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SIRT1 in neurodevelopment and brain senescence

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Abstract

Sirtuins are nicotinamide adenine dinucleotide (NAD⁺)-dependent deacetylases that have traditionally been linked with calorie restriction and aging in mammals. These proteins also play an important role in maintaining neuronal health during aging. During neuronal development, the SIR2 ortholog SIRT1 is structurally important, promoting axonal elongation, neurite outgrowth and dendritic branching. This sirtuin also plays a role in memory formation by modulating synaptic plasticity. Hypothalamic functions that affect feeding behavior, endocrine function and circadian rhythmicity are all regulated by SIRT1. Finally, SIRT1 plays protective roles in several neurodegenerative diseases including Alzheimer's, Parkinson's and motor neuron diseases, which may relate to its functions in metabolism, stress resistance and genomic stability. Drugs that activate SIRT1 may offer a promising approach to treat these disorders.

Keywords

sirtuin; histone deacetylase; aging; cognitive function; neurodevelopment; neurodegeneration; Alzheimer's disease; Parkinson's disease; Huntington's disease; motor neuron disease; multiple sclerosis

Introduction

The mammalian sirtuins are deacetylase proteins that have been shown to regulate diverse cellular processes including aging, inflammation and stress resistance (Brunet et al., 2004; Imai et al., 2000; Kaerberlein et al., 1999; Kim et al., 1999; North and Verdin, 2004). These enzymes were originally identified as genetic silencing factors in yeast (Klar et al., 1979; Rine et al., 1979) and can act on histones and other substrates in the presence of

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nicotinamide adenine dinucleotide (NAD⁺) (Imai et al., 2000; Massudi et al., 2012; Yoshino et al., 2011).

The sirtuins are categorized as class III histone deacetylases (HDACs) and the posttranslational modification of histone substrates can modulate chromatin condensation and gene transcription. Deacetylation of lysine residues is often associated with transcriptional repression, however many sirtuin substrates are non-histone proteins and several sirtuins do not have deacetylase activity (Dokmanovic et al., 2007; Gregoretta et al., 2004).

There are seven sirtuins in mammals with varied subcellular localization and enzymatic activity (Frye, 1999, 2000). SIRT1, SIRT2 and SIRT3 exhibit NAD-dependent deacetylase activity (Imai et al., 2000; Jeong et al., 2012; North et al., 2003; Onyango et al., 2002; Tanny et al., 1999). SIRT4 is an ADP-ribosyltransferase (Haigis et al., 2006), whereas SIRT5 has NAD-dependent demalonylase, desuccinylase and deacetylase activities (Du et al., 2011; Nakagawa et al., 2009; Peng et al., 2011). SIRT6 was initially shown to have deacetylase and ADP-ribosyltransferase activities (Liszt et al., 2005; Michishita et al., 2008; Mostoslavsky et al., 2006) and more recently has been shown to catalyze the hydrolysis of fatty acyl lysine residues, which may affect protein secretion (Park et al., 2012). SIRT7 is an NAD-dependent deacetylase (Barber et al., 2012; Vakhrusheva et al., 2008).

The sirtuins reside in different subcellular compartments, influencing their *in vivo* substrates and cellular functions. SIRT1 was initially described as a nuclear protein (Mouchiroud et al., 2013) that may also shuttle to the cytoplasm during neuronal differentiation and neurite outgrowth (Hisahara et al., 2008; Sugino et al., 2010; Tanno et al., 2007), tumor progression (Byles et al., 2010; Ramsey et al., 2008) and apoptosis (Jin et al., 2007). SIRT2 is a cytoplasmic protein that can deacetylate tubulin (North et al., 2003) but has also been described in the nucleus during cell cycle progression (Canto et al., 2012), cancer (Braidly et al., 2013), and bacterial infection (Eskandarian et al., 2013). SIRT3, SIRT4 and SIRT5 are mitochondrial sirtuins, however they each have distinct enzymatic activities within this organelle (Du et al., 2011; Haigis et al., 2006; Nakagawa et al., 2009). SIRT6 associates with chromatin in the nucleus (Liszt et al., 2005; Mostoslavsky et al., 2006) and is enriched in the nucleolus during the G1 phase of the cell cycle (Ardestani and Liang, 2012), and SIRT7 is a nucleolar protein (Ford et al., 2006).

Although there has been some controversy regarding the functions of sirtuins in calorie restriction and aging, many recent papers have reaffirmed the important roles of these proteins in both processes (reviewed in (Guarente, 2013). For example, SIRT3 was shown to be essential for calorie restriction to protect the neurons in the cochlea against oxidative damage and thus forestall hearing loss in mice (Someya et al., 2010).

Sirtuins have been recently shown to have many important functions during development, influencing brain structure through axon elongation (Li et al., 2013), neurite outgrowth (Sugino et al., 2010), and dendritic branching (Ferrante et al., 1997) as well as cellular fate of neuronal precursor cells (Prozorovski et al., 2008; Rafalski et al., 2013). These proteins also play a major role in the hypothalamus, affecting circadian rhythmicity (Asher et al.,

2008; Bellet et al., 2013; Bellet et al., 2011; Chang and Guarente, 2013; Nakahata et al., 2008; Nakahata et al., 2009), endocrine function (Cohen et al., 2009) and feeding behaviors (Ramadori et al., 2011; Sasaki et al., 2010; Satoh et al., 2010). In the adult brain, SIRT1 can also modulate synaptic plasticity and memory formation (Gao et al., 2010; Michan et al., 2010). In addition to its importance during normal brain aging, SIRT1 has also been shown to ameliorate a number of neurodegenerative disorders including Alzheimer's (Donmez et al., 2010; Min et al., 2010; Qin et al., 2006), Parkinson's (Donmez et al., 2012; Mudo et al., 2012), Huntington's disease (Jeong et al., 2012; Jiang et al., 2012), motor neuron diseases (Han et al., 2012; Kim et al., 2007; Montie et al., 2011) and multiple sclerosis (Fonseca-Kelly et al., 2012; Shindler et al., 2010; Shindler et al., 2007) in animal models of these diseases. Current therapies for these neurologic disorders are not curative and there is great interest in targeting sirtuin pathways pharmacologically.

