al*., 2006; Howitz *et al*., 2003; Wood *et al*., 2004), quercetin, curcumin, and catechins (Chung *et al*., 2010; Davis *et al*., 2009; de Boer *et al*., 2006; Howitz *et al*., 2003). Resveratrol is the first and most studied SIRT1 activator. While its stimulatory effect is strongly supported by many studies (Alcain and Villalba, 2009; Howitz *et al*., 2003; Kim *et al*., 2007a; Pervaiz, 2003; Raval *et al*., 2008; Sun *et al*., 2010), the underlying mechanisms are not fully understood. Additionally, resveratrol may have some biological functions other than activating SIRT1 (Beher *et al*., 2009; Pacholec *et al*., 2010; Tang, 2010). A viable explanation for the diversity of biological targets of resveratrol is that a direct interaction and allosteric mechanism are involved in its mechanism of action (Dai *et al*., 2010). More detailed information about SIRT1 activators and inhibitors can be found in reviews dedicated to this topic (Chung *et al*., 2010; Neugebauer *et al*., 2008).

2.6 Oxidative regulation of SIRTs activity

Reactive oxygen species (ROS) causes lipid peroxidation and generates unsaturated aldehydes, such as acrolein and 4-hydroxynonenal (4-HNE), which are reactive to cysteines in proteins. It is reported that these aldehydes react with the cysteine residues of human SIRT1 between amino acids 467 and 492 (Caito *et al*., 2010). This modification not only decreases the enzyme activity of SIRT1 but also promotes its proteasomal degradation (Caito *et al*., 2010). A recent report shows that 4-HNE covalently binds Cys-280 of human mitochondrial SIRT3, resulting in allosteric inhibition of SIRT3 deacetylase activity (Fritz *et al*., 2011). Collectively, these findings suggest that 4-HNE directly binds some sirtuins and inhibits their activities.

2.7 Metabolic regulation of SIRT1 activity

Sirtuins catalyze the deacetylation reaction of their targets, which is an NAD^+-dependent process. During this process, an acetyl group of the substrate is transferred to the ADP-ribose (ADPR) moiety of NAD^+. After losing the acetyl group, the SIRT1 substrate becomes a deacetylated protein. Once NAD^+ gains the acetyl group, it becomes destabilized, breaking down to one molecule of nicotinamide and one molecule of 2′-O-acetyl-ADP ribose (OAADPR) (Landry *et al*., 2000; Smith *et al*., 2000; Tanner *et al*., 2000; Tanny and

Moazed, 2001). SIRT1 thus has two coupled enzymatic activities: deacetylating targets and breaking down NAD^+, where NAD^+ functions as the substrate of SIRT1 and nicotinamide and OAADPR are the products of the deacetylation reaction. Therefore, it is a reasonable prediction that NAD^+ can increase the enzymatic activity of SIRT1, whereas nicotinamide and OAADPR may inhibit it (Bitterman *et al*., 2002; Neugebauer *et al*., 2008; Sauve and Schramm, 2003; Tong and Denu, 2010). Next, we review the literature showing the negative regulation of sirtuins via deacetylation byproducts.

2.7.1 Inhibition—As an end product of sirtuin deacetylation, nicotinamide is an effective inhibitor of SIRT1 activity both *in vivo* and *in vitro* (Luo *et al*., 2001; Sauve *et al*., 2001; Sauve and Schramm, 2003). At normal concentrations, nicotinamide inhibits Sir2 activity *in vitro* via binding to a conserved pocket on the enzyme and blocking the hydrolysis of NAD^+ (Bitterman *et al*., 2002; Jackson *et al*., 2003). In yeast cells, exogenous nicotinamide suppresses Sir2 activity and shortens life span. Nicotinamide is also known to inhibit mammalian SIRT1 (Vaziri *et al*., 2001; Zhao *et al*., 2004), promoting p53-dependent apoptosis in mammalian cells (Vaziri *et al*., 2001). Compared with nicotinamide, OAADPR is less characterized regarding its role in sirtuin regulation (Tong and Denu, 2010), although ADP-ribose is known to be a potent SIRT1 inhibitor (Zhao *et al*., 2004).

2.7.2 Activation—As discussed above, SIRT1 requires NAD^+ for activation, and NAD^+ plays a critical role in the positive regulation of SIRT1 activity. During calorie restriction, the ratio of NAD^+/NADH is increased, and the relatively high level of NAD^+ enhances the activity of sirtuins (Lin *et al*., 2004; Vaziri *et al*., 2001). However, it is difficult to study the biological effects of NAD^+ when it is exogenously supplied, due to its low membrane permeability and high compartmentalization within mitochondrial, nuclear, and cytosolic pools. In the case of SIRT1, the role of NAD^+ is highlighted through its endogenous synthesis. There are two pathways for NAD^+ synthesis, the *de novo* synthesis and salvage pathways (Chung *et al*., 2010; Sauve *et al*., 2006). The *de novo* synthesis is an eight-step process using tryptophan as the precursor (Penberthy and Tsunoda, 2009), and the salvage pathway is a two-step process using nicotinamide as the precursor. Thus, the salvage pathway turns the end product of SIRT1-mediated reactions into its substrate, therefore enhancing SIRT1 activity via two mechanisms: providing substrate and removing end product. In the salvage pathway, the two synthetic steps are catalyzed by two enzymes—nicotinamide phosphoribosyltransferase (NAMPT) and nicotinamide mononucleotide adenylyltransferase 1 (NMNAT-1) (Chung *et al*., 2010; Penberthy and Tsunoda, 2009). Of the two, NAMPT is the rate-limiting enzyme that catalyzes the conversion of nicotinamide to nicotinamide mononucleotide; NMNAT-1 then produces NAD^+ from nicotinamide mononucleotide.

The significance of the NAD^+ salvage pathway was initially supported by a yeast study demonstrating that an intact NAD^+ salvage pathway is needed to elongate the lifespan by caloric restriction, as mutations of the enzymes abolish lifespan extension (Lin *et al*., 2000). On the other hand, overexpression of these enzymes not only extends the lifespan of yeast (Anderson *et al*., 2003; Lin *et al*., 2000) but also the lifespan of human vascular smooth muscle cells (Ho *et al*., 2009).

Further studies show that knockdown of either NAMPT or NMNAT-1 indeed decreases total cellular NAD^+ levels (Fulco *et al*., 2008; Ramsey *et al*., 2009; Zhang *et al*., 2009). Individually, NAMPT directly reduces cellular nicotinamide levels (Fulco *et al*., 2008), increases NAD^+ production, and therefore increases the ratio of NAD^+/NADH in mammalian cells (Fulco *et al*., 2008; Nakahata *et al*., 2009; Ramsey *et al*., 2009). NMNAT-1 is especially important in the nervous system as it protects neurons against axonal injury in a SIRT1-dependent manner (Araki *et al*., 2004). This phenomenon remains

controversial as others have shown that NAD^+-dependent neuroprotection is SIRT1-independent (Wang *et al*., 2005b).

The notion that SIRT1 protects against axonal injury is supported by studies examining the Wallerian degeneration slow (wlds) gene, a fusion gene encoding the full-length NMNAT-1 and the N-terminal fragment of the ubiquitin assembly protein (Mack *et al*., 2001). In wlds transgenic mice, Wallerian degeneration, a process where the distal parts of axons undergo degeneration after injury, is slowed compared with that in wild-type mice (Araki *et al*., 2004; Conforti *et al*., 2000; Mack *et al*., 2001). Although not a rate-limiting enzyme, NMNAT-1 also plays an important role in Wallerian degeneration since knockdown of NMNAT-1 reduces total cellular NAD^+ levels and inhibits the deacetylation activity of SIRT1 on multiple targets (Zhang and Kraus, 2009). (For more information see section 4.1.2). Taken together, these results indicate that the regulation of SIRT1 activity by NAD^+, including its catabolism and synthesis, is an important link between cellular metabolism and gene transcription via protein deacetylation.

3. Distribution of sirtuins in the brain

During mouse embryogenesis, SIRT1 is highly expressed in the brain, spinal cord, and dorsal root ganglion, with the peak expression at E4.5 (Sakamoto *et al*., 2004). SIRT1 is also expressed in the adult brain, with high levels in the cortex, hippocampus, cerebellum, and hypothalamus, and low levels in white matter (Ramadori *et al*., 2008). Among the various cell types of brain, SIRT1 is predominantly, if not exclusively, expressed in neurons (Hisahara *et al*., 2008; Ramadori *et al*., 2008; Sakamoto *et al*., 2004). The only exception is that SIRT1 is found in microglia when co-cultured with neurons (Chen *et al*., 2005b). At the subcellular level, SIRT1 is viewed as a nuclear protein (Michishita *et al*., 2005). Yet, it is reported that SIRT1 has both nuclear import and export sequences, and that SIRT1 is present in the cytosolic fraction of mouse brain, although its cytosolic function is just beginning to be elucidated (Jin *et al*., 2007; Li *et al*., 2008; Tanno *et al*., 2007).

In brain, SIRT2 is a cytoplasmic protein expressed in oligodendrocytes and plays an important role in the formation of myelin sheath and in the myelin-axon interaction (Li *et al*., 2007c; Michishita *et al*., 2005; Schwer *et al*., 2010). The major target of SIRT2 is the Lys40 of α-tubulin (North *et al*., 2003). Additionally, SIRT2 is expressed in olfactory and hippocampal neurons (Suzuki and Koike, 2007).

SIRT5, a mitochondrial sirtuin, is highly expressed in the cortex of human brain, especially in layer II (Glorioso *et al*., 2011). Among the other sirtuins, SIRT3 and SIRT4 are also localized to the mitochondria (Ahn *et al*., 2008; Michishita *et al*., 2005), while SIRT6 and SIRT7 are nuclear proteins (Cooper and Spelbrink, 2008; Michishita *et al*., 2005; Schwer *et al*., 2010). Although they are all expressed in brain (Liszt *et al*., 2005; Michishita *et al*., 2005; Schwer *et al*., 2010), their cellular distributions and functions have yet to be elucidated.

4. Neuroprotective effects of sirtuins against neurological diseases

The effects of sirtuins on the outcomes of common neurological disorders are summarized in Table 3 and discussed in detail below.

4.1 Acute diseases

4.1.1 Cerebral ischemia—Ischemic stroke is a common neurological disease caused by the sudden reduction or cessation of blood flow to the brain, leading to infarction. The clinical management of stroke is difficult and unsatisfactory because the only method to

rescue ischemic brain tissue is to restore blood flow. For this purpose, the FDA has approved the clinical use of tissue plasminogen activator (tPA). However, this drug needs to be administered within three hours after the onset of the stroke to provide any clinical benefit, and this time window greatly limits the clinical use of tPA. Alternative and promising candidates for neuroprotective strategies include preconditioning, mild hypothermia, and the use of chemical and biological compounds targeting critical molecular mediators of neuronal death and survival. One example of these compounds is the SIRT1 activator resveratrol.

The neuroprotective effect of SIRT1 was first reported by Raval and colleagues (Raval *et al*., 2006; Raval *et al*., 2008). In their studies, they report that both ischemic preconditioning and resveratrol treatment reduce neuronal injury of hippocampal CA1 after NMDA challenge in slices and global cerebral ischemia in rats. They also show that increased SIRT1 activity is a common mechanism for the protective effects of preconditioning and resveratrol (Morris *et al*., 2011; Raval *et al*., 2006). Sirtinol, a SIRT1 activity inhibitor, abolishes the neuroprotection of preconditioning and resveratrol (Raval *et al*., 2006), indicating that SIRT1 plays a key role in mediating neuroprotection. The neuroprotective role of SIRT1 is further supported by two recent studies (Chong and Maiese, 2008; Della-Morte *et al*., 2009) showing that SIRT1 activation reduces ischemic neuronal injuries and that one possible mechanism is downregulation of the mitochondrial uncoupling protein 2 (Della-Morte *et al*., 2009).

