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Review

Therapeutic role of sirtuins in neurodegenerative disease

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ABSTRACT

The sirtuins are a family of enzymes which control diverse and vital cellular functions, including metabolism and aging. Manipulations of sirtuin activities cause activation of anti-apoptotic, anti-inflammatory, anti-stress responses, and the modulation of an aggregation of proteins involved in neurodegenerative disorders. Recently, sirtuins were found to be disease-modifiers in various models of neurodegeneration. However, almost in all instances, the exact mechanisms of neuroprotection remain elusive. Nevertheless, the manipulation of sirtuin activities is appealing as a novel therapeutic strategy for the treatment of currently fatal human disorders such as Alzheimer's and Parkinson's diseases. Here, we review current data which support the putative therapeutic roles of sirtuin in aging and in neurodegenerative diseases and the feasibility of the development of sirtuin-based therapies.

1. Introduction

Despite the significant progress in understanding the molecular basis of neurodegeneration, the lack of known useful molecular targets for effective therapeutic intervention has slowed down the drug discovery processes. Since the discovery of sirtuin functions in metabolism and aging, these activities were implicated as disease-modifiers and as potential therapeutic targets for developing treatments for neurodegenerative disorders.

2. Sirtuins

The yeast silent information regulator factor 2 (Sir2), a NAD^+-dependent class III histone deacetylase (HDAC), was the first sirtuin described [1,2]. The yeast SIR complex (Sir2, Sir3 and Sir4) plays a key role in heterochromatic gene silencing through regulation of histone deacetylation at ribosomal DNA (rDNA) loci, telomeres, and mating-type loci [3,4]. In *S. cerevisiae*, Sir2 extends the replicative lifespan through suppression of formation of extrachromosomal ribosomal DNA circles (ERCs) in the nucleoli [5].

The *Sir2* gene is evolutionary conserved from prokaryotes to humans. In *C. elegans*, the duplication of *sir-2.1* gene (*Sir2* ortholog) increases the lifespan up to 50%. This process is dependent on the daf-16 transcription factor, the member of forkhead box subgroup 'O' (FOXO) family, which is the downstream target of the insulin/IGF-1 signaling pathway [6]. An extra copy of the Sir2 gene in *D. melanogaster* (*dSir2*) increases the longevity of females and males by 29% and 18% respectively [7].

The Sir2 function is often mentioned in connection to a condition called calorie restriction (CR). CR is a reduction in calorie intake compared to normal (*ad libitum*) consumption. The link between the role of sirtuins, CR and longevity was first shown in *S. cerevisiae*. In yeast, reduction in glucose levels in the media (CR condition for yeast cells) leads to increased replicative lifespan [8]. The lifespan extension was not observed in yeast lacking the *Sir2* gene [8].

Currently, CR-mediated lifespan extension has been demonstrated in other organisms such as fruit flies (*D. melanogaster*) [9], nematodes (*C. elegans*) [10], spiders (*Frontinella pyramitela*) [11] and rodents [12].

There are seven members of the sirtuin family (Sir2 homologues) in mammals (SIRT1–SIRT7) (Table 1) [4,13]. The sirtuins act as NAD^+-dependent protein deacetylases on a variety of targets, including histones, transcription factors and apoptotic modulators [14,15]. The sirtuins also have mono-ADP-ribosyl transferase activity, which is the main enzymatic activity of SIRT4 and SIRT6 [16,17].

SIRT1, the nuclear protein which has the highest sequence similarity to the yeast Sir2p [18], is the best understood mammalian sirtuin in terms of its endogenous function and activity. SIRT1 has been linked to the control of metabolic processes in adipose tissue, liver and muscle through the regulation of the nuclear receptor peroxisome-proliferator activated receptor-γ (PPARγ) and its transcriptional co-activator PPARγ co-activator-1α (PGC-1α) [19,20]. Other non-histone substrates of SIRT1 are the tumor suppressor p53, the FOXO family of transcription factors and NF-κB transcription factor, which are involved in regulation of cell survival, proliferation and stress response [21–23]. SIRT1 could also regulate the cell survival by deacetylating the DNA repair factor Ku70, an inhibitor of Bax-

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Table 1
Mammalian sirtuins, subcellular localization, putative targets, and putative functions