Small molecules like resveratrol and synthetic SIRT1 activators were shown to activate the enzyme directly via an allosteric site adjacent to the catalytic domain (Hubbard et al., 2013). Although we discuss resveratrol throughout this review, it is important to remember the caveat that small molecules may also hit non-SIRT1 neuronal targets to affect biological outcomes *in vivo*. Resveratrol inhibits cAMP-degrading phosphodiesterases and activates the CamKK β -AMPK pathway by increasing cAMP and activating Epac1. In addition to increasing intracellular calcium levels this pathway also increases NAD⁺ and SIRT1 activity (Park et al., 2012). SIRT2 inhibitors have also been shown to be protective in animal models of Parkinson's and Huntington's diseases (Chopra et al., 2012; Outeiro et al., 2007). In this review, we will present an overview of SIRT1 function in the brain during neurodevelopment, normal aging and neurodegenerative disease.

Sirtuin 1 and normal brain aging

Neuronal structure

The early development of neurons begins with neurite process elongation followed by axon differentiation, dendritic arborization and synapse formation (Ferrante et al., 1997). Using cell culture models and *in utero* electroporation, SIRT1 has been shown to promote neurite outgrowth and the subcellular localization of this deacetylase is critical for its function (Figure 1). In PC12 cells, cytoplasmic SIRT1 stimulates NGF-dependent neurite outgrowth, however this effect is abolished when nuclear localized constructs or catalytically inactive mutants are analyzed (Sugino et al., 2010). A second study has confirmed and expanded on these observations reporting that SIRT1 briefly localizes to the nucleus during differentiation from neuronal precursor cells (NPCs) and SIRT1 inhibition decreases neurite length in culture and in mouse brain following *in utero* electroporation (Hisahara et al., 2008). A third study linked neurite outgrowth and neuronal viability with the downregulation of mammalian target of rapamycin (mTOR) (Guo et al., 2011).

SIRT1 has also been shown to promote axon development in embryonic hippocampal neurons. SIRT1 activates Akt, the upstream inhibitory kinase of glycogen synthase kinase 3 (GSK3), and promotes axonogenesis in cultured hippocampal neurons (Li et al., 2013). In embryonic cortical neurons, SIRT1 is the target of microRNA-138, a small noncoding RNA

that molecule suppresses axon growth (Liu et al., 2013). In response to peripheral nerve injury, SIRT1 is also able to suppress miR-138 creating a negative feedback loop.

Dendritic arborization is another important aspect of neuronal development because the degree of branching affects the number of synaptic inputs that each neuron can integrate. SIRT1 KO mice have been shown to have a reduced dendritic arbor but similar distribution of dendritic spines relative to wildtype mice (Michan et al., 2010). A second study corroborated these findings in neuronal culture and also found that the architecture of neuronal spines differed with SIRT1 overexpression and that SIRT1 catalytic activity was important for the maintenance of dendritic arborization by inhibition of ROCK kinase activity (Ferrante et al., 1997). These studies support a role for SIRT1 in the regulation and maintenance of dendritic growth.

Learning and memory

The development of synapses and modulation of their strength is important for memory formation and SIRT1 plays an important role in this process. SIRT1 knockout animals have morphologic alterations in neuronal structure, exhibiting dendrites with decreased complexity and shorter branches by Golgi staining (Michan et al., 2010). Studies using electron microscopy to examine synaptic morphology show that inhibiting SIRT1 decreases synaptic inputs to hippocampal neurons (Dietrich et al., 2010). Functionally, SIRT1 knockout mice have impaired hippocampal-dependent memory that is associated with decreased long-term potentiation in the CA1 region of the hippocampus. The expression of hippocampal genes was examined by microarray analysis and genes for synaptic function, membrane fusion, myelination, and metabolic function were altered in knockout mice (Michan et al., 2010).

Brain-specific SIRT1 knockout mice have decreased synaptic plasticity (Figure 2). SIRT1 interacts with a repressor complex containing the transcription factor YY that regulates miR-134 and this brain specific microRNA regulates cAMP response binding protein (CREB) expression and brain-derived neurotrophic factor (BDNF) (Gao et al., 2010). The relationship between SIRT1 and these targets is shown in figure 2. A subsequent study examining whether these alterations were reproducible using a pharmacologic approach (with attending caveats for non-SIRT1 effects) rather than genetic deletion confirmed that levels of miR-124 and miR-134 decreased after treatment with resveratrol (Zhao et al., 2013). Both CREB and BDNF increased while memory formation and long-term potentiation (LTP) induction improved in treated animals (Zhao et al., 2013).

Hypothalamic function

The hypothalamus regulates physiology and behavior by sensing metabolic changes and coordinating neuroendocrine responses that modulate appetite, temperature, circadian control and hormonal release to maintain homeostasis (Coppari, 2012). SIRT1 is expressed in several hypothalamic regions that regulate the response to food availability and circadian behaviors including the arcuate (ARC), ventromedial (VMH), dorsomedial (DMH), lateral hypothalamic (LH) and paraventricular nucleus (PVN) as well as the suprachiasmatic

nucleus (SCN) (Ramadori et al., 2008; Satoh et al., 2010). The role of SIRT1 in these brain regions is illustrated in figure 3.

The VMH nucleus regulates the balance between glucose and insulin, and steroidogenic factor 1 (SF1)-expressing neurons within this nucleus are particularly important for coordinating the autonomic response to high fat diet and obesity. SF1 neurons express SIRT1 (Ramadori et al., 2011) and send excitatory projections to pro-opiomelanocortin (POMC) cells in the arcuate nucleus of the hypothalamus that release α -melanocyte-stimulating hormone and cocaine-and-amphetamine-regulated transcript peptides to promote satiety (Coppari, 2012; Dietrich et al., 2010). The arcuate nucleus also contains a second population of neurons that inhibit POMC neurons, producing neuropeptide Y (NPY), agouti-related peptide (AgRP) and GABA to promote feeding behaviors (Dietrich et al., 2010).

SIRT1 plays an important role in regulating neuronal function in several hypothalamic regions (Figure 3). Mice that lack SIRT1 in SF1 or POMC neurons have decreased energy expenditure and are more sensitive to diet-induced obesity when fed high-fat diets (Ramadori et al., 2011; Ramadori et al., 2010). Knocking out SIRT1 in hypothalamic AgRP neurons decreases food intake (Dietrich et al., 2010), an effect that is recapitulated when pharmacologic or siRNA is used to inhibit SIRT1 nonspecifically in the hypothalamus, causing decreased weight and food intake (Cakir et al., 2009). The mechanism for how SIRT1 regulates the feeding response to caloric restriction is attributed to the deacetylation of FOXO and may also affect mTOR/S6K signaling (Cakir et al., 2009). SIRT1 also modulates the response to NPY, a neurotransmitter that increases food intake, by activating FOXO in response to phosphorylation by minibrain/Dyrk1a kinase (Hong et al., 2012).