Our previous study showed that, in primary neuronal culture, NAD^+ pretreatment markedly reduces neuronal death induced by oxygen-glucose deprivation (OGD) (Wang *et al*., 2008). Our unpublished data show that SIRT1 is necessary for NAD^+ neuroprotection, as NAD^+ treatment upregulates SIRT1 expression and activity, and SIRT1 knockdown attenuates the protection mediated by NAD^+ against excitotoxicity in neurons (Wang *et al*., 2009b). In addition, similar neuroprotection by NAD^+ is observed in astrocytes (Ying *et al*., 2005), and intranasal infusion of NAD^+ also decreases infarct volume in rat after focal cerebral ischemia (Ying *et al*., 2007). Moreover, NAMPT, the rate-limiting enzyme of the NAD^+ salvage pathway, also demonstrates a protective effect against stroke. NAMPT overexpression reduces ischemic infarct whereas NAMPT inhibition aggravates ischemic injuries. The protective effect of NAMPT is SIRT1-dependent, as SIRT1 knockout blocks the protection (Wang *et al*., 2011).

In addition to its direct protection, SIRT1 also mediates the benefits of some other neuroprotective agents, such as leptin (Avraham *et al*., 2010), icariin, and tetrahydroxystilbene glucoside (Wang *et al*., 2009a; Wang *et al*., 2009c; Zhu *et al*., 2010). Leptin is an adipose hormone that attenuates ischemic injury (Valerio *et al*., 2009; Zhang and Chen, 2008; Zhang *et al*., 2007). One of its protective mechanisms is to upregulate SIRT1 expression (Avraham *et al*., 2010). In a similar way, SIRT1 upregulation is involved in the neuroprotection of icariin, a flavonol (Wang *et al*., 2009a; Zhu *et al*., 2010), and tetrahydroxystilbene glucoside, a polyphenol (Wang *et al*., 2009c). In the case of icariin, SIRT1 is necessary for the protection, as the knockdown of SIRT1 diminishes the flavonol's protective effect (Zhu *et al*., 2010).

Despite the aforementioned evidence, controversy exists over the protective effect of SIRT1 against ischemia. In a study using SIRT1 transgenic mice, where human SIRT1 was overexpressed under the control of rat neuron-specific enolase (NSE) promoter, no neuroprotection was observed against stroke as SIRT1 and wild-type mice demonstrated almost indistinguishable infarct volumes and neurological deficiency scores (Kakefuda *et al*., 2009). The discrepancy between this study and the others probably derived from the sustained high level of SIRT1, because it may consume too much or even deplete NAD^+,

which could aggravate neuronal injury (Kakefuda *et al*., 2009; Liu *et al*., 2009; Wang *et al*., 2008). Therefore, it is possible that this detrimental effect of NAD^+ deficiency compromises the neuroprotective effect of SIRT1. In another study, nicotinamide, a compound with a SIRT1 inhibitory action, demonstrated a neuroprotective effect against ischemic injury, seemingly implying that SIRT1 might play a detrimental role against stroke (Chong *et al*., 2005). However, this report might overlook other functions of nicotinamide, including that of precursor for NAD^+ synthesis. In fact, the same group later reported that SIRT1 overexpression prevents neurons from apoptosis after oxidative stress (Chong and Maiese, 2008).

4.1.2 Wallerian degeneration—Wallerian degeneration refers to axonal death and degradation after focal injury, followed by myelin sheath breakdown. The neuroprotective effect of SIRT1 against Wallerian degeneration was first discovered in a study using wlds transgenic mice (Perry *et al*., 1990). These mice exhibited a significant delay in axonal degeneration after physical or chemical injury. The mechanistic basis for the delayed axonal damage was apparently associated with the mutant wlds chimeric protein. Wlds consists of the N-terminal 70 amino acids of the ubiquitin fusion degradation protein2a (Uf2a) and the complete sequence of NMNAT-1, a key enzyme in the NAD^+ salvage pathway (Coleman, 2005). NMNAT-1 activity plays an important role in the prevention of axonal damage (Araki *et al*., 2004; Babetto *et al*., 2010; Conforti *et al*., 2007; Sasaki *et al*., 2009), exerting its protective effects through SIRT1 activation, as the neuroprotection is blocked by the SIRT1 inhibitor sirtinol and siRNA-mediated SIRT1 silencing (Araki *et al*., 2004; Babetto *et al*., 2010; Sasaki *et al*., 2009). It should be noted that SIRT1 cannot fully account for the neuroprotective role of the wlds gene (Conforti *et al*., 2007; Sasaki *et al*., 2009; Wang *et al*., 2005b). Recent studies indeed show that both the N-terminal sequence and intact NMNAT-1 activity are required for full wlds activity (Avery *et al*., 2009; Conforti *et al*., 2009), and that cytosolic translocation of NMNAT1 to axons is necessary for its neuroprotection (Babetto *et al*., 2010). However, the role of SIRT1 remains controversial as both SIRT1-dependent (Araki *et al*., 2004) and –independent mechanisms are reported (Wang *et al*., 2005b).

4.1.3 Retinal injury—The retina is part of the nervous system, and it is susceptible to various injuries such as ultraviolet light, ischemia, inflammation and degeneration. SIRT1 is expressed in all layers of normal retina and is necessary for retinal health (Shindler *et al*., 2007). In SIRT1-deficient mice, however, retina have reduced cell numbers in multiple layers, and demonstrate disorganized cellular patterns, which are accompanied by p53 hyperacetylation (Cheng *et al*., 2003). Furthermore, a neuroprotective role of SIRT1 has been reported against retinal injury. For instance, upregulation of SIRT1 by resveratrol protects the retina from antibody-induced apoptotic cell death (Anekonda and Adamus, 2008). In retinal degeneration 10 (rd10) mice, an animal model of retinal degeneration, SIRT1 is not detected in the retina, and this absence of SIRT1 contributes to retinal degeneration (Shindler *et al*., 2007). Similarly, a deficiency in E2Fs, the transcription factor for SIRT1, leads to the downregulation of SIRT1, p53 hyperacetylation, and elevated apoptosis in retina (Chen *et al*., 2009). Collectively, these results indicate a beneficial role of SIRT1 in retina health and protection.

4.2 Neurodegenerative diseases

4.2.1 Alzheimer's disease—Alzheimer's disease (AD) is a terminal neurodegenerative disease, causing neuronal death and brain atrophy. The pathological hallmarks of AD are the intracellular tangles and extracellular plaques. The tangles, also known as neurofibrillary tangles, are the accumulation of insoluble tau proteins, and the plaques are deposits of β-amyloid (Aβ) peptides, typically consisting of 40-42 amino acid residues.

The protective effect of SIRT1 against AD was initially observed in caloric restriction studies, where calorie restriction reduced Aβ and plaque generation in the brains of transgenic AD mice (Patel *et al*., 2005; Wang *et al*., 2005a). Similarly, the reduction of Aβ is also noticed in the cortex of starved squirrel monkeys and is inversely correlated with SIRT1 levels (Qin *et al*., 2006a). These studies imply that SIRT1 is involved in the neuroprotection against AD. Indeed, recent studies demonstrate that SIRT1 activation reduces the neuronal death and brain atrophy induced by AD (Chen *et al*., 2005b; Donmez *et al*., 2010; Kim *et al*., 2007a; Min *et al*., 2010; Qin *et al*., 2006b). SIRT1 deficiency is associated with increased levels of phosphorylated-tau in neurons (Min *et al*., 2010) and the amount of neurofibrillary tangles in AD brains (Julien *et al*., 2009).

SIRT1 targets both tau and Aβ, two pathological hallmarks of AD. For example, degradation of phosphorylated tau improves cognitive function and reduces neuronal death in mice (Santacruz *et al*., 2005; Sydow *et al*., 2011); however, when tau is acetylated by the histone acetyltransferase, p300, the breakdown of tau is inhibited (Min *et al*., 2010). SIRT1 deacetylates the acetylated tau and consequently reduces its level; conversely, SIRT1 inhibition leads to the opposite effect—increasing the levels of tau and exacerbating the accumulation of pathogenic forms of phosphoryated-tau (Min *et al*., 2010).

Moreover, recent studies show that either resveratrol administration or SIRT1 overexpression reduces Aβ level both *in vitro* and *in vivo* (Chen *et al*., 2005b; Donmez *et al*., 2010; Qin *et al*., 2006b) Aβ is generated from a physiological protein, amyloid precursor protein (APP). Normally, APP is processed by α-secretase, generating soluble APP with a neurotrophic role. When sequentially processed by the β- and γ-secretases, however, APP is converted to the toxic Aβ. SIRT1 overexpression stimulates the production of α-secretase in neurons and mice via two pathways: activating the retinoic acid receptor (RAR) (Donmez *et al*., 2010) and inhibiting the Rho-associated, coiled-coil-containing protein kinase 1 (ROCK1) (Qin *et al*., 2006b). Increased level of α-secretase enhances normal precess of APP, leading to decreased generation of toxic Aβ. In addition, SIRT1 also reduces the NF-kappaB pathway in microglia and decreases Aβ level (Chen *et al*., 2005b). Taken together, these results show that SIRT1 is protective against AD via multiple mechanisms, including causing the degradation of tau and reducing levels of Aβ.

4.2.2 Parkinson's disease—Parkinson's disease (PD) is a common neurodegenerative disease caused by the death of dopaminergic neurons of the substantia nigra in the brain stem. The major symptoms of PD are rigidity, tremor, and bradykinesia. Early studies found that caloric restriction or use of 2-deoxy-D-glucose, a glucose analogue, reduces the loss of dopaminergic neurons in mice and improves motor function, implying that SIRT1 may be involved in the protection (Duan and Mattson, 1999). The levels of SIRT1 in dopaminergic neurons are sharply decreased when treated with neurotoxins, such as rotenone, 6-hydroxydopamine, α-synuclein, or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Albani *et al*., 2009; Alvira *et al*., 2007; Pallas *et al*., 2008), which are agents widely used to model PD. Additionally, SIRT1 overexpression (Wareski *et al*., 2009) or activation by resveratrol (Albani *et al*., 2009; Chao *et al*., 2008; Okawara *et al*., 2007) slows neuronal death as well as neurodegeneration in both *in vivo* and *in vitro* PD models, indicating a neuroprotective role of SIRT1 against PD. However, not all studies demonstrated a protective role of sirtuins. For example, no protection is noticed in a MPTP-induced PD model using SIRT1 transgenic mice (Kakefuda *et al*., 2009). The cytoplasmic sirtuin, SIRT2, even increases the toxicity of alpha-synuclein, as pharmaceutical and genetic inhibition of SIRT2 protects against dopaminergic cell death in a model of Parkinson's disease (Outeiro *et al*., 2007b). Nevertheless, despite the controversy, most research demonstrates a protective role of SIRT1 against PD, although the mechanisms are unclear.