Sirtuin	Subcellular localization	Main targets	Putative function	Reference
SIRT1	Nucleus	p53, Ku70, PPARγ, PGC-1α,NFκB, FOXO	Regulation of cell survival and metabolism, stress response control	[19–25]
SIRT2	Cytoplasm/ nucleus	α-tubulin, histone H4	Regulation of microtubule stability, heterochromatin formation, cell cycle regulation	[38,42–44]
SIRT3	Mitochondria	AceCS2	Activation of mitochondria function, thermogenesis regulation	[36,37]
SIRT4	Mitochondria	Glutamate dehydrogenase	Downregulation of insulin secretion in response to amino acids	[16]
SIRT5	Mitochondria	Unknown	Unknown	
SIRT6	Nucleus (associated with heterochromatin)	DNA pol β	DNA repair control	[38,39]
SIRT7	Nucleus (concentrated in nucleoli)	RNA polymerase I	Regulation of rRNA synthesis and ribosome production	[40]

Summary of functions, cellular localization, and enzymatic substrates of currently known sirtuin family members (SIRT1–SIRT7).

mediated apoptosis [24,25]. Studies on SIRT1 knockout mice and SIRT1 expression in embryos indicate its role in mammalian development [26–28].

The understanding of the biological roles of sirtuins was greatly advanced after discovery of resveratrol, a natural polyphenol present in red grapes and red wine. The potential health benefits of red wine, namely the cardioprotective effects, have been attributed to this compound. Resveratrol exhibits strong antioxidant activity [29,30] and has been shown to have anti-carcinogenic and anti-inflammatory effects [31–33]. Remarkably, it was found that resveratrol activates the yeast Sir2 and its mammalian homologue SIRT1 [34].

In mice, resveratrol protects against diet-induced obesity and insulin resistance and significantly increases their aerobic capacity [35]. It was suggested that the effects of resveratrol are mediated by the induction of SIRT1 and the consequent decrease in PGC-1α acetylation which results in an increase of its activity.

Other three members of the sirtuin family which have been linked to metabolic regulation are the mitochondrial proteins SIRT3, SIRT4 and SIRT5 [36]. These three proteins were found localized in different compartments of the mitochondria, indicating unique function(s) of each enzyme isoform in this organelle [37].

In mice, SIRT3 expression is induced in brown adipose tissue upon cold exposure, consequently activating the expression of mitochondrial genes such as those encoding for uncoupling protein 1 (UCP1), PGC-1α, cytochrome *c* oxidase subunits II and IV, and ATP synthetase [38]. CR also induces expression of SIRT3 in mice, both in white and brown adipose tissue. Furthermore, SIRT3 decreases mitochondrial membrane potential and the production of reactive oxygen species while increasing cellular respiration [38]. Recent studies also revealed that SIRT3 deacetylates and activates acetyl-CoA synthetase 2 (AceCS2) in mitochondria, both *in vitro* and *in vivo*, thus modulating directly the activity of a metabolic enzyme [39].

SIRT4 does not possess detectable deacetylase activity *in vitro*; however, it has mono-ADP-ribosyl transferase activity [16]. Recently, SIRT4 has been shown to ADP-ribosylate and downregulate mitochondrial glutamate dehydrogenase (GDH) in pancreatic β-cells, thereby downregulating insulin secretion in response to amino acids [16].

SIRT4 and SIRT5 more closely resembled prokaryotic sirtuin sequences, suggesting their ancient, evolutionary conserved function(s) in bacterial cells and mitochondria of higher organisms [40]. In comparison with SIRT3, SIRT5 possesses weak deacetylase activity *in vitro*, but since the protein substrates are currently unknown it is hard to pinpoint the exact function(s) of the protein. When SIRT3 and SIRT5 were co-expressed, the localization of SIRT3 changed from the mitochondria to the nucleus [37]. This intriguing observation might suggest SIRT5-dependent regulation of SIRT3 nuclear translocation, and a novel role for SIRT3 in the nucleus.