SIRT1 is also a critical mediator of the response to ghrelin, a peptide hormone that stimulates food intake. Ghrelin increases SIRT1 activity causing p53 deacetylation and AMPK activation, affecting fatty acid metabolism and feeding behavior (Velasquez et al., 2011). Under caloric restriction, SIRT1 increases levels of the orexin type 2 receptor (Ox2r) in DMH and LH neurons increasing responsiveness to ghrelin (Satoh et al., 2010). The extended life span of SIRT1 brain-specific transgenic mice has also been attributed to upregulation of Ox2r due to deacetylation of the transcription factor Nk2 homeobox 1 (Satoh et al., 2013).

Other functions attributed to hypothalamic AgRP neurons including regulation of adaptive immunity, exploratory drive and response to cocaine are also altered in mice when SIRT1 is ablated in these cells (Dietrich et al., 2012; Matarese et al., 2013). Immunologic changes are caused by disinhibition of POMC neurons that project to the thoracic spinal cord, increasing sympathetic tone. Deletion of SIRT1 in AgRP neurons creates a proinflammatory environment, with enhanced effector T-cell activity and decreased regulatory T-cell function (Matarese et al., 2013). AgRP neurons also innervate the ventral tegmental area (VTA) of the midbrain, and SIRT1 deletion results in higher levels of dopamine in the forebrain and facilitates long-term potentiation in a spike-timing dependent protocol (Dietrich et al., 2012).

In addition to its role in metabolic regulation of feeding behavior and energy expenditure SIRT1 has also been linked with circadian control. It was originally shown to regulate circadian rhythm in peripheral tissues, and BMAL1 and PER2 were identified as SIRT1 targets in the liver (Asher et al., 2008; Nakahata et al., 2008). In the suprachiasmatic nucleus of the hypothalamus, SIRT1 levels decrease with aging, and functional circadian decline is suppressed by over-expressing SIRT1 in the brain (Chang and Guarente, 2013). SIRT1 affects BMAL1 transcription by acting cooperatively with PGC1 α at ROR α -binding sites. BMAL1 is important for maintaining functional connections between neurons, synaptic terminals, regulating cerebral redox homeostasis, linking circadian clock proteins with neurodegeneration (Musiek et al., 2013). BMAL1 and CLOCK proteins form heterodimers that activate the transcription of cryptochrome, period and NAMPT, an enzyme that synthesizes NAD⁺ (Asher et al., 2008; Nakahata et al., 2008; Nakahata et al., 2009). Circadian regulation of NAD⁺ was recently found to be a major regulator of metabolism and mitochondrial oxidation and metabolism across the daily cycles of fasting and feeding (Peek et al., 2013).

SIRT1 in neurodegenerative disorders

Alzheimer's disease

Over 35 million people have dementia worldwide and Alzheimer's disease (AD) is the most common cause of cognitive impairment (Gomes et al., 2013). Familial AD is an autosomal dominant neurologic disorder that affects individuals in their 50s and 60s and is associated with mutations in the genes for amyloid precursor protein (APP), presenilin 1 (PS1) or presenilin 2 (PS2). APP is cleaved by β - and γ -secretase complexes leading to the formation of amyloid- β (a β) peptides that coalesce to form extracellular plaques. Tau protein also becomes abnormally aggregated during AD pathogenesis and forms neurofibrillary tangles within cells.

One of the initial observations raising the possibility that sirtuins might ameliorate AD pathology was the finding that resveratrol can reduce a β -induced toxicity in cell lines (Conte et al., 2003; Jang and Surh, 2003; Sun et al., 2001) and hippocampal neurons (Han et al., 2004). Parallel studies *in vivo* showed that resveratrol could also reduce plaque formation in transgenic mouse models of AD (Karuppagounder et al., 2009; Vingtdoux et al., 2010). In order to link sirtuins more definitively with decreased amyloid toxicity, lentiviral infection with SIRT1 was performed and decreased a β -neurotoxicity was observed due to decreased microglial expression of NF- κ B (Chen et al., 2005). A second group identified an alternate mechanism using cell culture and murine models that neuronal SIRT1 expression promoted a non-amyloidogenic APP processing pathway by decreasing levels of ROCK1 kinase (Qin et al., 2006). *In vivo* evidence supporting the idea that SIRT1 overexpression can decrease plaque burden and improve behavioral phenotypes was performed in the APP/PS1 mouse model. The retinoic acid receptor β was identified as a SIRT1 substrate that up-regulates alpha-secretase activity by increasing ADAM10 gene. This results in greater processing of APP along a non-amyloidogenic pathway (Donmez et al., 2010).

SIRT1 has also been shown to ameliorate tau pathology in the p25 (Kim et al., 2007) and P301L mouse models (Min et al., 2010; Min et al., 2012) affecting cognitive impairment and

mortality. Tau protein is acetylated at multiple residues early in the disease process and deacetylation by SIRT1 may allow ubiquitin ligases to target tau for degradation, promoting clearance rather than pathologic intracellular aggregation of this protein (Cohen et al., 2011; Min et al., 2010). These mechanisms are schematically represented in figure 4.

While these studies support the idea that SIRT1 may influence both A β and neurofibrillary tau pathology, more work is needed to investigate whether SIRT1 activators can be used to treat patients with AD. The majority of patients with AD have the late onset disorder that is not associated with the same mutations in APP, PS1 and PS2 that are found in familial AD and are used to study the disease in mouse and cell-based models. The clinicaltrials.gov registry indicates that there are several ongoing or recently completed clinical trials testing various formulations of resveratrol in AD patients. More specific SIRT1 activators, when they are available, will be invaluable in assessing whether SIRT1 activating compounds are efficacious in humans.

Parkinson's disease

Parkinson's disease (PD) is the second most common neurologic disease affecting over 600,000 patients in the United States (Kowal et al., 2013). Patients develop tremors, rigidity and postural instability due to the loss of dopaminergic neurons in the substantia nigra of the midbrain. Inclusions of α -synuclein and ubiquitin are a pathologic hallmark of the disease (Blesa et al., 2012).

A substantial body of literature supports the hypothesis that SIRT1 is protective in cell culture and animal models of PD (Albani et al., 2009; Blanchet et al., 2008; Donmez et al., 2012; Raynes et al., 2012; van Ham et al., 2008; Wu et al., 2011). Several mechanisms for this effect have been proposed as SIRT1 deacetylates heat shock factor 1 (HSF1), which increases transcription of molecular chaperones such as heat shock protein 70 (Donmez et al., 2012; Raynes et al., 2012; Westerheide et al., 2009). Another relevant mechanistic pathway may be that SIRT1 can deacetylate PGC1 α as overexpressing PGC1 α or resveratrol protect dopaminergic neurons against MPTP-induced cell degeneration (Mudo et al., 2012). SIRT1 may also function to regulate autophagy and mitophagy, which may affect α -synuclein toxicity in the context of PD (Sampaio-Marques et al., 2012; Wu et al., 2011). Several SIRT1 targets that are relevant to its effects in PD are illustrated in figure 4.