4.2.3 Huntington's disease—Huntington's disease (HD) is an autosomal dominant hereditary disease with a middle-age onset. It is caused by a trinucleotide repeat mutation in the huntingtin gene that results in an increased number of glutamine residues in the huntingtin N-terminus, which causes abnormal protein aggregation and ultimately neuronal death. Parker and colleagues showed that the upregulation of SIRT1 or resveratrol treatment rescues neurons from injury induced by mutant huntingtin in *C. elegans* (Parker *et al*., 2005). In a yeast model of HD, activation of sir2 decreases mutant polyQ aggregation (Sorolla *et al*., 2011). SIRT1 activation by resveratrol reduced peripheral nerve deficits in HD transgenic mice, but the benefit was not observed in the brain (Ho *et al*., 2010). On the other hand, SIRT2 is detrimental to HD, as inhibition of SIRT2 protects neurons from death induced by huntingtin (Luthi-Carter *et al*., 2010; Pallos *et al*., 2008). A phase 1 clinical trial is underway to treat HD with the highly specific SIRT1 inhibitor, EX-527. When released, this result will help to elucidate the role of SIRT1 in HD protection and to provide a clinically meaningful treatment for this devastating disease.

4.2.4 Prion diseases—Prion diseases, or transmissible spongiform encephalopathies, include human Creutzfeldt–Jakob disease and kuru in humans, bovine spongiform encephalopathy or mad cow disease in bovine mammals, and goat scrapie. A normal cellular prion protein (PrP^{C}) is a membrane glycoprotein involved in several signaling pathways. The infectious form endogenous PrP^{C}, scrapie PrP (PrP^{Sc}), has a distinct tertiary conformation from PrP^{C} and thus is processed differently and ultimately forms aggregates. Furthermore, PrP^{Sc} is thought to be amplified following infection leading to progressive insoluble aggregate formation, ultimately causing neurotoxicity (Aguzzi *et al*., 2008; Bizat *et al*., 2010). The role of SIRT1 in prion disease was first reported in a study showing that calorie restriction reduces the level of prion protein in brain and delays the onset of prion disease (Chen *et al*., 2008). Further studies also demonstrate a protective effect of SIRT1 against prion diseases in *C. elegans* or mice models, as resveratrol and SIRT1 overexpression via adenoviral vector reduce neuronal dysfunction and death (Bizat *et al*., 2010; Seo *et al*., 2011), and SIRT1 inhibition exacerbates neuronal dysfunction (Bizat *et al*., 2010). In contrast, SIRT1 may have different effects on the neurotoxicity of prions, as SIRT1 knockout also delays the onset of prion disease (Chen *et al*., 2008). Further studies are necessary to fully elucidate the role of SIRT1 in prion-related diseases.

4.2.5 Amyotrophic lateral sclerosis—Amyotrophic lateral sclerosis (ALS) is a chronic and fatal neurodegenerative disease, characterized pathologically by the death of motor neurons in the spinal cord and cortex, possibly induced by a deficiency in the enzyme superoxide dismutase 1 (SOD1) (Rosen, 1993). In the animal model of ALS where a mutant form of SOD1 is expressed, SIRT1 levels are upregulated in motor neurons (Kim *et al*., 2007a). SIRT1 overexpression protects neurons against toxicity induced by the mutant SOD1 in both cultured neurons and mouse brain (Kim *et al*., 2007a). This protection corresponds to the increased deacetylation of p53 (Kim *et al*., 2007a). Resveratrol also enhances the protective effect of SIRT1 in a mouse model of ALS (Kim *et al*., 2007a; Markert *et al*., 2010), but it seems that multiple doses are necessary to improve neurological function and increase the longevity of mice (Markert *et al*., 2010).

4.2.6 Multiple sclerosis—Multiple sclerosis is a myelin sheath disease with lesions typically located in the brain, spinal cord or cranial nerves, and, most commonly, in the optic nerve. The causes of multiple sclerosis are not fully identified but likely arise from an autoimmune etiology; therefore, it is traditionally treated as an inflammatory disease. Recently, however, multiple sclerosis has also been considered a neurodegenerative disease because of the co-existence of permanent axonal damage, neuronal loss, and neurological disability in patients with multiple sclerosis (Lassmann, 2010; Shindler *et al*., 2010). In a

mouse model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), SIRT1 activation by SRT501 or SRT1720 maintains axonal density, prevents neuronal loss and improves neuronal dysfunction (Shindler *et al*., 2010; Shindler *et al*., 2007). SIRT1 inhibition with Sirtinol attenuates the neuroprotective effects of SRT501 (Shindler *et al*., 2010), suggesting a protective role of SIRT1 in multiple sclerosis. However, further investigations are necessary to fully delineate the role of SIRT1 in multiple sclerosis.

5. Cellular targets and protective mechanisms of sirtuins

Sirtuins are deacetylases, having both histone and non-histone substrates. The switch between acetylated and deacetylated conditions alters the activities of their substrates. Therefore, the protective mechanisms of sirtuins are closely related to their substrates, including histones, transcription factors, transcriptional co-activators, DNA repair enzymes, protein kinases, phosphatases, and tau, a pathogenic protein of AD. We next discuss the neuroprotective targets of sirtuins in the order of the numbers of genes they influence, with the targets that influence the largest number of genes discussed first.

5.1 Nuclear targets

5.1.1 Histones—In nuclei, core histones, including H2, H3 and H4, form ball-like structures for the DNA to wrap around, keeping DNA in a resting status. These interactions occur between the basic lysines (and arginines) of histones and the acidic phosphates of DNA chains. When acetylated on the lysines, however, histones lose their positive charges and release DNA, allowing DNA unwinding and subsequent gene transcription. In contrast, deacetylation polarizes histones and promotes their binding to DNA, leading to genome-wide but non-specific transcription silencing (Figure 3). Sirtuins are histone deacetylases. For example, SIRT1 deacetylates H3 at Lys9 and Lys14, and it also deacetylates H4 at Lys16, leading to genomic silencing (Imai *et al*., 2000). Genomic silencing could therefore further reduce protein synthesis and energy consumption. For instance, in PC12 cells, the upregulation of SIRT1 reduces cellular oxygen consumption by about 25% (Nemoto *et al*., 2005).

Reducing metabolic and energy requirements appears to be a common strategy for cells and organisms to survive through unfavorable conditions, such as calorie restriction, hypothermia, or hibernation. Coincidentally, these measures also induce neuronal tolerance, and protect against neuronal injuries induced by ischemic stroke (Frerichs and Hallenbeck, 1998; Kitagawa *et al*., 1990; Maier *et al*., 1998; Paschen *et al*., 2007; Yu and Mattson, 1999), AD (Patel *et al*., 2005; Wang *et al*., 2005a), and PD (Duan and Mattson, 1999). Together, these results imply that SIRT1-mediated transcription inhibition could contribute to reducing energy requirements for neuroprotection (Morris *et al*., 2011).

5.1.2 Transcriptional coactivators—Sirtuins may also confer neuroprotection via a mechanism similar to ischemic tolerance (Kitagawa *et al*., 1990; Stenzel-Poore *et al*., 2003). One way for neurons to gain tolerance is to reprogram their gene expression in order to upregulate pro-survival proteins, downregulate pro-apoptotic proteins, and decrease overall energy requirements while concomitantly increasing energy metabolism efficiency (Frerichs and Hallenbeck, 1998; Paschen *et al*., 2007; Stenzel-Poore *et al*., 2003). Sirtuins are able to make such contributions via deacetylating a set of proteins, including transcriptional coactivators, transcription factors, and nuclear receptors. This is summarized in Figure 4 and discussed in the next three sections.

5.1.2.1 Inhibition: In addition to genome-wide gene silencing, SIRT1 also suppresses gene transcription at the subgenomic level by inhibiting a transcriptional coactivator. In contrast to transcription factors, coactivators do not have DNA-binding motifs, but they can affect

the transcriptional activity of several specific transcription factors. P300 is one such coactivator (Goodman and Smolik, 2000). It has built-in histone acetyltransferase activity through which p300 neutralizes histones and therefore relaxes DNA, promoting the transcription of many transcription factors, including p53 and NF-κB (Goodman and Smolik, 2000; Iyer *et al*., 2004). A recent study showed that SIRT1 physically interacts with p300, deacetylates it at Lys1020 and 1024, and consequently inhibits the transcriptional activity of p300 (Bouras *et al*., 2005). Additionally, SIRT2 also deacetylates and inhibits p300 (Black *et al*., 2008). Considering that knockout of p300 increases neuronal resistance to amyloid toxicity in mice (Duclot *et al*., 2010), the inhibitory effect of SIRT1 and SIRT2 on p300 could also be protective, although direct evidence has not been reported.

5.1.2.2 Activation: Although SIRT1 suppresses a wide range of gene transcription, it can also increase the transcription of a specific group of genes. This is achieved via activating PGC-1α, a transcriptional coactivator, as SIRT1 physically interacts with PGC-1α to increase its activity (Nemoto *et al*., 2005; Rodgers *et al*., 2005). PGC-1α was initially reported to increase the transcriptional activities of two transcription factors—PPARγ and thyroid hormone receptor (Puigserver *et al*., 1998)—increasing mitochondrial energy metabolism and biogenesis (Lin, 2009; Nemoto *et al*., 2005; Rodgers *et al*., 2005). Currently, its targets have extended to PPARα (Vega *et al*., 2000), hepatic nuclear factor-4α (HNF-4α) (Yoon *et al*., 2001), and FOXO1 (Puigserver *et al*., 2003).

Most of the aforementioned transcription factors are neuronal, such as the PPARs and FOXO1, and their activation leads to neuroprotection (Bordet *et al*., 2006; Luo *et al*., 2006; Mysiorek *et al*., 2009; Zhan *et al*., 2010). For example, PPARα reduces the expression of matrix metalloproteinase-9 (MMP-9) (Cheng *et al*., 2009), and protects endothelial cells against ischemic injury, thus maintaining the integrity of the blood-brain barrier (Mysiorek *et al*., 2009). PPARγ possesses both anti-apoptotic and anti-inflammatory functions, and reduces brain damage induced by a number of diseases, including stroke, AD, and PD (Bordet *et al*., 2006; Luo *et al*., 2006). Lastly, FOXO1 is reported to mediate ischemic tolerance against global cerebral ischemia in rats (Zhan *et al*., 2010).

5.1.3 Transcription factors

5.1.3.1 Inhibition

5.1.3.1.1 P53: As the first-known non-histone substrate of SIRT1, p53 plays a detrimental role in most neurological disorders because it is responsible for the upregulation of a number of pro-apoptotic molecules, especially the BH3-only members of the Bcl-2 family (Hong *et al*., 2010; Yi and Luo, 2010). The transcriptional activity of p53 increases when it is acetylated at its multiple lysine residues; conversely, its activity is suppressed when deacetylated. SIRT1 deacetylates p53 and reduces its transcriptional activity (Luo *et al*., 2001; Vaziri *et al*., 2001), which could be one of the mechanisms of SIRT1-mediated neuroprotection. In fact, it is reported that SIRT1 protects neurons in models of AD (Karuppagounder *et al*., 2009; Kim *et al*., 2007a), amyotrophic lateral sclerosis in mice (Kim *et al*., 2007a), and PD in midbrain slice (Okawara *et al*., 2007) via the deacetylation and inhibition of p53.

5.1.3.1.2 NF-κB: NF-κB is the major transcription factor that transcribes pro-inflammatory mediators in the nervous system, and its activation exacerbates neuronal damage after neurological insults, especially ischemic stroke (Pizzi *et al*., 2009; Teng and Tang, 2010; Zheng and Yenari, 2004). SIRT1 deacetylates the p65 subunit of NF-κB at Lys310 and reduces its transcriptional activity, protecting cells from apoptosis (Yeung *et al*., 2004). In a mixed culture of neurons and microglia, SIRT1 deacetylates NF-κB signaling in microglia, and protects neurons from Aβ toxicity (Chen *et al*., 2005b). In addition, the inhibition of NF-

κB by SIRT1 also contributes to the neuroprotection afforded by Ginkgo extract or glucoside against AD and ischemia (Longpre *et al*., 2006; Wang *et al*., 2009c).