Together with SIRT1, SIRT6 and SIRT7 are nuclear proteins [36]. However, their subnuclear localization differs and while SIRT7 is concentrated in the nucleoli, SIRT6 is excluded from the nucleoli and is highly associated with the heterochromatic regions [36]. SIRT6-deficient cells display defective base excision repair (BER, one of the DNA repair systems) and elevated levels of spontaneous genomic instability [41]. Moreover, SIRT6 deficiency in mice leads to aging-like degenerative processes (acute loss of subcutaneous fat, lordokyphosis, osteopenia, lymphopenia and metabolic defects) [41]. SIRT7 interacts with RNA polymerase I and histones and positively regulates the transcription and expression of ribosomal RNA genes [42]. It has been suggested that SIRT7 may regulate rRNA synthesis and ribosome production in response to changes in NAD^+/NADH ratio [43].

SIRT2 is a predominantly cytoplasmic tubulin-deacetylase protein [36]. During G2/M transition and mitosis, SIRT2 is localized in the nucleus, where it interacts with and deacetylates histone H4, which leads to the formation of condensed chromatin [44]. Increased SIRT2 activity significantly delays cell cycle progression through mitosis, suggesting a SIRT2 function as a mitotic checkpoint protein [45]. Moreover, SIRT2 prevents chromosomal instability as well as formation of hyperploid cells in the early metaphase [46].

Currently, the role of sirtuins in the regulation of mammalian lifespan is not clear. However, taking into account that the sirtuins are an evolutionary conserved family of proteins, it is fair to assume that, similar to their role in yeast and invertebrates, the sirtuins also play a role in the modulation of aging-related processes in higher organisms.

Diverse biological functions of sirtuin family members pave the ground for further investigations of the therapeutic potential of these molecules for currently untreatable neurodegenerative diseases.

3. Neurodegenerative diseases

Over the past decades, numerous studies have demonstrated that the pathogenesis of neurodegenerative diseases includes broad changes and recruitment of multiple biochemical pathways. These common biochemical and cellular processes include protein misfolding, oligomerization and aggregation, proteolysis, post-translational modifications, mitochondrial dysfunction, abnormal energy metabolism, activation of stress, inflammation and pro-apoptotic responses, and others (Fig. 1). Environmental factors affect probability of disease on-set and progression.

Aging has been known as a major risk factor for a variety of neurodegenerative disorders. However, while aging has been being recognized as a strong disease modifier, until discovery of sirtuins, this pathway was not amenable for therapeutic manipulation to intervene with neurodegeneration.

4. Alzheimer's disease

Alzheimer's disease (AD) is one of the most devastating age-related neurodegenerative diseases. The symptoms of this disorder can vary greatly but the individuals affected present progressive cognitive decline and behavioral changes. The increased life expectancy of human beings has made AD one of the predominant medical problems for elderly people. The vast majority of cases are idiopathic, but a small fraction of cases are associated with autosomal dominant mutations in the amyloid-precursor protein (APP) gene, presenilin-1 (*PSEN1*) and presenilin-2 (*PSEN2*) [47,48].

The histopathological hallmarks of AD are the presence of intraneuronal neurofibrillary tangles and the accumulation of extracellular amyloid plaques in the brains of affected individuals. Neurofibrillary tangles are filamentous inclusions composed of hyperphosphorylated forms of the microtubule-associated protein tau [49]. The main component of amyloid plaques is the amyloid β-peptide (Aβ) that results from the proteolytic cleavage of amyloid-precursor protein (APP) by the sequential action of β- and γ-secretase. The widely accepted β-amyloid hypothesis suggests that Aβ is the major etiological agent of AD pathology and, therefore, broad therapeutic strategies have been focused on the inhibition of neurotoxic Aβ production and aggregation [50].

There is growing evidence for a link between SIRT1 and Alzheimer's disease [51–53]. SIRT1 protects against Aβ-induced neurotoxicity by inhibiting NF-κB signaling in microglia [54]. It was recently reported that an increase of SIRT1 deacetylase activity could be a mechanism by which CR modulated AD-type amyloid neuropathology in Tg2576 mice [53]. Overexpression of SIRT1 or pharmacological activation of SIRT1 by NAD^+ promotes α-secretase activity and attenuates the generation of Aβ peptides in embryonic Tg2576 mouse neurons *in vitro*. This mechanism involves the regulation of serine/threonine Rho kinase ROCK1, known for its role in the inhibition of the non-amyloidogenic α-secretase processing of APP [53].