Huntington's disease

Huntington's disease (HD) is a rare movement disorder that causes chorea, loss of motor coordination, cognitive dysfunction and dementia. It is an autosomal dominant disease caused by the expansion of a CAG repeat that codes for a polyglutamine stretch in the huntingtin protein that affects its aggregation propensity (La Spada, 2012)

SIRT1 has been evaluated as a potential pharmacologic target for HD in multiple animal and cell culture systems with mixed results depending on the organism, HD model and endpoints measured for evaluation. In *Drosophila* models, SIRT1 inhibition using either genetic or pharmacologic strategies can suppress pathogenesis of HD (Pallos et al., 2008). In *C. elegans* models, the converse is true and SIRT1 overexpression or resveratrol treatment is

protective (Parker et al., 2005; Parker et al., 2012). In mammalian systems, studies using pharmacologic agents have not shown conclusive results with several studies indicating SIRT1 may be protective (Kumar et al., 2006) and others showing a modest improvement in motor deficits or peripheral tissues without a clear improvement in survival (Hathorn et al., 2011; Ho et al., 2010).

Genetic models of SIRT1 overexpression have yielded greater clarity with two studies showing that sirtuins can protect against mutant huntingtin toxicity in three different mouse models of HD (Jeong et al., 2012; Jiang et al., 2012). One proposed mechanism is that SIRT1 deacetylates the CREB coactivator TORC1, facilitating its nuclear localization and BDNF transcriptional activation via CREB (Jeong et al., 2012). Mutant huntingtin protein was found to inhibit the enzymatic activity of SIRT1 during HD pathogenesis. An alternate explanation for the protective effect of SIRT1 in HD mice was that this protein might maintain TrkB signaling and DARPP32 levels as HD progresses. Foxo3a deacetylation was another SIRT1 target implicated in promoting cell survival in the HD models (Jiang et al., 2012). The major mechanisms for neuroprotection identified in mouse models of HD are illustrated in figure 4. Thus several different molecular mechanisms may explain the improvements in HD symptoms in these genetic models, and future experiments will clarify which targets are critical components of the neuroprotective phenotype and whether these findings can be translated into new therapies for patients with HD.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive disease that affects motor neurons, compromising muscle strength and coordination. Over the past few decades a number of mutations in a functionally diverse set of genes have been identified including SOD1 (Rosen et al., 1993), TDP43 (Arai et al., 2006; Neumann et al., 2006), FUS (Kwiatkowski et al., 2009), VCP (Johnson et al., 2010), UBQLN2 (Deng et al.) and C9ORF72 (DeJesus-Hernandez et al.; Renton et al.). There are many proposed etiologies for ALS including RNA metabolism, mitochondrial dysfunction, oxidative damage, protein misfolding, glutamate-mediated excitotoxicity and axonal transport defects (Cozzolino et al., 2012).

Several studies using resveratrol and lentiviral injection have indicated that SIRT1 may be protective in tissue culture (Wang et al.; Yanez et al.) and mouse models of ALS (Han et al., 2012; Kim et al., 2007). Method of delivery is an important consideration as two studies have examined the effects of resveratrol in whole animal SOD mouse models. Intraperitoneal injection of the compound yielded significant improvements in morbidity and mortality (Han et al., 2012) whereas dietary treatment with resveratrol was not found to improve disease progression (Markert et al.).

The proposed mechanism for SIRT1's activity in motor neuron disease parallels its role in mouse models of PD. SIRT1 has been shown to deacetylate HSF1, which increases transcription of molecular chaperones including HSP70 and HSP25 that help to maintain intracellular protein homeostasis, reducing toxicity to motor neurons (Han et al., 2012; Raynes et al., 2012; van Ham et al., 2008; Westerheide et al., 2009). In cell culture models of ALS, SIRT1 activation may increase mitochondrial biogenesis through PGC1 α (Wang et

al.). These mechanisms are illustrated in figure 4. SIRT1 is altered both in the SOD mutant mouse lines (Kim et al., 2007; Lee et al.) as well as in patient samples (Korner et al., 2013) and therefore may be promising both as a disease marker and a therapeutic target for ALS.

Spinal and bulbar muscular atrophy

Spinal and bulbar muscular atrophy (SBMA) is a rare neurologic disorder that causes muscle weakness and endocrine problems in males due to its effects on motor and sensory neurons. Also known as Kennedy's disease, this disorder is caused by a CAG trinucleotide expansion in the amino-terminal region of the androgen receptor (Brinkmann; La Spada et al., 1991; Merry). Testosterone reduction by surgical or chemical methods improves the disease phenotype in animal models (Katsuno et al., 2003; Katsuno et al., 2002), but has not been shown to improve symptoms in patients with SBMA (Fernandez-Rhodes et al.; Katsuno et al.).

Recent work has shown that the androgen receptor (AR) can be repressed through deacetylation by SIRT1 (Fu et al., 2006). SIRT1 can also deacetylate the polyglutamine-expanded androgen receptor in SBMA (Montie et al., 2011). If the androgen receptor is a SIRT1 substrate in patients, then this finding has great therapeutic potential because SIRT1 activation may have fewer side effects relative to androgen withdrawal and other therapies that have been explored for SBMA treatment.

Multiple sclerosis

Multiple sclerosis (MS) is a chronic, demyelinating disorder characterized by intermittent episodes of focal inflammation and neurologic dysfunction. The disease often leads to gradual decline and permanent neuronal damage. One of the most established models for MS is experimental autoimmune encephalitis (EAE), an induced disorder where T cells react against myelin antigens and form demyelinating lesions in the CNS of mice (Olitsky and Yager, 1949).

Several studies show resveratrol may be protective in mouse models of MS. In a relapsing-remitting EAE model, resveratrol was able to reduce neuronal damage but did not affect inflammation (Shindler et al., 2010; Shindler et al., 2007). In chronic EAE models, resveratrol treatment has also delayed symptom onset, decreased neuronal loss and paralysis (Fonseca-Kelly et al., 2012; Singh et al., 2007). In these studies the mechanism of action for resveratrol was not established and could be related to the activity of SIRT1 or other proteins including AMPK or PGC1 α .