5.1.3.1.3 Yin Yang 1: MicroRNAs are negative post-transcriptional mediators that function in gene silencing. The miR-134 is one such short sequence. One of its targets is CREB, and the transcription of miR-134 itself is controlled by the transcription factor Yin Yang 1 (YY1) (Gao *et al*., 2010). The level of miR-134 is low in brain under normal conditions, because SIRT1 forms a repressor complex with YY1, which binds to the promoter of miR-143 and inhibits its transcription (Gao *et al*., 2010). In brain-specific SIRT1 knockout mice, however, miR-134 is upregulated in the hippocampus, and this is accompanied by decreased levels of CREB and brain-derived neurotrophic factor (BDNF), leading to impaired synaptic plasticity (Gao *et al*., 2010). This finding is interesting in that SIRT1 helps maintain the levels of CREB and BDNF, two molecules with established neuroprotective function, implying that this may be one of the mechanisms underlying the neuroprotection of SIRT1.

5.1.3.1.4 Nuclear factor (erythroid-derived 2)-like 2: Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is a key transcription factor in the regulation of xenobiotic and oxidative stresses. The target genes of Nrf2 are collectively called phase II enzymes; these include heme oxygenase 1, NADH quinone oxidoreductase, and glutathione synthase and transferase, among others. Nrf2 activation is generally cytoprotective (Li *et al*., 2007a). When overactivated, however, it may be carcinogenic (Kensler and Wakabayashi, 2010). In an immortalized cell line of human leukemia, Nrf2 is acetylated at Lys591, which increases its nuclear retention and transcription activity. Conversely, SIRT1 deacetylates Nrf2 and reduces its gene transcription (Kawai *et al*., 2011). Considering that Nrf2 plays a protective role in brain (Li *et al*., 2007a), it is of interest to test whether the findings in tumor cells are translatable to neurons. This will help elucidate the role of the interaction between SIRT1 and Nrf2 in brain.

5.1.3.1.5 FOXO1: SIRT1 is reported to bind and deacetylate FOXO1, causing a reduction in its transcriptional activity (Yang *et al*., 2005). However, it remains unclear whether its deacetylation is neuroprotective. FOXO1 is also modified by phosphorylation, with opposite effects mediated by different kinases. For instance, when phosphorylated by Akt, FOXO1 demonstrates a neuroprotective effect against ischemic neuronal injury; when phosphorylated by mammalian sterile 20-like kinase 1 (MST1), it promotes the apoptosis of cerebellar granule neurons upon the withdrawal of growth factors (Yuan *et al*., 2009). Notably, these findings were determined in different model systems, and further research is necessary to fully characterize the effect of deactylated FOXO1 on neuronal viability.

5.1.3.2 Activation

5.1.3.2.1 FOXO3: SIRT1 deacetylates FOXO3 and increases the cellular resistance to oxidative stress in HEK293 cells (Brunet *et al*., 2004). In addition, SIRT2 also deacetylates FOXO3 and increases its transcription after calorie restriction in mice and hydrogen peroxide treatment of fat and kidney cells, reducing cellular levels of ROS (Wang *et al*., 2007a). Motta and colleagues also reported that SIRT1 deacetylates FOXO3; however, they show that SIRT1 inhibits the activity of FOXO3 in HeLa cells (Motta *et al*., 2004). In brain, overexpression of nuclear-targeted FOXO3 protects motor neurons from apoptosis induced by mutant SOD1 or polyQ-expanded androgen receptor (Mojsilovic-Petrovic *et al*., 2009). Knockdown of FOXO3 increases neuronal apoptosis during zebrafish development (Peng *et al*., 2010), indicating a neuroprotective role of FOXO3. However, this is not a universal finding. For example, it is reported that FOXO3 promotes neuronal apoptosis after overexpression (Gilley *et al*., 2003) or due to activation by the withdrawal of neurotrophic

factors (Barthelemy *et al*., 2004). More studies are therefore needed to clarify the role of SIRT1 on FOXO3 activity, and to determine the overall effects of the SIRT1-FOXO3 interaction on neuronal fate.

5.1.3.2.2 FOXO4: In HEK293 cells, FOXO4 is acetylated after hydrogen peroxide treatment, leading to decreased transcriptional activity (Kobayashi *et al*., 2005; van der Horst *et al*., 2004). In contrast, its deacetylation by SIRT1 leads to increased transcriptional activity of FOXO4, increases cellular resistance against oxidative stress and promotes survival (Kobayashi *et al*., 2005; van der Horst *et al*., 2004). Although it is modestly expressed in the brain (Furuyama *et al*., 2000), the role of FOXO4 in neuroprotection remains unknown.

5.1.3.2.3 HIFs: Hypoxia-inducible factors (HIFs) are a family of transcription factors that also function as oxygen sensors. Once activated, HIFs upregulate proteins involved in oxygen transport, angiogenesis, cell survival, and glycolysis. Some more notable proteins in these categories include the neuroprotective proteins erythropoietin (EPO) (Sakanaka *et al*., 1998; Zhang *et al*., 2006; Zhang *et al*., 2010) and vascular endothelial growth factor (VEGF) (Wang *et al*., 2007b; Wick *et al*., 2002). The HIFs thus have protective roles against hypoxia and ischemia (Correia and Moreira, 2010). SIRT1 was first linked with HIF activity in hepatoma cells, where HIF2 was acetylated at its C-terminal during hypoxia, leading to decreased transcriptional activity of HIF2 (Dioum *et al*., 2009). SIRT1 activation reverses the acetylation of HIF2, and increases its transcription and EPO production (Dioum *et al*., 2009). In HEK293 cells, SIRT1 binds to HIF-1 and deacetylates it at Lys674, blocking its association with the transcriptional coactivator, p300 (Lim *et al*., 2010). Hypoxia suppresses SIRT1 activity due to NAD^+ insufficiency, leading to the activation of HIF1 (Lim *et al*., 2010). Currently, no reports are available showing if or how SIRT1 can protect the brain via the HIF pathways.

5.1.4 Nuclear receptors—Unlike membrane receptors, nuclear receptors are a group of proteins that localize to the cytosol or nucleus without association with the cell membrane. Once bound by their ligands, such as some hormones and fatty acids, nuclear receptors change their conformational structures, translocate to nucleus and directly bind DNA to regulate gene expression. Therefore, nuclear factors are also considered transcription factors. The transcription efficiency of nuclear receptors is adjusted by acetylation and deacetylation. SIRT1 is one of the enzymes that can deacetylate some nuclear receptors. Below is a discussion of the known nuclear receptor targets of SIRT1.

5.1.4.1 Retinoic acid receptors: One type of nuclear receptor targeted by SIRT1 is the retinoic acid receptor (RAR). RAR has three isoforms, RAR-α, RAR-β, and RAR-γ, and all have retinoic acid as a ligand. A recent report demonstrates that SIRT1 directly binds to and deacetylates the β isoform of RAR, which is the predominant isoform in the brain (Donmez *et al*., 2010). The deacetylation of RAR-β increases its transcription of α-secretase, the secretase that is involved in the cleavage of APP to generate soluble APP. Simultaneously, it reduces the production of toxic Aβ (Donmez *et al*., 2010). Thus, it may play a role in reducing the pathogenesis of AD.

5.1.4.2 Liver X receptors: Liver X receptor (LXR) is a group of nuclear receptors with oxysterols as ligands. They are expressed in the brain, and demonstrate protective roles against cerebral ischemia, traumatic brain injury, and amyloid toxicity (Cheng *et al*., 2010; Fitz *et al*., 2010). LXR is acetylated at Lys432, blunting its response to agonists in liver (Li *et al*., 2007d). SIRT1 deacetylates LXR, and SIRT1 knockout increases its acetylation but

reduces the expression of its target genes (Li *et al*., 2007d), suggesting SIRT1 may protect brain via enhancing LXR activity.

5.1.4.3 Peroxisome proliferator-activated receptors: Peroxisome proliferator-activated receptors (PPARs), including PPARα, PPARβ, and PPARγ, are another group of nuclear receptors whose activities are regulated by SIRT1 (Picard *et al*., 2004; Purushotham *et al*., 2009). Activation of PPARα by a two-week treatment of fenofibrate, a PPARα activator, decreases infarct volume in mice via anti-oxidant and anti-inflammatory mechanisms (Deplanque *et al*., 2003). In PPARα-deficient mice, however, the neuroprotection is blocked (Deplanque *et al*., 2003), indicating a beneficial effect of PPARα in brain. In hepatocytes, SIRT1 physically interacts with PPARα at several sites, and this increases the transcriptional activity of PPARα (Deplanque *et al*., 2003).

PPARγ is activated by thiazolidinedione and 15-deoxy-delta 12,14-Prostaglandin J2. When this happens, PPARγ negatively regulates the expression of some inflammatory cytokines and macrophage activation. Accordingly, PPARγ shows protective effects against neuronal injuries in a number of neurological diseases such as stroke, Alzheimer's disease, and traumatic brain injury (Kapadia *et al*., 2008; Luo *et al*., 2006; Shie *et al*., 2009). In adipocytes, SIRT1 suppressed the transactivation of PPARγ by blocking its binding to DNA sequences of target genes (Picard *et al*., 2004). SIRT1 also directly interacts with and deacetylates PPARγ (Han *et al*., 2010), though the influence of deacetylation on the activity of PPARγ is not clear.

Thus far, all the mechanisms we have discussed are related to the transcriptional regulation of sirtuins. This is not an exhaustive list of the capabilities of sirtuins as they also deacetylate other proteins not involved in gene expression, including DNA repair enzymes in the nucleus, protein kinases and phosphatases in cytosol, and mitochondrial proteins.

5.1.5 DNA repair enzymes

5.1.5.1 Base excision repair: DNA damage occurs in daily life and is aggravated following metabolic and oxidative stresses. Accordingly, DNA repair is essential to maintenance of genomic integrity and cellular viability. The severity of DNA damage varies from single base damage to double-stranded DNA breaks. Base excision repair (BER) is the process of repairing single base damage that is predominantly due to oxidative DNA damage (Parsons *et al*., 2004; Srivastava *et al*., 1998). Apurinic/apyrimidinic endonuclease-1 (APE1) is one of the key enzymes in the base excision repair (BER) pathway; its function is to cleave the apurinic/apyrimidinic sites (Parsons *et al*., 2004; Srivastava *et al*., 1998). Our previous studies demonstrate that APE1 contributes to inducible DNA repair after ischemic preconditioning (Li *et al*., 2005) and to the neuroprotective effects of pituitary adenylate cyclase-activating polypeptide (PACAP) (Stetler *et al*., 2010). We also show that NAD^+ treatment protects cultured neurons against ischemic injury via enhancing the BER pathway (Wang *et al*., 2008).

Recent studies show that multiple lysines of APE1 are acetylated in the N-terminus of mammalian APE1, which is associated with decreased enzymatic activity (Fantini *et al*., 2010; Yamamori *et al*., 2010). Correspondingly, overexpression of SIRT1 or resveratrol treatment deacetylates APE1 by increasing its binding to the enzyme and thus increases APE enzyme activity, while knockdown of SIRT1 increases cellular abasic DNA content and sensitizes cells to death after genotoxic and oxidative stresses (Yamamori *et al*., 2010). These results suggest that deacetylation of APE1 to increase DNA repair could be one of the protective mechanisms of SIRT1 in the brain.