Likewise, CR treated monkeys have significantly reduced content of Aβ in the temporal cortex, compared to normally fed monkeys. The Aβ content reversely correlates with SIRT1 concentration in the same brain area [55].

Since the discovery of the cholesterol-carrying apolipoprotein E as major risk factors for AD there has been a mounting interest in the role of this lipid as a possible pathogenic agent [56]. Recently SIRT1 was identified as a potential modulator of cellular cholesterol biosynthesis, thus implicating another sirtuin neuroprotective mechanism [57].

In a recent report SIRT1 was found to be upregulated in mouse models for AD and amyotrophic lateral sclerosis (ALS), a devastating human motor neuron disorder [52]. In cell-based models of AD tauopathy and ALS, both activation of SIRT1 and resveratrol promote neuronal survival. In the inducible transgenic mouse model of AD tauopathy, resveratrol reduces neurodegeneration in the hippocampus, and prevents learning impairment, which correlates with decreased acetylation of the known SIRT1 substrates PGC-1α and p53. Lastly, injection of SIRT1-expressing lentivirus in the hippocampus of transgenic mice conferred significant protection against

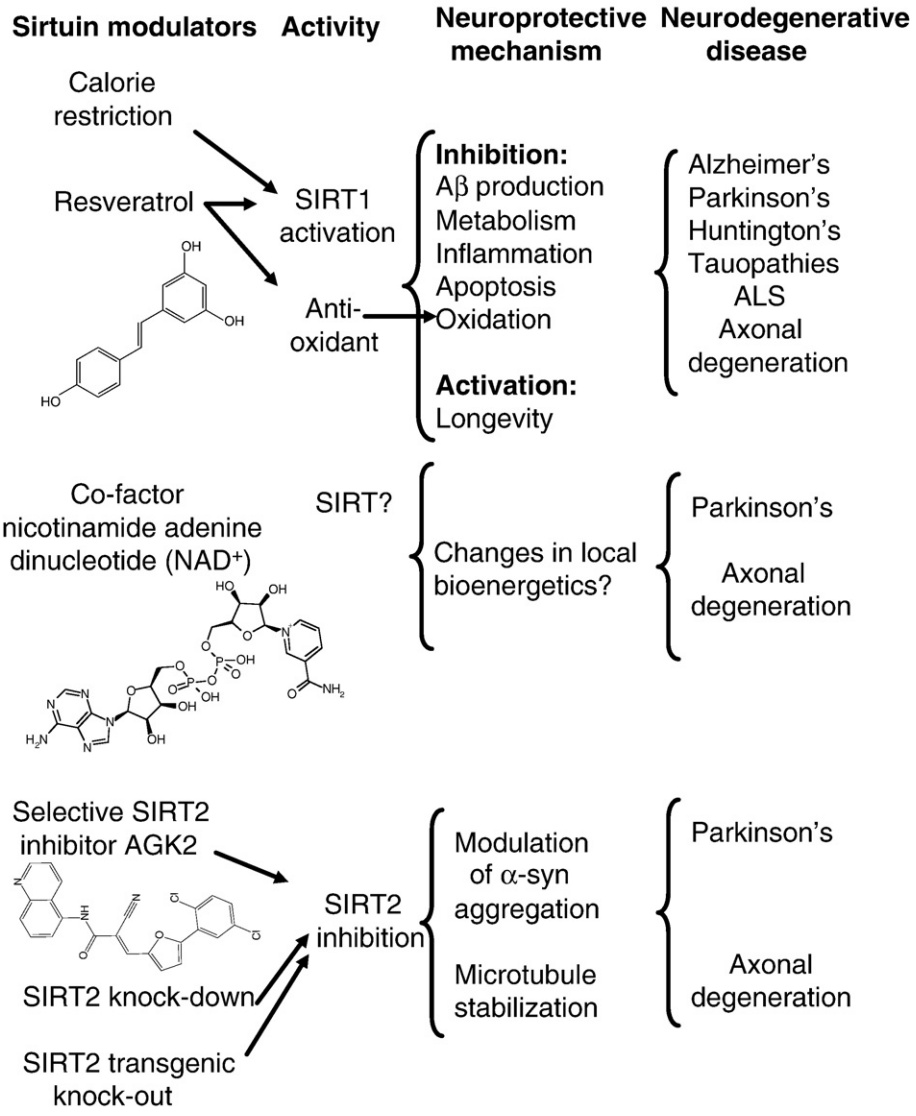

Fig. 1. Sirtuin modulators and their effects on experimental models of neurodegenerative diseases. Multiple neuroprotective mechanisms targeted by the modulation of sirtuin activities are shown.

neurodegeneration. Collectively these data strongly suggest strong therapeutic benefits of SIRT1 activation for tauopathies and, possibly, ALS.