A more recent study used genetic overexpression of SIRT1 in a chronic EAE model and found that clinical symptoms were improved with less axonal injury and fewer apoptotic cells observed in the presence of SIRT1 overexpression. This protective phenotype was associated with increased brain-derived neurotrophic factor and NAD levels (Nimmagadda et al., 2013). Other studies examining the effect of SIRT1 in adult neuronal precursor pools (NPCs) have not shown as clear a picture regarding the effect of SIRT1 on EAE. In a study examining the influence of redox state on neural precursor cell (NPC) differentiation, SIRT1 levels increased in glial fibrillary acidic protein (GFAP) positive cells near EAE inflammatory lesions. This group found that SIRT1 increases in NPCs and binds Hes1 under

oxidative conditions, inhibiting Mash1 transcription and driving NPCs toward astroglial differentiation (Prozorovski et al., 2008). This pathway may comprise part of the endogenous response to demyelinating disorders such as MS and is depicted in figure 4. A subsequent study showed that deleting SIRT1 in NPC and neural progenitors prior to induction delayed onset of paralysis in a chronic EAE model (Rafalski et al., 2013). Taken together, these results suggest that increasing the oligodendrocyte population may help remyelinate lesions, reduce axonal damage or decrease astrogliosis (Rafalski et al., 2013), however the specificity of these genetic models for NPCs may be less clinically relevant as this small population of cells may be difficult to target pharmacologically.

Prion disease

Prion diseases are a group of fatal neurodegenerative conditions resulting from accumulation of misfolded prion protein that causes degeneration and apoptosis of neurons. These diseases are transmitted when infectious, conformationally altered prion (PrP^{sc}) converts normal cellular prion (PrP) into a pathologic form that has high β -sheet content (Prusiner, 1998). The disease can be modeled *in vitro* by inoculating cells with synthetic peptides from the disordered N-terminal domain of the prion protein, which causes aggregation of endogenous cellular prion. Disease manifestations are modeled *in vivo* by direct intracranial inoculation of infectious material or by using transgenic mouse lines that overexpress mutant prion protein. In mouse strains with genetically deleted SIRT1, the propagation of prion protein was delayed (Chen et al., 2008). Other models do not show the same effect, with genetic and pharmacologic studies in both nematode and *in vitro* models of prion toxicity showing protection against neurodegeneration in the presence of increased SIRT1 activity (Bizat et al., 2010; Jeong et al., 2013; Seo et al., 2012). Mechanistically SIRT1-mediated deacetylation of p53 and p65 may regulate apoptotic signaling proteins affecting cell survival (Seo et al., 2012). It has also been shown that SIRT1 may protect against prion disease by inducing autophagy, which decreases mitochondrial impairment in neurons (Jeong et al., 2013). Further work will be needed to resolve the differences in outcomes between these studies and to clarify whether modulating sirtuin activity is likely to affect the severity or outcome of prion infection in patients.

SIRT1 in psychiatric disorders

A number of genetic association studies have evaluated the relationship between SIRT1 haplotypes and psychiatric disorders including schizophrenia, bipolar disorder, anxiety disorder, major depressive disorder and drug induced psychosis and several SIRT1 single nucleotide polymorphisms (SNPs) were overrepresented in patients with depression and anxiety disorders (Kishi et al., 2011a; Kishi et al., 2011b; Kishi et al., 2010; Libert et al., 2011). Another approach investigating a link between sirtuins and mood disorders found that levels of SIRT1, SIRT2 and SIRT6 transcripts decreased in peripheral white blood cells during depressive and remissive states of patients with major depression and bipolar disorder (Abe et al., 2011).

In animal models, genetic modulation of SIRT1 levels correlates with anxiety and exploratory drive and is mechanistically linked with serotonin levels in the brain. SIRT1 deacetylates NHLH2, a transcription factor that regulates monoamine oxidase A (MAO-A).

This enzyme converts serotonin to 5-hydroxyindole-acetic acid (5-HIAA). Thus, mice lacking brain SIRT1 have low levels of MAO-A and high levels of its substrate, serotonin, whereas mice over-expressing brain SIRT1 are serotonin deficient. Moreover, behavioral differences in the mice can be normalized by treatment with anxiolytic or antidepressant medications used in patients such as MAO inhibitors and selective serotonin reuptake inhibitors (Libert et al., 2011).

SIRT1 may also play an important role in addiction and substance abuse. Cocaine or morphine administration increases SIRT1 expression in the nucleus accumbens, a brain region that regulates motivation and reward (Ferguson et al., 2013; Renthal et al., 2009). Chronic drug administration increases binding of activator protein 1 (AP1) sites in the sirtuin promoter with FosB, a transcription factor that modulates addiction associated behaviors and induces expression of SIRT1 and SIRT2. Importantly viral-mediated over-expression of SIRT1 in this region enhanced the reward response, while knockdown decreased it (Ferguson et al., 2013). Resveratrol was also found to have acute effects on cocaine-mediated neurotransmission by enhancing dopamine neurotransmission (Shuto et al., 2013). In contrast, in the AgRP neurons of the hypothalamus, knockdown of SIRT1 enhanced responses to cocaine (Dietrich et al., 2012). In summary, SIRT1 plays important roles in behavioral processes by affecting neurotransmitter processing in multiple brain circuits.

Conclusions and future directions

Sirtuins play a critical role in the maintenance of neural systems and behavior during normal aging. SIRT1 affects neuronal morphology during development and also is important in maintaining metabolic and circadian homeostasis during aging. Due to its hypothalamic effects and peripheral targets, modulation of SIRT1 activity may be an effective treatment strategy for diabetes and obesity. It is also a promising therapeutic target for a number of neurodegenerative disorders where it affects proteostasis and facilitates aggregate clearance.

Modulation of mammalian sirtuins like SIRT1 may thus be a valuable strategy to slow the trajectory of aging related degenerative changes in the central nervous system and neurologic disorders. However much still needs to be learned about the safety and efficacy profiles of sirtuin activators. One exciting new finding in the field of aging research is that the levels of NAD⁺, the cosubstrate for SIRT1-7, decreases with aging in mice (Mouchiroud et al., 2013; Ramsey et al., 2008), rats (Braidy et al., 2013), worms (Mouchiroud et al., 2013), and even humans (Massudi et al., 2012). This reduction in NAD⁺ is expected to reduce the activities of SIRT1-7, and may thus compromise protection against neurological decline and neurodegenerative diseases. Moreover, supplementation of the diet with of NAD⁺ precursors, such as nicotinamide mononucleotide or nicotinamide riboside, can restore NAD⁺ levels and reverse untoward metabolic phenotypes in aging mice (Canto et al., 2012; Gomes et al., 2013; Yoshino et al., 2011). The decline in NAD⁺ may be due to chronic activation of poly-ADP-ribose polymerase by DNA damage, since PARP inhibition can also restore aging-depleted stores of NAD⁺ (Bai et al., 2011; Gomes et al., 2013; Mouchiroud et al., 2013).