5.1.5.2 Nucleotide excision repair: Xeroderma pigmentosum (XP) is a genetic disease with seven subtypes and is characterized by causing skin cancers. The external cause of the carcinogenesis is the exposure to ultraviolet (UV) light, but the intrinsic reason is the deficiency in DNA repair, in particular, the nucleotide excision repair (NER) pathway (Taylor, 2008). The NER pathway recognizes and repairs multiple-base damages, especially thymine dimmers caused by UV exposure. Seven genes are involved in the NER pathway, named xeroderma pigmentosum A to G (XPA to XPG), and mutation in each of the XP genes causes a specific type of xeroderma pigmentosum (Taylor, 2008). Among the seven genes, *XPA* and *XPC* are more frequently mutated than others. In addition to skin cancers, neurodegeneration also occurs in patients with xeroderma pigmentosum, manifested by cognitive and neurological impairments and brain atrophy (Anttinen *et al*., 2008). Overall, this suggests that the NER pathway may play an important role in the well-being of the brain.

Recent studies demonstrate that SIRT1 enhances the function of the NER pathway (Fan and Luo, 2010; Ming *et al*., 2010). For instance, SIRT1 directly interacts with XPA and deacetylates it at Lys63 and Lys67 in HEK293 cells. Deacetylated XPA demonstrates an increased binding affinity to its partner, replication protein A32, and is necessary for optimal DNA repair activity (Fan and Luo, 2010). SIRT1 also upregulates the expression of XPC, which is required for DNA repair after UV exposure in mouse embryonic fibroblasts and keratinocytes. Lastly, loss of SIRT1 leads to DNA repair inhibition and apoptotic cell death (Ming *et al*., 2010). Though the NER pathway may be involved with DNA repair in the brain, its role in providing neuroprotection against neurologic diseases is currently unknown.

5.1.5.3 Single-stranded DNA breaks: SIRT1 has a role in the repair of more severe DNA damage, such as single-stranded DNA breaks. This type of repair requires several enzymes, one of which is poly(ADP-ribose) polymerase 1 (PARP-1) (Woodhouse *et al*., 2008). PARP-1 binds the DNA breaks and transfers ADP-ribose units from the metabolism of NAD^+ to its substrates, a process known as ADP-ribosylation. When overactivated, however, PARP-1 is fatal to host cells due to the severe depletion of NAD^+ and consequent release and translocation of apoptosis-inducing factor (AIF) from mitochondria to the nucleus (Moroni, 2008). In neurons, PARP-1 is highly activated following cerebral ischemia and PD, contributing to neuronal apoptosis, and inhibition of PARP-1 protects brain from neuronal death (Moroni, 2008; Outeiro *et al*., 2007a; Zhang *et al*., 2005). In cardiomyocytes, PARP-1 is acetylated after physical stress, an indicator of increased enzyme activity, and the acetylation is further enhanced in SIRT1 knockout mice (Rajamohan *et al*., 2009). SIRT1 directly binds and deacetylates PARP-1 in a SIRT1 catalytic site-dependent manner, which consequently reduces the enzyme activity of PARP-1 and ultimately promotes cell survival (Kolthur-Seetharam *et al*., 2006; Rajamohan *et al*., 2009). Experiments are currently underway to determine if the SIRT1-PARP-1 interaction plays a role in NAD^+-mediated neuroprotection following excitotoxic insults in neurons.

5.1.5.4 Double-stranded DNA breaks: Ku70 is a 70-kDa nuclear protein involved in the repair of double-strand DNA breaks by binding to the break ends. It also has a distinct anti-apoptotic role, via binding Bax and inhibiting its mitochondrial translocation (Sawada *et al*., 2003). Following cerebral ischemia in mice, levels of Ku70 are decreased as early as 4 hours in the ischemic area and remain low thereafter. This is accompanied by DNA fragmentation and neuronal death (Kim *et al*., 2001). On the other hand, ischemic preconditioning upregulates the expression of Ku70 in the CA1 region of rat hippocampus, indicating that Ku70 plays a protective role against stroke (Sugawara *et al*., 2001). It is reported that SIRT1 deacetylates Ku70 on Lys539 and Lys543 of its C-terminus (Cohen *et al*., 2004), and increases its DNA repair activity after cellular exposure to radiation (Jeong *et al*., 2007).

Nijmegen breakage syndrome protein 1 (NBS1), also known as nabrin or p95, is another protein with a role in the repair of double-strand DNA breaks. It is an early sensor of DNA breaks, and its mutation results in Nijmegen breakage syndrome, a rare autosomal recessive disease in humans characterized by microcephaly, growth retardation, and radiation sensitivity (Varon *et al*., 1998). In HEK293 cells, NBS1 is acetylated at 10 of its 70 lysine residues, leading to decreased activity (Yuan *et al*., 2007). SIRT1 directly interacts with and deacetylates NBS1, increasing its activity, and this increases cell resistance to radiation challenge (Yuan *et al*., 2007), indicating a protective role of SIRT1. Cumulatively, current data suggest that SIRT1 enhances DNA repair activity via several mechanisms, and this may contribute to its neuroprotective effects against neurological diseases.

In addition to SIRT1, SIRT6 also plays a role in the repair of DNA double-strand breaks. Following oxidative stress in human fibroblast cell lines, SIRT6 is recruited to the DNA breaks; it then interact with PARP1 on Lys-521 and enhances PARP1 acitivity of DNA repair (Mao *et al*., 2011). However, it needs further investigated whether these findings apply in brain.

5.2 Cytosolic targets

5.2.1 Protein kinases and phosphatases—Protein activation and inactivation are governed by a number of post-translational modifications. Phosphorylation is a predominant means for mediating a protein's activity status, and this is balanced by protein kinases that phosphorylate a protein and phosphatases that remove the phosphate. In addition to themselves being regulated by phosphorylation, kinases and phosphatases can also be regulated by acetylation and deacetylation.

One example is serine/threonine kinase 11 (STK11 or LKB1), the primary kinase that phosphorylates and activates AMP-activated protein kinase (AMPK) (Lan *et al*., 2008; Shaw *et al*., 2004; Zu *et al*., 2010). LKB1 is known to be acetylated at Lys48 in HEK293 cells, which decreases its enzymatic activity (Lan *et al*., 2008). Recent studies show that LKB1 physically binds to SIRT1, resulting in deacetylation (Lan *et al*., 2008; Wang *et al*., 2011; Zu *et al*., 2010). The effects of LKB1 deacetylation, however, are variable in different cell types. In porcine endothelial cells, deacetylation of LKB1 stimulates its proteasomal degradation and reduces phosphorylation of AMPK and endothelial senescence (Zu *et al*., 2010). In most cases, however, SIRT1-mediated deacetylation enhances the activity of LKB1. For instance, SIRT1 increases the activity of LKB1 in HEK293 cells, rat hepatocytes, and mouse neurons (Lan *et al*., 2008; Wang *et al*., 2011). This notion is further supported by a study showing that resveratrol stimulates AMPK activity in neurons (Dasgupta and Milbrandt, 2007). Furthermore, the overexpression of NAMPT, the rate-limiting enzyme of the NAD^+ salvage pathway, increases SIRT1 activity and LKB1 deacetylation in mouse brain, which is related to a 2-3-fold amplification of AMPK activity (Wang *et al*., 2011). Following stroke, NAMPT transgenic mice develop a smaller infarct volume compared with wild-type mice. The protective effects disappear when SIRT1 or AMPK is knocked out (Wang *et al*., 2011), indicating a neuroprotective role of LKB1 deacetylation by SIRT1. It should be noted that the role of AMPK is controversial. As discussed here, AMPK is necessary for the protective effect of the MAMPT/LKB1 pathway against stroke (Wang *et al*., 2011); however, a previous study showed that AMPK activation was detrimental to the brain following cerebral ischemia (Li *et al*., 2007b).

Another example is the phosphatase and tensin homologue deleted in chromosome 10 (PTEN). This phosphatase primarily targets phosphatidylinositol (3,4,5)-trisphosphate (PIP3), therefore inhibiting the neuroprotective Akt signaling pathway. Multiple lysines of PTEN are acetylated by histone acetyltransferases, including Lys125 and Lys128 in its catalytic motif (Okumura *et al*., 2006). The acetylation at the catalytic motif inhibits the

enzymatic activity of PTEN (Okumura *et al*., 2006). Acetylation also occurs at Lys402 at the PDZ domain of PTEN, enhancing its binding ability to PDZ domains of other proteins; however, it is unclear how the acetylation affects the activity of PTEN (Ikenoue *et al*., 2008). SIRT1 is reported to deacetylate PTEN at Lys402 and hinder the interaction of PTEN with its binding partners (Ikenoue *et al*., 2008). Similarly in mouse embryonic stem cells, SIRT1 deficiency leads to increased levels of acetylated PTEN, which is associated with apoptosis in response to oxidative stress (Chae and Broxmeyer, 2011). However, it has not been determined whether SIRT1 can also deacetylate PTEN in neurons, and if this action will be neuroprotective.

5.2.2 Endothelial nitric oxide synthase—Endothelial nitric oxide synthase (eNOS) plays an important role in the generation of endothelial nitric oxide (NO) and vasodilatation. In the brain, the activity of eNOS is uncoupled following subarachnoid hemorrhage (Sabri *et al*., 2011), and knockout or inhibition of eNOS exacerbates ischemic brain damage in mice (Atochin *et al*., 2007; Huang *et al*., 1996), indicating a protective role of eNOS. The activity of eNOS can be augmented by SIRT1 (Mattagajasingh *et al*., 2007). In endothelial cells, SIRT1 coprecipitates with and deacetylates eNOS at Lys496 and 506, and this stimulates eNOS activity and NO production, leading to vasodilatation (Mattagajasingh *et al*., 2007). It is also reported that the SIRT1 activator resveratrol reduces infarct volume in rat via an eNOS-dependent mechanism (Tsai *et al*., 2007). Therefore, it is likely that SIRT1 protects against ischemic and hemorrhagic strokes via eNOS-mediated blood flow improvement.

5.2.3 Tau protein—Tau is a microtubule-binding protein enriched in neurons, and it promotes the assembly of microtubules and then stabilizes them (Kar *et al*., 2003). These tau-related functions are compromised when tau is phosphorylated, leading to disruption of the microtubule structure. The accumulation of hyperphosphorylated tau in neurons is a hallmark of neurodegenerative tauopathies, especially in AD (Ittner and Götz, 2011; Min *et al*., 2010). It has been reported that tau is acetylated at multiple lysine residues and that SIRT1 is able to regulate the level of phosphorylated tau via deacetylation (Min *et al*., 2010). In supportive of this notion, SIRT1 directly interacts with tau and a deficiency in SIRT1 elevates both acetylated-tau and phosphorylated-tau *in vivo*. Moreover, inhibition of SIRT1 activity blocks tau polyubiquitination and thus the turnover of tau, resulting in accumulation of phosphorylated-tau in neurons (Min *et al*., 2010).

The results cited in the previous three sections indicate that, in addition to functioning in the nucleus, SIRT1 also functions in the cytosol (Figure 5), which is consistent with previous reports that SIRT1 has a cytosolic signaling sequence (Jin *et al*., 2007; Tanno *et al*., 2007).

5.3 Mitochondrial targets

Mitochondria are not only the powerhouse for ATP production but also the main sites where ROS are generated and the intrinsic apoptotic signaling pathway is initiated (Niizuma *et al*., 2010; Zhang *et al*., 2004). The functions of mitochondrial proteins are altered when they are deacetylated by NAD^+-dependent mitochondrial deacetylases, including SIRT3, SIRT4, and SIRT5. All mitochondrial sirtuins are present in the mitochondrial matrix, but SIRT5 also appears in the intermembrane space (Nakamura *et al*., 2008; Schlicker *et al*., 2008). Since mitochondria contain their own DNA, transcription factors, histone-like proteins, and protein synthesis systems, mitochondrial sirtuins deacetlyate a set of targets within the mitochondria that are distinctive from nuclear proteins (Garrido *et al*., 2003; Katherine *et al*., 2010; Kutsyi *et al*., 2005). Although the precise mechanistic information is still lacking, evidence is emerging to suggest that mitochondrial sirtuins are protective against oxidative stress and excitotoxic injury (Fritz *et al*., 2011; Kim *et al*., 2011). The sections described below summarize the earlier studies that examined the role of mitochondrial sirtuins in

energy metabolism, protection against oxidative stress or excitotoxicity, apoptosis, and mitochondrial protein synthesis.