5. Parkinson's disease

Parkinson's disease (PD) is one of the most common progressive neurodegenerative disorders, affecting about 2% of people over 65 years old and 4–5% of people over 85. PD is characterized by a loss of dopaminergic neurons in the *substantia nigra*, which is accompanied by muscle rigidity, bradykinesia, resting tremor and postural instability. While the underlying causes for neuronal cell loss are unknown, in some PD cases concentric hyaline cytoplasmic inclusions called Lewy bodies (LB) can be seen via histological analysis. LBs contain the protein α-synuclein (α-syn), as well as proteasomal and lysosomal subunits and molecular chaperones [58,59].

While misfolding, oligomerization and aggregation of α-syn have been implicated in PD pathology, the exact mechanisms of neurodegeneration remained elusive. It has been recently shown that SIRT2 inhibition prevented α-syn cytotoxicity and modulated its aggregation in cultured cells; ameliorated mutant α-syn neurotoxicity in rat primary dopamine-positive neurons; and rescued degeneration of dopaminergic neurons from α-syn toxicity in a *Drosophila* animal PD model [60]. The results suggested that modulation of α-syn aggregation pathway could be one of the sirtuin neuroprotective mechanisms.

Studies of the neuroprotective effect of resveratrol on dopaminergic neurons in organotypic midbrain slice culture showed that resveratrol, together with another sirtuin-activating compound, quercetin, prevented the decrease of dopaminergic neurons induced by a dopaminergic neurotoxin 1-methyl-4-phenyl pyridinum (MPP^+) [61]. The authors suggested the involvement of antioxidant properties of resveratrol in its neuroprotective effect rather than SIRT1 activation in this model, since other sirtuin inhibitors like sirtinol or nicotinamide did not attenuate the protective resveratrol effects. However, resveratrol as well as sirtuin activator NAD inhibited dopaminergic neurotoxicity of a DNA alkylating agent, *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG) [61]. It is unclear whether it is the antioxidant or sirtuin-activating activity (or both) that underlies the neuroprotective effect of resveratrol.

6. Huntington's disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder, typically affecting mid-life individuals [62]. Slow progressive HD is fully penetrable, and characterized by personality changes, cognitive decline, abnormal motor movements, and ultimate patient death. There is a loss of specific neuronal types in several regions in HD brain, particularly in the striatal region of the basal ganglia, where medium spiny neurons are the most affected [63]. HD is caused by the mutant expansion of CAG-repeats encoding polyglutamines (polyQ) within the huntingtin (htt) protein [64]. This polyQ expansion leads to the misfolding of mutant htt and the formation of mutant htt-containing protein aggregates in both neuronal and glial cells in brains of HD patients and mouse transgenic models of HD [65]. Despite the great strides in understanding the molecular underpinnings of HD, no therapeutics are currently available that prevent progression of this devastating disease.

The role of resveratrol and SIRT1 in neuroprotection has also been studied in models of HD. The mutant huntingtin protein causes neuronal degeneration and neuronal death [66]; however the mechanisms remain elusive. In a *C. elegans* model of HD, treatment with resveratrol protected neurons overexpressing a huntingtin fragment from huntingtin-mediated cytotoxicity in a daf-16-dependent manner [67]. Moreover, resveratrol also rescued neurons from polyglutamine-specific cell-death in a HdhQ111 knock-in mouse model [67].

Several mechanisms have been uncovered that are likely to contribute to the selective neurodegeneration observed in the disease. These include protein aggregation, transcriptional dysregulation, oxidative stress, perturbations in the kynurenine pathway, impaired energy metabolism, defective vesicle trafficking in axons, and impairment of ubiquitination and proteasomal function [68].