It remains to be seen if this kind of NAD⁺ depletion occurs in neurodegenerative diseases. But this is a real possibility, since these diseases feature a high degree of chronic DNA damage (Adamec et al., 1999; Ferrante et al., 1997; Robison and Bradley, 1984). One exciting possibility is that sirtuin activators in combination with NAD⁺ supplementation will provide a one-two punch to prevent or even treat neurodegenerative diseases. This possibility would provide a novel broad-based approach, which is complementary to developing disease-targeted strategies.

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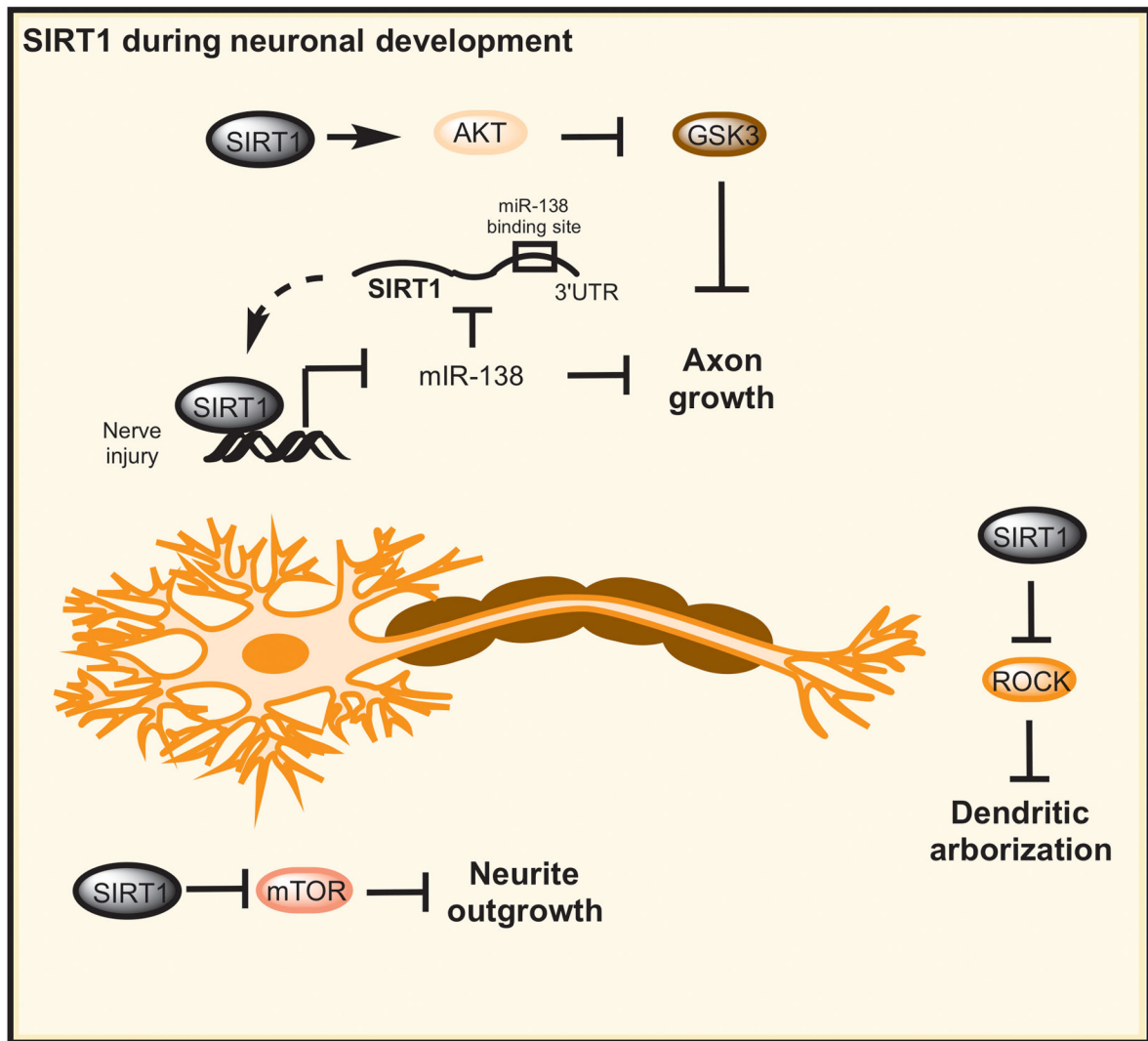


Figure 1. The influence of sirtuin 1 on neuronal architecture. The role of SIRT1 on structural features of neuronal cells are depicted

SIRT1 can promote axon development by deacetylating Akt and inhibiting Gsk3 affecting microtubule dynamics during axon elongation (Li et al., 2013). SIRT1 also interacts with microRNA-138 via a negative feedback loop and this microRNA suppresses axon growth (Liu et al., 2013). SIRT1 also affects dendritic arborization (Michan et al., 2010) and dendritic spine morphology by inhibition of ROCK kinase activity (Ferrante et al., 1997). Cytoplasmic SIRT1 can stimulate NGF-dependent neurite outgrowth (Hisahara et al., 2008; Sugino et al., 2010), which is due to downregulation of mTOR and inhibition of its downstream effectors (Guo et al., 2011).