5.3.1 Energy metabolism

5.3.1.1 Fuel switch: Glucose is the major energy source for cells. When its availability is limited, however, alternative fuels become increasingly important for cell survival. The first step of glycolysis is the conversion of glucose to glucose-6-phosphate, a reaction catalyzed by hexokinases. In tumor cells, hexokinase II is attached to the mitochondrial outer membrane, leading to increased ATP access and enzymatic activity (Mathupala *et al*., 2009). When glucose is replaced by galactose in culture medium, hexokinase II disassociates from the mitochondria in tumor cells, causing decreased activity toward glucose. Alternatively, the cells consume galactose (Shulga *et al*., 2010). It is reported that SIRT3 deacetylates cyclophilin D (Hafner *et al*., 2010; Shulga *et al*., 2010), which leads to the dissociation of hexokinase II and mitochondria, decreases glucose metabolism, and stimulates oxidative phosphorylation (Shulga *et al*., 2010).

At the mitochondrial level, the main energy source is pyruvate, a product of glycolysis. Alternatively, mitochondria also burn fatty acids, amino acids, and acetates when there is a deficiency in pyruvate. In the case of fatty acid catabolism, long-chain acyl coenzyme A dehydrogenase (LCAD) is a key enzyme that breaks down fatty acids and generates acetyl-CoA, stimulating β-oxidation. In SIRT3 knockout mice, LCAD is hyperacetylated at Lys42, leading to decreases in enzymatic activity, β-oxidation, and ATP level (Hirschey *et al*., 2010). Interestingly, these mice do not tolerate cold exposure during fasting (Hirschey *et al*., 2010). SIRT3 directly deacetylates LACD at Lys42 and increases LACD activity (Hirschey *et al*., 2010). In addition, SIRT3 may promote β-oxidation via multiple mechanisms, such as by deacetylating other β-oxidation enzymes, including the short-chain L-3-hydroxyacyl-CoA dehydrogenase and the very-long-chain acyl coenzyme A dehydrogenase (Hallows *et al*., 2011), facilitating mitochondrial adaptation to fuel changes.

Amino acids can also be used as fuels. Glutamate dehydrogenase (GDH) is a key enzyme for amino acid catabolism as it converts glutamate to α-ketoglutarate, and α-ketoglutarate can directly enter the Krebs cycle. SIRT3 interacts with and deacetylates GDH in mice, and might increase its activity (Cimen *et al*., 2009; Lombard *et al*., 2007; Schlicker *et al*., 2008). On the other hand, SIRT4 suppresses GDH via ADP-ribosylation in pancreatic β-cells (Haigis *et al*., 2006). A by-product of amino acid breakdown is ammonia, which is toxic to mammals as an elevated ammonia level causes neurologic disorders due to encephalopathy and coma. Therefore, ammonia is largely converted to urea through the five-step urea cycle. Carbamoyl phosphate synthetase 1 (CPS1) catalyzes the rate-limiting and first step of the urea cycle. In SIRT5 knockout mice, blood ammonia level is increased due to the decreased activity of carbamoyl phosphate synthetase 1 (Nakagawa *et al*., 2009). SIRT5 deacetylates this enzyme and increases its activity during calorie restriction (Nakagawa *et al*., 2009; Ogura *et al*., 2010). Ornithine transcarbamylase (OTC) catalyzes the second reaction of the urea cycle. A recent study showed that Sirt3 directly deacetylates this enzyme and stimulates its activity (Hallows *et al*., 2011). Collectively, these results suggest that SIRT3 and SIRT5 may play a protective role by promoting amino acid catabolism and converting ammonia to non-toxic urea.

Derived from acetic acid and alcohol, acetate is also used as a mitochondrial fuel, though this only occurs in extreme circumstances of nutrient depletion. The initial step is for conversion of acetate to acetyl-CoA catalyzed by acetyl-CoA synthetases. Acetyl-CoA synthetase 2 is the mitochondrial form of the enzyme. Its enzymatic activity is inhibited when it is acetylated at Lys661 in mouse or Lys642 in human (Hallows *et al*., 2006; Schwer

et al., 2006). SIRT3 deacetylates acetyl-CoA synthetase 2 and enhances its activity, leading to increased production of acetyl-CoA (Hallows *et al*., 2006; Schwer *et al*., 2006).

5.3.1.2 Krebs cycle: As discussed above, the acetyl-CoA from fatty acids and acetates can enter the Krebs cycle, and α-ketoglutarate from amino acids can also promote the Krebs cycle. These two reactions are enhanced by SIRT3 (Hallows *et al*., 2006; Lombard *et al*., 2007; Schlicker *et al*., 2008; Schwer *et al*., 2006).

Additionally, SIRT3 directly stimulates the Krebs cycle. The third step of the cycle is the conversion of 6-carbon isocitrate to 5-carbon α-ketoglutarate, a process catalyzed by isocitrate dehydrogenase 2 (IDH2). A recent study shows that SIRT3 directly deacetylates this dehydrogenase to increase its activity (Someya *et al*., 2010).

5.3.1.3. Electron transport and ATP synthesis: NADH dehydrogenase 1 alpha subcomplex subunit 9 (NDUFA9) is an enzyme of mitochondrial complex I which is acetylated at Lys370 (Kim *et al*., 2006). SIRT3 physically interacts with NDUFA9 and deacetylates it. SIRT3 knockout enhances its acetylation and reduces the activity of complex I (Ahn *et al*., 2008), indicating that SIRT3 is a positive regulator of complex I.

Complex II, also known as succinate dehydrogenase, is composed of four subunits, including the flavoprotein succinate dehydrogenase subunit A (SdhA). In SIRT3 knockout mice, SdhA is hyperacetylated at several lysine residues, and shows decreased activity of complex II (Cimen *et al*., 2009). SIRT3 overexpression reverses the acetylation of SdhA and increases complex II activity (Cimen *et al*., 2009), indicating that SdhA is a SIRT3 substrate, and that SIRT3 is also a positive regulator of complex II.

It is not clear whether mitochondrial sirtuins are able to affect the activities of complex III and complex IV, though it is reported that SIRT5 deacetylates cytochrome *c* (Yang *et al*., 2007a), a protein involved in electron-transfer in both complex III and IV. SIRT3 is also reported to bind the alpha subunit 1 of the F1 particle of ATP synthase (Law *et al*., 2009), but the function is unclear. Taken together, these results suggest that SIRT3 promotes ATP generation through enhancing several enzymes in energy metabolism. In further support of the role of SIRT3 in energy metabolism, SIRT3-knockout mice demonstrate substantial acetylation of mitochondrial proteins, and have reductions in ATP levels at baseline and during cellular stress (Ahn *et al*., 2008). Taken together, those findings suggest that the mitochondrial sirtuins play a role in adjusting energy metabolism when energy sources are changed.

5.3.2 Anti-oxidative proteins—Mitochondria are the major sites for the generation of the reactive oxygen species superoxide. It is also the site where the superoxide is dismuted by mitochondrial SOD, also known as SOD II or MnSOD. Recent reports show that SIRT3 deacetylates MnSOD at Lys122 and increases its activity, reducing oxidative and radiation stress in mice (Qiu *et al*., 2010; Tao *et al*., 2010). SIRT3 is also protective against cardiac hypertrophy via an anti-oxidative mechanism as overexpression of Sirt3 increases MnSOD level, reduces cellular ROS, and blocks cardiac hypertrophy (Sundaresan *et al*., 2009). In the citric acid cycle, the third step is the conversion of the 6-carbon isocitrate to 5-carbon α-ketoglutarate, with simultaneous reduction of NAD^+ to NADH, and this process is catalyzed by isocitrate dehydrogenase 2. A recent study demonstrates that SIRT3 directly deacetylates this dehydrogenase and increases its activity (Someya *et al*., 2010). In addition to stimulation of ATP production, the deacetylation of this enzyme also increases the levels of reduced glutathione, and overexpression of SIRT3 protects HEK293 from oxidative stress and prevents age-related cochlear cell death in mice (Someya *et al*., 2010). Overall, this suggests anti-oxidative and neuroprotective roles of SIRT3.

5.3.3 Pro-apoptotic proteins—The mitochondrial apoptotic pathway, or intrinsic cell death pathway, plays a key role in neuronal death after cerebral ischemia and neurodegenerative disease (Azarashvili *et al*., 2010; Zhang *et al*., 2004). The cascade is initiated by the release of pro-apoptotic proteins from mitochondria (Azarashvili *et al*., 2010; Kinnally and Antonsson, 2007), with cytochrome *c* release playing a central role in the mitochondrial apoptotic pathway. SIRT5 is found in the intermembrane space (Nakamura *et al*., 2008; Schlicker *et al*., 2008), where it co-localizes with cytochrome *c* (Schlicker *et al*., 2008). An *in vitro* experiment demonstrates that SIRT5 also deacetylates cytochrome *c* (Schlicker *et al*., 2008). However, it is not clear how this reaction affects the release and pro-apoptotic activity of cytochrome *c*.

The mitochondrial permeability transition pore (mPTP) is composed of several proteins, including cyclophilin D and adenine nucleotide translocase (ANT). When open, the mPTP causes the leak of mitochondrial components, which is a key mechanism underlying neuronal death after excitotoxicity and stroke (Kinnally and Antonsson, 2007; Lemasters *et al*., 2009). Both cyclophilin D and ANT are acetylated and deacetylated. For example, cyclophilin D is acetylated in HeLa cells (Shulga *et al*., 2010), in HEK293 cells, and in mouse cardiomyocytes (Hafner *et al*., 2010). In the heart, Lys166 of cyclophilin D is acetylated, and SIRT3 deacetylates it to increase cell survival after cardiac stress (Hafner *et al*., 2010). ANT, another component of mPTP, co-immunoprecipitates with SIRT4 in pancreatic beta-cells (Ahuja *et al*., 2007), but its role in apoptotic regulation is not clear. Another study demonstrates that SIRT3 also deacetylates Ku70 outside the mitochondria of cardiomyocytes, which increases the binding ability of Ku70 to Bax, thus inhibiting Bax translocation to mitochondria (Sundaresan *et al*., 2008).

Under certain conditions, SIRT3 can be pro-apoptotic. In human epithelial tumor cells, SIRT3 is required to induce apoptosis by Bcl-2 silencing (Allison and Milner, 2007); however, SIRT3 is not necessary for cell death of normal human epithelial cells, nor is it needed for stress-induced apoptosis (Allison and Milner, 2007).

5.3.4 Protein synthesis—The mitochondrial genome encodes 13 proteins involved in the electron transport chain and ATP synthesis, and these proteins are synthesized by mitochondrial ribosomes (Jacobs and Turnbull, 2005). Mitochondrial ribosomal protein L10 (MRPL10) is a component of mitochondrial ribosomes (Yang *et al*., 2010). A recent study reports that MRPL10 is acetylated at several lysine residues, including Lys162 and Lys196, and is accompanied by increased protein synthesis. The increase in protein synthesis is further enhanced in SIRT3 knockout mice (Yang *et al*., 2010). Accordingly, SIRT3 deacetylates MRPL10, and further inhibits ribosomal function and mitochondrial protein synthesis (Yang *et al*., 2010).

