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REVIEW

Therapeutic potential and challenges of targeting sirtuins in neurodegenerative diseases

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Abstract Aging is the predominant risk factor for major neurodegenerative diseases. The underlying mechanisms are largely unknown. Members of the sirtuin family of protein deacetylases support and promote longevity in diverse organisms and can extend lifespan when upregulated. Sirtuins are involved in fundamental mechanisms in age-related neurodegenerative diseases, including protein aggregation and homeostasis, survival and stress responses, and inflammatory processes. In this review, we will discuss the neurobiology of sirtuins and their multifaceted roles in the pathogenesis of neurodegenerative diseases. We will also examine the potential and challenges of targeting sirtuin pathways to treat these devastating conditions.

Keywords Sirtuins, aging, neurodegenerative disease

1 Introduction

The proportion of older persons is rising rapidly in populations worldwide, and age-associated neurodegenerative diseases pose major medical and economic challenges for modern societies. Although neurodegenerative diseases have distinct clinical manifestations, mostly due to the impairment of specific neural networks, they have features in common, including the intra- or extracellular accumulation of misfolded proteins, compromised stress responses, mitochondrial dysfunction, and chronic inflammation. Most of these processes are strongly influenced by aging — the predominant and unifying risk factor for neurodegenerative diseases. Thus, activating molecular pathways that slow aging may provide a broad strategy to treat and prevent these conditions (Gan and Mucke, 2008). In this review, we will focus on sirtuins, whose activation slows aging in organisms ranging from protozoa to metazoa.

Sirtuins are class III histone deacetylases (HDACs or KDACs) that are phylogenetically conserved from bacteria to humans. Sirtuins regulate cell functions by deacetylating both histone and nonhistone targets, resulting in deacetylated proteins, nicotinamide, and O-acetyl-ADP-ribose (Tanner et al., 2000). Sirtuins are dependent on the relative levels of NAD^+ and nicotinamide adenine dinucleotide (NADH) and are thus uniquely responsive to the redox and metabolic states of a cell. Sir2 in *Saccharomyces cerevisiae* is the founding member of the sirtuin gene family. Its deacetylase activity is required for chromatin silencing at mating-type loci, telomeres, and the ribosomal DNA locus (Buck et al., 2004). In mammals, there are seven homologs (SIRT1–7), which are divided into four classes based on phylogenetic analysis (Frye, 2000). SIRT1 is the most studied among mammalian sirtuins. SIRT1–3 are robust deacetylases, whereas SIRT4–6 exhibit weak deacetylase activity on substrates tested so far. The distinct subcellular localizations of the sirtuins also contribute to their diverse functions (Saunders and Verdin, 2007). SIRT1, SIRT6, and SIRT7 reside predominantly in the nucleus and have been implicated in genomic stability and cell proliferation.

2 Activation of sirtuins extends life span

In *S. cerevisiae*, deletion of *SIR2* shortens the replicative life and overexpression of Sir2 lengthens it (Kaeberlein et al., 1999). In *Caenorhabditis elegans*, Sir-2.1 (the Sir2 orthologue) extends lifespan through activation of Forkhead box, class O (FOXO) transcription factor DAF-16 (Tissenbaum and Guarente, 2001). The direct interaction of Sir-2.1 with DAF-16 is dependent on Sir-2.1's association with 14-3-3 proteins (Berdichevsky et al., 2006) but is independent of insulin/insulin-like growth factor (IGF)-1 signaling, which also regulates longevity by activating DAF-16 (Kenyon, 2001). In *Drosophila melanogaster*, overexpression of dSir2 in the nervous system extends lifespan considerably (Rogina and Helfand, 2004).

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The most studied nongenetic strategy to extend lifespan is caloric restriction (CR), which activates sirtuin pathways (Kenyon, 2001). However, the link between CR-induced longevity and sirtuin activation is somewhat tenuous. There is evidence that CR extends lifespan by increasing the activity of Sir2 in *S. cerevisiae* (Lin et al., 2000) or the activities of its orthologs in *C. elegans* and *D. melanogaster* (Wood et al., 2004). Under certain conditions, however, CR also extends lifespan in *S. cerevisiae* in a Sir2-independent manner (Kaeberlein et al., 2004). CR increases SIRT1 expression in various rat tissues, but it is not known whether CR-induced lifespan extension in mammals is mediated by SIRT1. Notably, SIRT1 was required for serum from CR rats to inhibit Bax-mediated apoptosis in cultured human cells (Cohen et al., 2004). Moreover, CR-induced increases in locomotor activity were observed in wildtype mice but not in SIRT1 knockout mice (Chen et al., 2005a). Some of the beneficial effects of CR in wildtype mice have also been observed in SIRT1-overexpressing transgenic mice on a regular diet (Bordone et al., 2007). These findings raise the possibility that at least some of the beneficial effects of CR in mammals are mediated by sirtuins.