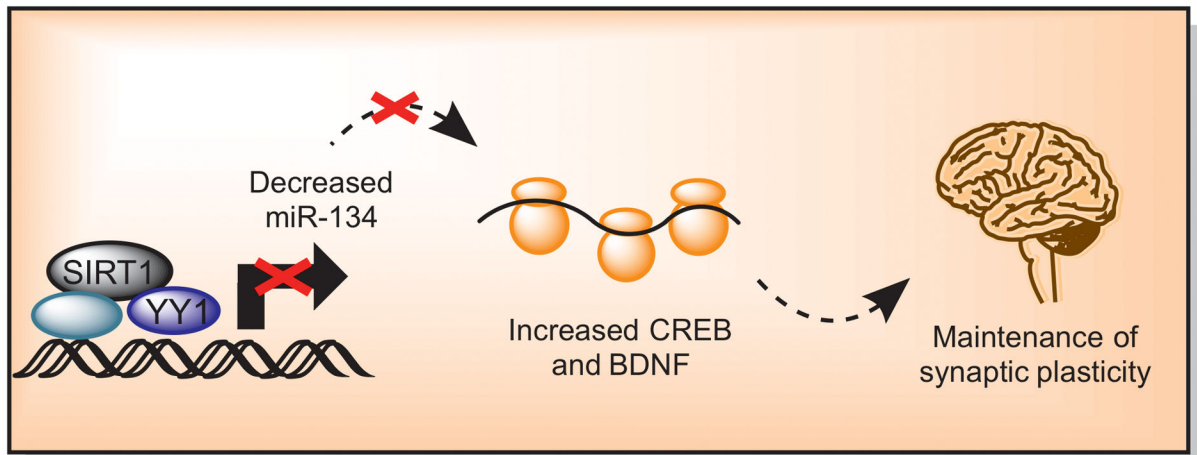


Figure 2. The regulation of learning and memory by sirtuin 1

In the hippocampus, SIRT1 affects synaptic plasticity via a repressor complex containing the transcription factor YY1, which regulates microRNA-134 (miR-134). This brain specific microRNA regulates cAMP response binding protein (CREB) expression and brain-derived neurotrophic factor (BDNF) (Gao et al., 2010). These proteins are important for synapse formation and long-term potentiation. SIRT1 knockout mice have impaired hippocampal-dependent memory that is associated with decreased long-term potentiation in the CA1 region of the hippocampus (Gao et al., 2010).

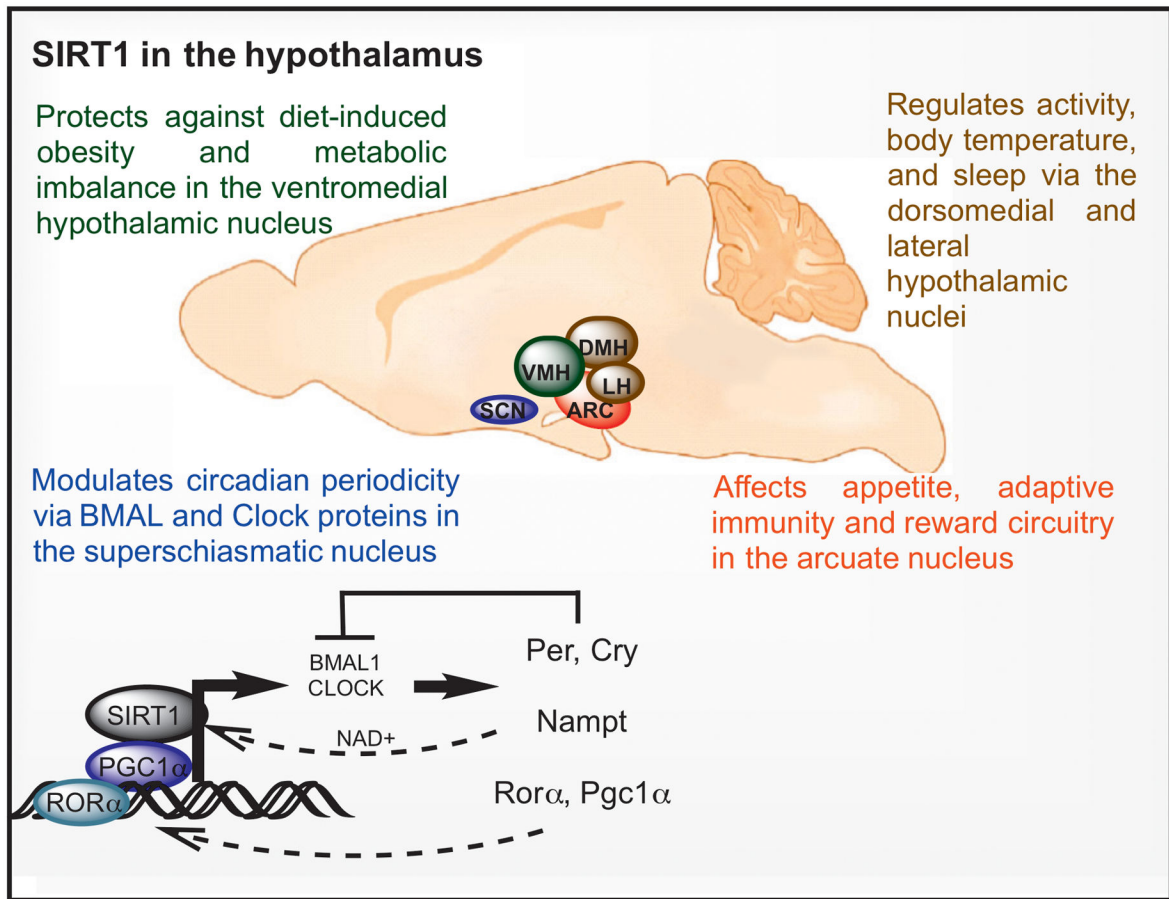


Figure 3. Sirtuin1 and hypothalamic function

The hypothalamus regulates physiology and behavior by coordinating neuroendocrine responses that modulate appetite, temperature, circadian control and hormonal release to maintain homeostasis (Coppari, 2012). In the ventromedial hypothalamic nucleus, SIRT1 increases energy expenditure and protects against diet-induced obesity under fed high-fat diets (Ramadori et al., 2011; Ramadori et al., 2010). SIRT1 also regulates activity and body temperature in the dorsomedial and lateral hypothalamus (Satoh et al., 2010). In arcuate nucleus, SIRT1 modulates appetite, adaptive immunity and reward circuitry (Dietrich et al., 2010; Matarese et al., 2013). In the suprachiasmatic nucleus of the hypothalamus, SIRT1 levels decrease with aging, affecting the activity pattern and circadian period. Overexpressing brain SIRT1 activates the transcription of BMAL and CLOCK proteins enabling animals to be protected from aging related changes to the central circadian clock (Chang and Guarente, 2013).