Mitochondrial sirtuins are cytoprotective in non-neural cells; in contrast, their role in brain is less clear. However, emerging evidence suggests that SIRT3 may be cytoprotective in neural cells as well (Kim *et al*., 2011). In the study by Kim et al (2011), it was demonstrated that overexpression of SIRT3 protects against NMDA-induced neuronal death in mouse cortical neuron cultures whereas knockdown of SIRT3 expression exacerbates neuronal death. Nonetheless, further investigations are needed to determine the functional role of various mitochondrial sirtuins in the central nervous system

6. Conclusions and future perspectives

Over the last decade, our understanding of the biology of sirtuins has undergone vast expansion from its original description as a NAD^+-dependent class III histone deacetylase that can control the life span of yeast. Of particular interest is the discovery that SIRT1

deacetylates not only histones, but also some well-known transcriptional regulators, thereby modulating a wide array of biological processes. An exciting aspect is that SIRT1 mediates neuroprotection against both acute and chronic neurological diseases. Importantly, SIRT1 activity is enhanced by small-molecule compounds; therefore, development of small-molecule activators could lead to novel therapies against neurological diseases. One of the broad protective mechanisms of sirtuins is to suppress genome-wide gene transcription via histone deacetylation. Furthermore, SIRT1 selectively suppresses genes involved in fat storage, apoptosis, and inflammation. Adding to the complexity of SIRT1-mediated cell survival, SIRT1 specifically promotes the transcription of a set of genes related to cell survival, energy metabolism, and mitochondrial biogenesis. Sirtuins thus have multifaceted mechanisms with the end goal to increase cell viability.

Although extensively studied, the biological functions of SIRT1 and other sirtuins remain only partially characterized. The new frontiers of sirtuin study will include their role in autophagy (Kume *et al*., 2010; Madeo *et al*., 2010), neurogenesis (Ichi *et al*., 2011; Prozorovski *et al*., 2008), and angiogenesis (Lim *et al*., 2010; Zhao *et al*., 2010). In terms of mechanism, there are several substantial unknowns. For example, it is not known how SIRT1 specifically increases transcription of beneficial genes while it simultaneously suppresses universal transcription. It is known that when protein synthesis is inhibited globally, select chaperone proteins such as heat shock proteins are translated either via the use of internal ribosome entry sequences (IRESs) (Jackson, 2005) or by a shunting mechanism (Yueh and Schneider, 2000). It is worthy of investigation to determine whether similar mechanisms exist for genes upregulated by SIRT1-mediated activation of transcription. Another issue is the paradoxical effects of SIRT1 on PPARγ. For example, SIRT1 directly suppresses PPARγ transcriptional activity (Picard *et al*., 2004), but SIRT1 also activates PGC-1α (Nemoto *et al*., 2005; Rodgers *et al*., 2005), which could increase the transcriptional activities of PPARγ (Puigserver *et al*., 1998).

Our current knowledge is even more deficient with regard to the other sirtuins. Like SIRT1, SIRT6 and SIRT7 are nuclear sirtuins, but their molecular targets, biological functions, and possible roles in neuroprotection are largely unknown. In regard to mitochondrial sirtuins, little is known about SIRT4 and SIRT5. Further investigation into the targets and functions of these sirtuins will help develop new strategies for protection against and recovery from common neurological diseases.

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Abbreviations

4-HNE	4-Hydroxynonenal
Aβ	beta-amyloid
AD	Alzheimer’s disease
ADPR	ADP-ribose
ALS	amyotrophic lateral sclerosis
AMPK	AMP-activated protein kinase

APE1	apurinic/apyrimidinic endonuclease-1
APP	amyloid precursor protein
AROS	active regulator of SIRT1
Bax	Bcl-2 associated X protein
BDNF	brain-derived neurotrophic factor
CREB	cAMP response binding protein
DBC1	deleted in breast cancer 1
CHK1	cycle checkpoint kinase 1
CK2	casein kinase II
DYRK	dual specificity tyrosine phosphorylation-regulated kinase
E2F1	E2F transcription factor 1
eNOS	endothelial nitric oxide synthase
FOXO	forkhead box protein O
HD	Huntington's disease
HIC1	hypermethylated in cancer 1
HuR	Hu family of RNA-binding proteins
IRES	internal ribosomal entry sequence
JNK1	c-jun N-terminal kinase 1
LXR	liver X receptor
miR	microRNA
MST1	mammalian sterile 20-like kinase 1
MRPL10	mitochondrial ribosomal protein L10
NAD^+	nicotinamide adenine dinucleotide
NADH	NAD^+ reduced
NDUFA9	NADH dehydrogenase 1 alpha subcomplex subunit 9
NAMPT	nicotinamide phosphoribosyltransferase
NBS1	Nijmegen breakage syndrome protein 1
NF-κB	nuclear factor κ-light-chain-enhancer of activated B cells
NMNAT-1	nicotinamide mononucleotide adenylyltransferase 1
NO	nitric oxide
Nrf2	nuclear factor (erythroid-derived 2)-like 2
OA-ADPR	2′-O-acetyl-ADP ribose
PARP-1	poly(ADP-ribose)polymerase 1
PD	Parkinson's disease
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator-1α
PPARs	peroxisome proliferator-activated receptors

PTEN	phosphatase and tensin homologue deleted in chromosome 10
RAR	retinoic acid receptor
ROS	reactive oxygen species
SdhA	succinate dehydrogenase subunit A
sir2	silent information regulator 2
SIRT	sirtuin
sirtuins	silent information regulator 2 proteins
SODs	superoxide dismutases
SUMO	small ubiquitin-like modifier
Wlds	Wallerian degeneration slow
XP	xeroderma pigmentosum

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Article highlights

- Sirtuins are NAD^+-dependent histone deacetylases
- SIRT1 is the best characterized sirtuin expressed in neurons
- SIRT1 is protective against acute and chronic neurological diseases
- Deacetylation on histone and non-histone targets contributes to the protective effects of SIRT1
- The activity of SIRT1 is adjustable, making it a neuroprotective target.

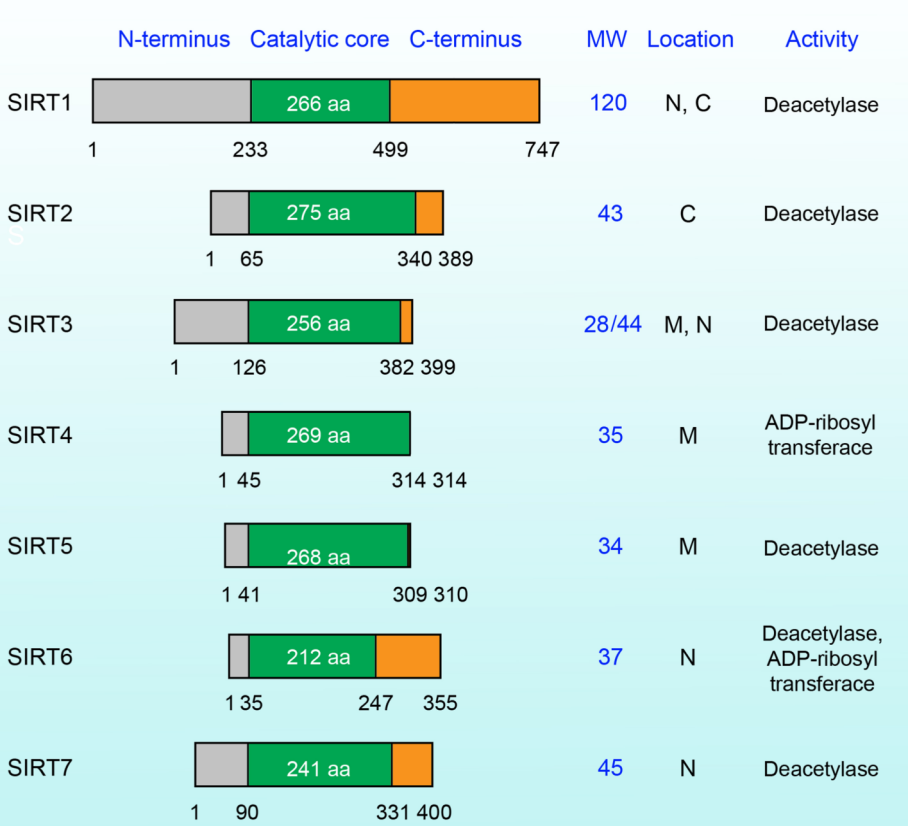

Figure 1. Molecular comparison of SIRT1 to SIRT7

The SIRT family consists of 7 proteins that all have a conserved catalytic core domain. This diagram illustrates the protein domains in relation to the catalytic core domain along with the molecular weights, cellular localizations, and enzymatic activities of the seven human sirtuins. Molecular weights are in kDa. SIRT3 has two isoforms; the long form is 44 kDa and a short truncated form without the N-terminus is 28 kDa. ADP, adenosine diphosphate; C, cytosol; M, mitochondrial; N, nucleus.

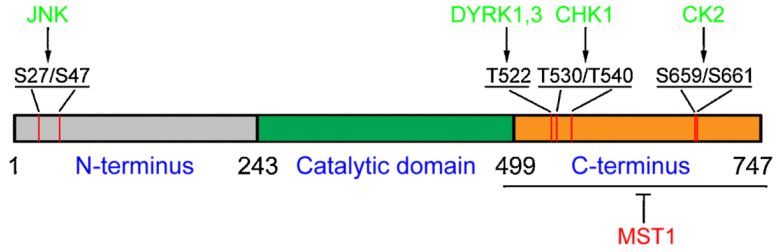

Figure 2. Regulation of SIRT1 activity via phosphorylation

The activity of SIRT1 is regulated by several post-translational modifications, including phosphorylation. Here we provide a diagram illustrating the phosphorylation sites of SIRT1 by several protein kinases. Kinases depicted in green increase the enzymatic activity of SIRT1 upon phosphorylation. The kinase depicted in red, MST1, inhibits SIRT1 activity. CHK1, checkpoint kinase 1; CK2, casein kinase II; DYRK1/3, dual specificity tyrosine phosphorylation-regulated kinase 1/3; JNK, c-jun N-terminal kinase 1; S, serine; T, threonine.

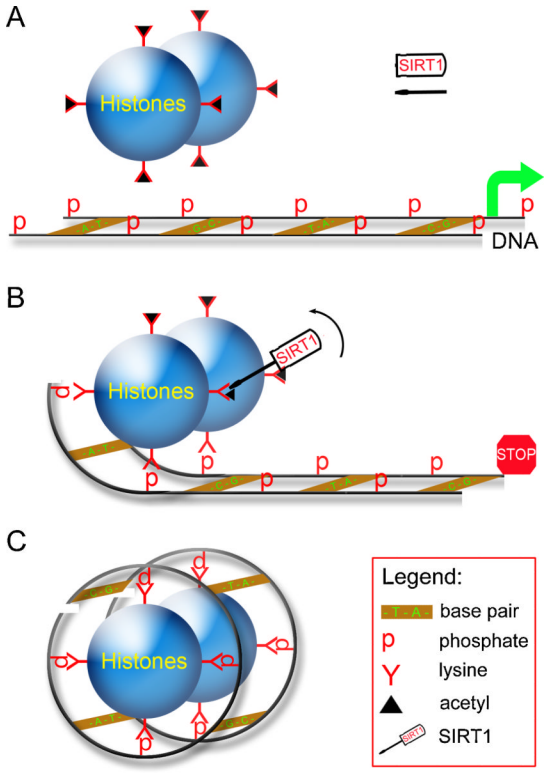

Figure 3. SIRT1 globally silences gene transcription by deacetylating histones

(a) When SIRT1 is not active, the histones are acetylated and unable to bind DNA, thus facilitating gene transcription. (b) Once activated, SIRT1 deacetylates histones, giving them a net positive charge. Histones are then free to bind DNA at phosphate moieties and interfere with gene transcription. (c) Once histones have fully gained their positive charge upon complete deacetylation of histone lysines, DNA winds around the histones, making gene transcription unavailable and leading to genome-wide gene silencing.