Neuroprotective mechanisms, underlying efficacy of SIRT1 activation and resveratrol treatment in HD models, are currently under investigation. Of the multiple molecular defects that trigger neuronal dysfunction and ultimately cause cell-death, transcriptional dysregulation may be the major pathophysiological mechanism, perturbing many cellular functions and leading to a cascade of secondary pathological effects [69]. There is strong evidence that transcriptional dysfunction, caused by altered nucleosomal dynamics, is a contributing factor in HD and, to lesser extent, in AD, PD, and other neurodegenerative diseases. It is also strongly implicated in other neurological disorders such as Rubinstein–Taybi, Rett's syndromes, fragile X syndrome, and Friedreich's ataxia [70–73]. SIRT1 is involved in the regulation of transcriptional silencing as well as in the deacetylation of both histone and a growing number of non-histone substrates. Some of these non-histone substrates include NF-κB and its subunit RelA/p65, TAFI68, histone acetyltransferase p300, p300/CBP-associated factor (PCAF), MyoD, p53, Ku70, and others [14]. Global transcriptional repression in HD is mediated by aberrant interactions of mutant huntingtin with components of basal transcriptional machinery (TBP, SP1) and histone acetyl transferases (CBP, p300), while protein interactions with specific transcriptional factors (p53, NF-κB) are involved in pathological dysregulation of selective pathways [69]. Therefore, it is highly plausible, that the basis for the efficacy of SIRT1 activation in HD models is the restoration of transcriptional dysregulation by modulation of the activity of transcription factors and chromatin remodeling. While the amelioration of global transcriptional repression by SIRT1 activation remains to be elucidated, SIRT1-dependent modulation of specific pathways, relevant to pathophysiological changes in HD, appears as a likely basis of observed neuroprotection.

This notion is supported by recent studies, revealing a critical role for PGC-1α in HD [74]. Mutant huntingtin causes disruption of mitochondrial function by inhibiting the expression of PGC-1α in a mouse model of HD [75]. In another study it was reported that expression of PGC-1α target genes was reduced in HD patients and in the striatum of HD transgenic mice [76]. Since the activity of PGC-1α can be regulated by SIRT1, it is conceivable that up-regulation of this pathway underlies SIRT1 neuroprotection in HD models.

The undisputable efficacy of resveratrol in HD models, however, has to be evaluated cautiously. The resveratrol molecule is subject to rapid oxidation in the cell and, as a consequence, may play a little role in activating sirtuins in the brain [77]. It is indeed possible that the therapeutic effects of resveratrol in HD may be the result of its well-known antioxidant properties [61,78–80]. The neuroprotective effects of anti-oxidants, minocycline, coenzyme Q10, and others have been shown in various models of neurodegeneration, including in HD models [69].

7. Wallerian neurodegeneration

Axon degeneration is an active process that occurs in neurodegenerative diseases and peripheral neuropathies. In a mutant mouse strain called slow Wallerian degeneration (*Wld*^{s}) the anterograde degeneration of transected axons is markedly delayed because of a mutation resulting in overexpression of a chimeric protein (Wld^s) composed of the ubiquitin assembly protein Ufd2a and the nicotinamide adenine dinucleotide (NAD) biosynthetic enzyme Nmnat1 [81]. It was suggested that the activity of Nmnat1 alone (independent on Ufd2a) provides the axon-protective activity of the Wld^s protein and that it is mediated by NAD production [82]. Resveratrol- or NAD-

pretreated neurons exhibit a decrease in axonal degradation after axon transection. Furthermore, SIRT1 knock-down or treatment with sirtinol blocked NAD-dependent axonal protection.

Therefore SIRT1 was proposed as the downstream effector in the Nmnat/NAD axonal protection activity. However, other groups suggested that other, SIRT1-non-dependent mechanisms lay below the Nmnat/NAD neuroprotective effect. In another study it was reported that the degeneration of transected axonal segments could be prevented by NAD exogenous local application 24 h before axon transection. Furthermore, similar protective effects of NAD could be observed in axons exposed to NAD directly at the time of transection or even until 5 h after transection [83]. This suggests that the NAD-dependent axon protection may be mediated primarily by its effect on local bioenergetics than through NAD-induced transcription and other nuclear events. In addition, neither the SIRT1 inhibitor sirtinol, nor resveratrol affected the protective effects of NAD in the same assay [83].