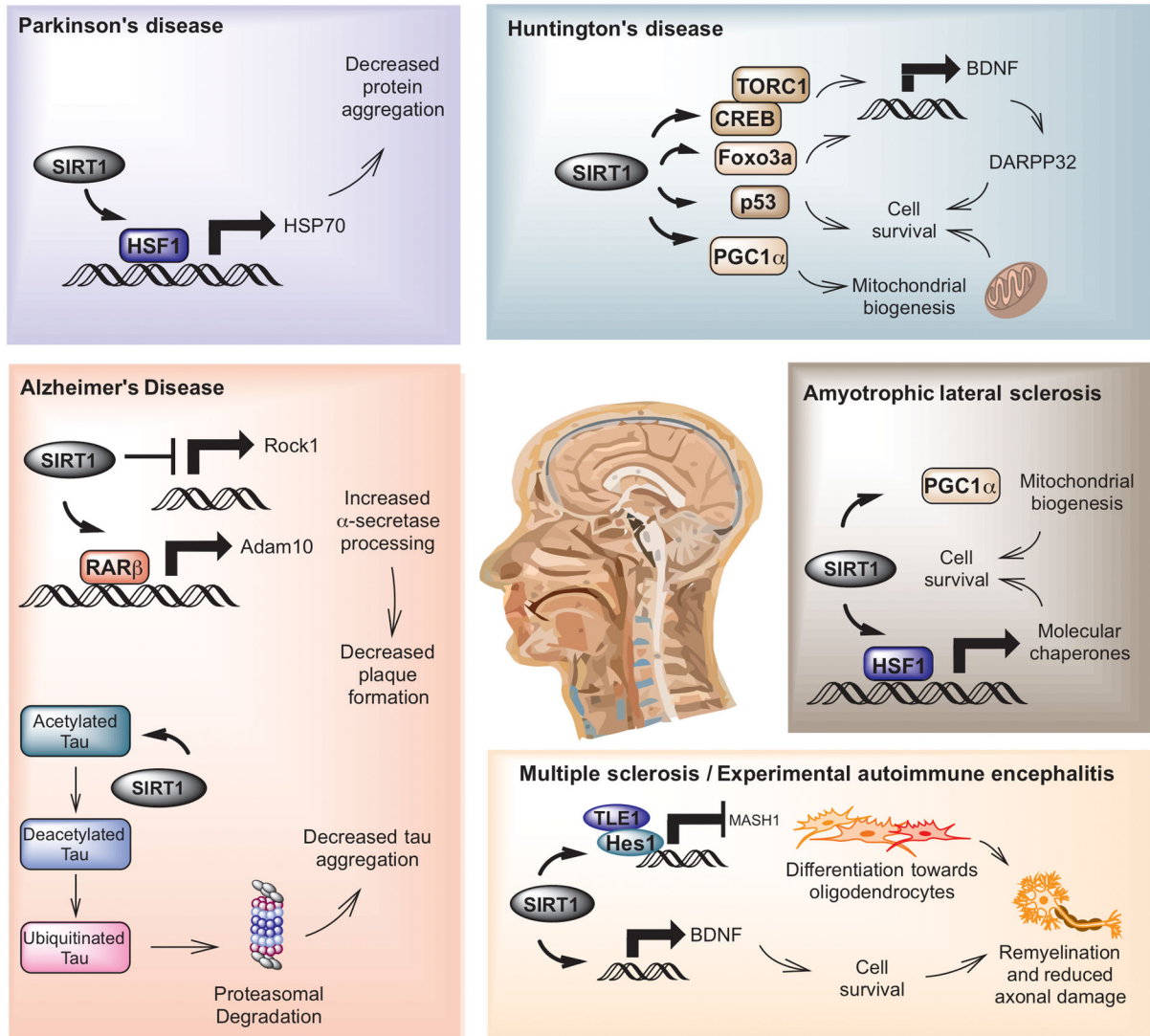


Figure 4. Major targets and mechanisms of SIRT1 in mouse models of neurodegenerative disease
Alzheimer's disease (highlighted in red) In Alzheimer's disease, SIRT1 has been shown to promote non-amyloidogenic APP processing pathway by decreasing levels of ROCK1 kinase (Qin et al., 2006). SIRT1 may also target the retinoic acid receptor β , which activates ADAM10 to facilitate processing of APP along a non-amyloidogenic pathway (Donmez et al., 2010). SIRT1 has also been shown to directly deacetylate tau in several tauopathy models enabling ubiquitin ligases to promote clearance of this protein (Cohen et al., 2011; Min et al., 2010). **Parkinson's disease** (highlighted in blue) SIRT1 has been shown to deacetylate HSF, which induces transcription of molecular chaperones that promote protein folding (Donmez et al., 2012; Raynes et al., 2012; Westerheide et al., 2009). In addition to its effects on the heat shock response, SIRT1 may also function to regulate autophagy and mitophagy, which may affect α -synuclein toxicity in the context of PD (Sampaio-Marques et al., 2012; Wu et al., 2011). There is also evidence that PGC1 α may be a relevant target in mouse models of PD (Mudo et al., 2012). **Huntington's disease** (highlighted in green) Several different molecular mechanisms account for the protective effect of SIRT1

overexpression against mutant huntingtin toxicity (Jeong et al., 2012; Jiang et al., 2012). Mutant huntingtin protein was found to inhibit the enzymatic activity of SIRT1 during HD pathogenesis. One proposed mechanism is that SIRT1 deacetylates TORC1, facilitating BDNF transcription through CREB (Jeong et al., 2012). An alternate explanation for the protective effect of SIRT1 in HD mice was that this protein might maintain TrkB signaling and DARPP32 levels as HD progresses. Foxo3a deacetylation was another SIRT1 target implicated in promoting cell survival in the HD models (Jiang et al., 2012). **Amyotrophic lateral sclerosis** (highlighted in beige) The proposed mechanism for SIRT1's activity in Amyotrophic lateral sclerosis parallels one of the pathways observed in PD. SIRT1 has been shown to deacetylate HSF1, which increases transcription of molecular chaperones including HSP70 and HSP25 that help to maintain intracellular protein homeostasis, reducing toxicity to motor neurons (Han et al., 2012; Raynes et al., 2012; van Ham et al., 2008; Westerheide et al., 2009). It has also been shown to affect mitochondrial biogenesis in cell culture models of ALS and this may be due to deacetylation of PGC1 α (Wang et al.) **Multiple sclerosis** (highlighted in orange) In experimental autoimmune encephalitis (EAE), the mouse model for multiple sclerosis (MS), the mechanism of protection in whole animal models has not been completely elucidated. In adult neuronal precursor cells (NPCs), SIRT1 binds Hes1 under oxidative conditions, inhibiting Mash1 transcription and driving NPCs toward astroglial differentiation (Prozorovski et al., 2008) and increasing the oligodendrocyte population may help remyelinate lesions, reduce axonal damage or decrease astrogliosis. An alternate approach has identified increased BDNF and NAMPT as possible targets to explain neuroprotection due to SIRT1 overexpression in EAE (Nimmagadda et al., 2013).