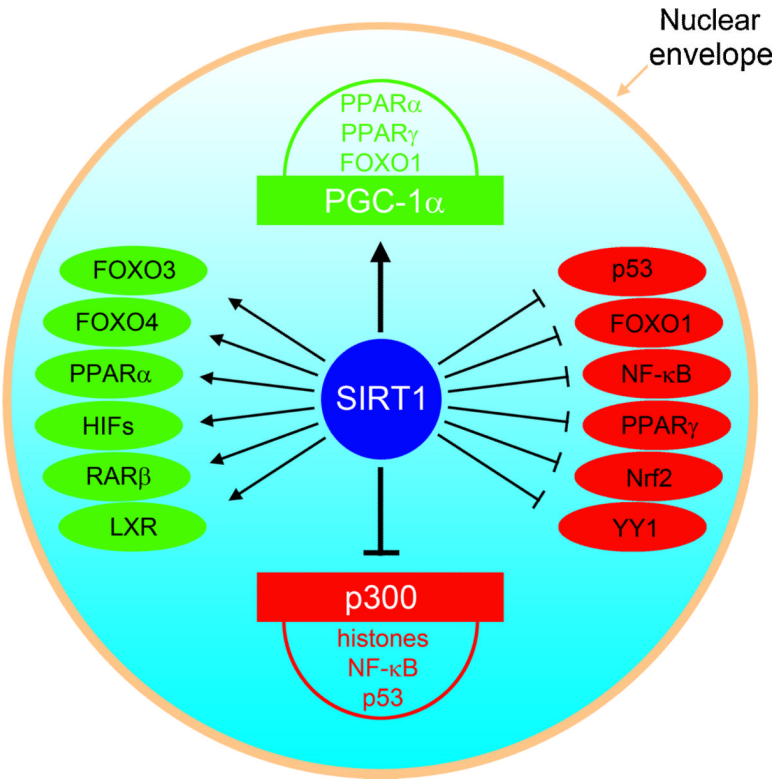

Figure 4. SIRT1 regulates gene transcriptions at a subgenomic level

SIRT1 deacetylates two transcriptional coactivators, PGC-1α and p300, and more than a dozen transcription factors. By deacetylating and stimulating PGC-1α, SIRT1 promotes the transcriptional activity of FOXO1, PPARα, and PPARγ. By deacetylating and inhibiting p300, SIRT1 reduces the transcriptional activity of p53 and NF-κB. SIRT1 also increases the deacetylation of histones via p300. In addition, SIRT1 directly increases transcriptional activity of FOXO3, FOXO4, PPARα, HIF1, RARβ and LXR via deacetylation; and it decreases transcriptional activity of p53, NF-κB, FOXO1, YY1, Nrf2 and PPARγ. Transcriptional coactivators and transcription factors depicted in green are activated by SIRT1, while those depicted in red are inhibited by SIRT1.

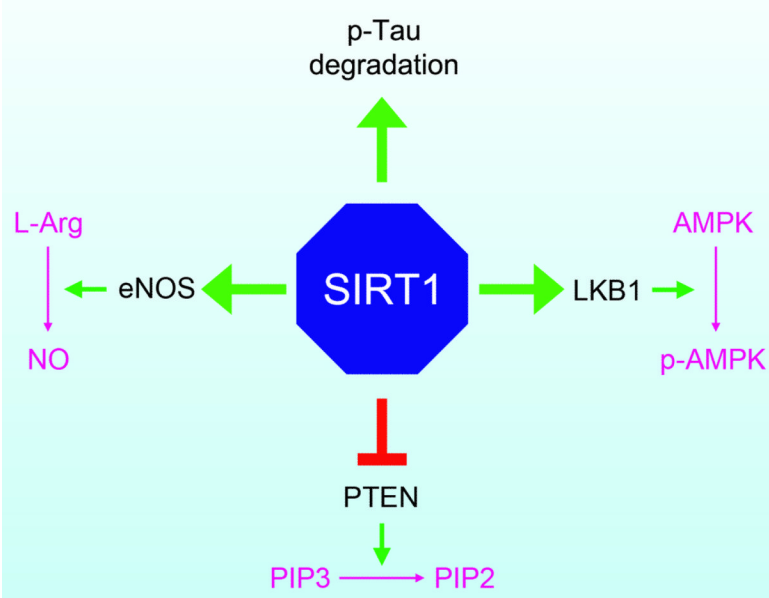

Figure 5. Cytosolic targets of SIRT1

In addition to its numerous actions in the nucleus, SIRT1 also has some newly discovered cytosolic targets. SIRT1 deacetylates and activates LKB1, leading to increased AMPK activity and attenuating ischemic brain injury. SIRT1 activity can also inhibit enzyme activity. Deacetylation of PTEN by SIRT1 inhibits the phosphatase's ability to bind and dephosphorylate PIP3, and results in unhindered activity of the neuroprotective PI3K/Akt signaling pathway. Deacetylation of eNOS stimulates the production of NO, a potent vasodilator. Putatively, this improves cerebral perfusion following ischemic stroke or subarachnoid hemorrhage. Finally, SIRT1 also deacetylates phosphorylated tau, facilitating its degradation and reducing neuronal death in models of Alzheimer's disease.

Table 1

Regulation of SIRT1 levels via transcription and post-transcriptional modification

Levels	Regulators	Roles	Results	References
Transcription	E2F2	TF	↑	Wang, 2006
	FOXO1	TF	↑	Xiong, 2011
	FOXO3	TF	↑	Nemoto, 2004
	TLX	NR	↑	Iwahara, 2009
	HIC1	TF	↓	Chen, 2005c
	p53	TF	↓	Nemoto, 2004
	PPARγ	NR	↓	Han, 2010
Post-transcription	HuR	RNA-binding proteins	↑	Brennan, 2001; Abdelmohsen, 2007
	miR-9	MicroRNA	↓	Saunders, 2010
	miR-34a	MicroRNA	↓	Yamakuchi, 2008; Lee, 2010
	miR-132	MicroRNA	↓	Strum, 2009
	miR-199a	MicroRNA	↓	Rane, 2009
	miR-217	MicroRNA	↓	Menghini, 2009

Abbreviations: NR, nuclear receptor; TF, transcription factor.

Table 2

Regulators of SIRT1 activity

Routes	Regulators	Results	Mechanisms	References
Protein-protein interaction	AROS	↑	Binds and enhances deacetylating activity to p53	Kim, 2007b
	DBC-1	↓	Interacts with leucine zipper motif and the catalytic domain	Kim, 2008; Zhao, 2008
Post-translational modification	Sumo	↑	Sumoylation of Lys734	Yang, 2007b
	JNK1	↑	Phosphorylation of Ser27 and Ser47	Beausoleil, 2004
	DYRK1,3	↑	Phosphorylation of Thr522	Guo, 2010
	CHK1	↑	Phosphorylation of Thr530 and Thr540	Sasaki, 2008
	CK2	↑	Phosphorylation of Ser659 and Ser661	Zschoernig, 2009
	MST1	↓	Phosphorylation of C-terminus	Yuan, 2011
Pharmacological	Resveratrol	↑	Unclear	Howitz, 2003; Wood, 2004
	Quercetin	↑	Unclear	de Boer, 2006
	Sirtinol	↓	Interferes with body axis formation	Grozinger, 2001
	Splitomicin	↓	Inhibits the access of the acetylated lysines with SIER1	Bedalov, 2001
Oxidative	4-HNE, acrolein	↓	Reacts with Cys467 and Cys692	Caito, 2010
Metabolic	NAD+	↑	Substrate of sirtuins	Vaziri, 2001; Araki, 2004
	Nicotinamide	↓	Switches between deacetylation and base exchange	Sauve, 2001; Jackson, 2003
	ADP-ribose	↓	Unclear	Zhao, 2004

Table 3

Sirtuins and neurodegenerative diseases

Disease	Experimental settings	Result	Mechanism	References
Ischemia	Res in rat global	+	Increased SIRT1 activity; decrease UCP2	Raval, 2006; Della-Morte, 2009
	Res, sirtinol and SIRT1 OE in NO exposure	+	Increased SIRT1 activity;	Chong, 2008
	SIRT1 KO in mouse focal	+	Nampt stimulates SIRT1, SIRT1 deacetylates LKB1, LKB activates AMPK	Wang, 2011
	SIRT1 Tg in mouse focal	+/−	SIRT1 overexpression	Kakefuda, 2009
	Focal in rat and mouse	+	SIRT1 mediates protection of leptin, icariin and tetrahydroxystilbene glucoside	Wang, 2009a; Wang, 2009c; Avraham, 2010; Zhu, 2010
WD	Axonal injury in Wlds mice	+	NMNAT increases NAD^+ and activates SIRT1	Araki , 2004; Sasaki, 2009; Babetto, 2010
Retinal injury	Res in antibody-induced apotosis	+	Upreguates SIRT1 expression	Anekonda, 2008
	SIRT1 KO mice	+?	Reduced retinal cell numbers	Cheng, 2003
AD	SIRT1 KO enhances tau acetyaltion and tauopathy	+?	SIRT1 deacetylates tau and promotes tau degradation	Min, 2010
	CR in mice increases SIRT1 and reduces Aβ neuropathy	+	SIRT1 inhibits ROCK1 and activates α-secrease	Qin, 2006b
	SIRT1 OE suppress Aβ production in mice	+	SIRT1 stimulate RAR and upregulates α-secrease	Donmez, 2010
PD	SIRT1 OE in neuron after mutant α-synuclein transfection	+	SIRT1 activates PGC-1 and increases mitochondrial density	Wareski, 2009
	Res in mice or SK-N-BE cells	+	Res stimulates SIRT1	Albani, 2009; Chao, 2008
	Res in midbrain slice	+	SIRT1 deacetylates p53	Okawara, 2007
	MPTP-induced PD model in SIRT1 tg mice	+/−		Kakefuda, 2009
	SIRT2 inhibition in Drosophila model of PD	−		Outeiro, 2007
HD	Res or SIRT1 OE in neurons after mutant huntingtin transfection	+	SIRT1 activates PGC-1 and increases mitochondrial density	Parker, 2005; Wareski, 2009
	Res in HD mice	+/−		Ho, 2010
	Sir2 inhibition in Drosophila or striatal neuronal models of HD	−	SIRT2 inhibition decreases sterol biosynthesis	Pallos, 2008; Luthi-Carter, 2010
Prion disease	Res or SIRT1 OE in neurons infected with mutant prion	+		Bizat, 2010; Seo, 2011
ALS	Res or SIRT1 OE in a mouse model of ALS	+	SIRT1 deacetylates p53	Kim, 2007; Markert, 2010
MS	SIRT1 activation in a mouse model of MS	+		Shindler, 2007; Shindler, 2010

Signs abbreviation used in the table: +, protective; −, detrimental; +/−, neither protective nor detrimental; Aβ, beta amyloid; ALS, amyotrophic lateral sclerosis; CR, calorie restriction; Drosophila nicotinamidase (DN); KO, knockout; MCAO, middle cerebral artery occlusion; MS, multiple sclerosis; NO, nitric oxide; OE, overexpression; OGD, oxygen-glucose deprivation; Res, resveratrol; ROCK1, Rho-associated, coiled-coil containing protein kinase 1; Tg, transgenic; UCP2, uncoupling protein 2; WD, Wallerrian degeneration.