The role of SIRT2 in Wallerian degeneration has been studied as well. In a recent study, the authors focused on the hypothesis that suppression of microtubule depolymerization delays axonal degeneration, taking into account that *Wld*^{s} phenotype shows a substantial resistance to microtubule depolymerizing drugs [84–86]. The basal level of microtubule acetylation (stabilization) is increased in cultured cerebellar granule cells from Wld^{s} mice. SIRT2 overexpression abolished microtubule hyperacetylation and resistance to axonal degeneration in these cells. Furthermore, SIRT2 knock-down enhanced microtubule acetylation and resistance to axonal degeneration in wild-type cerebellar granule cells [84].

8. Future perspectives

A variety of pathological mechanisms are evidently associated with human neurodegenerative disorders, with no particular mechanism emerging as a major contributor. Apparently the outcomes of any effective neuroprotective strategy, targeting specific disease components, will remain uncertain until validation in human subjects. Despite recent exciting data, the feasibility of developing sirtuin-based therapy for human neurodegenerative diseases has yet to be demonstrated in animal models, and then in human trials.

At this stage, genetic and pharmacological manipulations in rodent disease models are crucial for target validation of sirtuin activities. While the former approach could be obscured by functional redundancy of HDAC family members, assessing the efficacy of highly potent and selective sirtuin ligands in rodent disease models appears as a key step of therapeutic development. Several formidable features are associated with chemical development of sirtuin ligands, including non-specific toxicity, cellular impermeability, poor PK properties, and brain-permeability. There are apparent liabilities associated with resveratrol structure, such as the low bioavailability in mammals, low solubility, and sensitivity to light and oxidation, which limit the use of this molecule in animal studies [87]. The discovery of synthetic SIRT1 agonists is an important step for the development of next generation of potent, selective, bioavailable, and brain-permeable SIRT1 activators [88]. Similarly, the discovery and development of therapeutic-grade activators and inhibitors against other sirtuin isoforms will be necessary to assess the therapeutic potential of these targets in rodent models of neurodegenerative diseases. The identification of efficacious molecules in animal models will expedite the development of lead-candidates for human clinical trials.

A major concern in the development of novel therapies is their safety for human subjects. One of the potential downsides associated with SIRT1 activation is the over consumption of NAD^+, an important bio-energetic molecule in the cell. Energy depletion has also been suggested to play a major role in neuronal cell-death in the neurodegenerative diseases [89]. The function of several enzymes that play important roles in the cellular responses to stress require NAD^+ for their activity including poly ADP-ribose polymerases (PARPs) and some histone deacetylases [4,90]. By consuming NAD^+, PARP1 may render neurons vulnerable to excitotoxicity and to cell-death [91–93]. SIRT1 activity also consumes NAD^+ and, as such, has the potential to deplete cellular energy. SIRT1 activity may be beneficial or detrimental depending upon the magnitude of SIRT1 activity and the cellular energy state. Indeed, it was reported that elevated SIRT1 levels increased the vulnerability of cardiac myocytes to age-dependent apoptosis, whereas lower levels of SIRT1 overexpression were protective, possibly by inducing a mild adaptive stress response [94]. However, the 'dark side' of SIRT1 activation, pertinent to the energy depletion, is likely to be less harmful for neurons than PARP1 activation. This notion rests on the fact that SIRT1 uses NAD^+ as a co-factor for its enzymatic activity and that PARP1, activated in response to oxidative stress and DNA damage, utilizes and cleaves a large fraction of NAD^+ molecules while it generates poly ADP-ribose polymers on histones and other protein substrates. Nevertheless, the potential negative effects of SIRT1 activation, including conditions of oxidative stress, have to be thoroughly investigated in rodent models. Interestingly, recent findings showed that nicotinamide riboside elevates NAD^+ and increases Sir2 function, thus potentially providing an alternative therapeutic pathway for SIRT1 activation which is harmless for the energy state of the cell [95]. Thus, sirtuins hold a great potential as therapeutic targets in neurodegeneration.

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