3 Sirtuins modulate protein homeostasis

3.1 Production of pathogenic proteins

Aβ peptides are of central importance in Alzheimer's disease (AD) pathogenesis. According to the “amyloid hypothesis,” accumulation of Aβ peptides triggers neuronal and synaptic damage, inflammatory responses, and the formation of neurofibrillary tangles, leading to neurotransmitter deficits and cell death (Hardy and Selkoe, 2002). Some of the most compelling evidence for the amyloid hypothesis came from the genetic analysis of a small subset of AD patients with familial mutations, most of which are associated with increased production of Aβ peptides (Tanzi and Bertram, 2005). Specific types and forms of soluble Aβ assemblies have been implicated as the earliest triggers in the amyloid toxicity pathway (Klein, 2002; Lesne et al., 2006). SIRT1 activation reduces Aβ production by promoting the anti-amyloidogenic cleavage of amyloid protein precursor (APP) by α-secretase, a process that involves inhibition of Rho-associated coiled-coil protein kinase 1 (ROCK-1) expression (Qin et al., 2006).

In contrast to the protective role of SIRT1 in AD pathogenesis, the onset of the prion disease is delayed by CR or by the absence of SIRT1 in knockout mice fed *ad libitum*. Surprisingly, SIRT1 levels are downregulated in certain brain regions of CR mice, and deleting SIRT1 lowers the expression of PrP mRNA and protein in the brain (Chen et al., 2008). Thus, SIRT1 inhibition protects against prion disease, possibly by reducing the production of PrP. These studies highlight the complexity of the role of SIRT1 in regulating the homeostasis of pathogenic proteins.

3.2 Clearance of pathogenic misfolded proteins

Besides affecting the production of pathogenic proteins, sirtuins may also regulate the removal of misfolded proteins. In mammalian cells, misfolded proteins can be removed by the proteasome-mediated pathway or the autophagy-lysosomal pathway. For example, SIRT1 deacetylates autophagy genes and stimulates basal rates of autophagy (Lee et al., 2008), which has emerged as an important route for the removal of toxic misfolded protein aggregates that accumulate in neurodegenerative diseases (Levine and Kroemer, 2008). Lysine deacetylation induced by sirtuins could also enhance proteasome-mediated degradation by allowing more lysine residues to be ubiquitinated, as in the cases of p53 (Ito et al., 2002), Runx (Jin et al., 2004), and Smad7 (Gronroos et al., 2002).

3.3 Aggregation of toxic protein aggregates

Neurodegenerative diseases are also considered proteinopathies, as misfolded proteins appear to play a pivotal role in diverse neurodegenerative diseases. Aging is important in the accumulation of pathogenic protein assemblies. In *C. elegans*, for instance, the accumulation and toxicity of mutant huntingtin were markedly delayed in an *age-1* mutant with reduced IGF-1 signaling and extended lifespan (Morley et al., 2002). This effect depended on the FOXO transcription factor DAF-16, the downstream mediator of Sir-2.1 (the worm ortholog of mammalian SIRT1). DAF-16 was also required for reduced insulin/IGF-1 signaling to protect against Aβ toxicity in *C. elegans*, an effect that may relate to increased formation of larger Aβ aggregates, which are less toxic than smaller Aβ assemblies (Cohen et al., 2006). Similarly, reducing IGF signaling protected AD transgenic mice against behavioral impairment, neuroinflammation, and neuronal loss. This protection appeared to correlate with the hyperaggregation of Aβ, which leads to tightly packed, ordered plaques (Cohen et al., 2010). These findings indicate that the IGF signaling-regulated mechanism that protects from Aβ toxicity is conserved from worms to mammals. However, the direct involvement of SIRT1 in the assembly of Aβ peptides has not been established.

4 Sirtuins modulate neuronal functions

Aging and neurodegenerative diseases are both associated with the loss of neurons and neuronal processes, although the pattern of cell loss differs between the two conditions. It has been hypothesized that oxidative stress, DNA damage, and defects in DNA repair play a causal role in neuronal loss (Rass et al., 2007).

4.1 DNA damage

In response to DNA damage and oxidative stress, SIRT1 directly deacetylates p53, thereby repressing p53-dependent apoptosis (Luo et al., 2001; Vaziri et al., 2001). Treatment with resveratrol results in deacetylation of p53, reduced neuronal loss, and improved associative learning in p25 transgenic mice; these mice have increased levels of cyclin-dependent kinase 5 activity and, without treatment, show significant neuronal loss and cognitive impairments (Kim et al., 2007). Similarly, overexpression of SIRT1 protects against neurodegeneration induced by a mutant form of superoxide dismutase I in a model of amyotophic lateral sclerosis (Kim et al., 2007). Whether SIRT1 protects neurons in these models by deacetylating and inactivating p53 remains to be determined. Other cellular substrates in the DNA repair and stress-response pathway may be involved. For example, SIRT1 deacetylates the DNA repair protein Ku70, enabling it to interact with Bax, which prevents Bax from interacting with mitochondria and inducing apoptosis (Cohen et al., 2004).

4.2 Stress response

Forkhead transcription factors of the FOXO subfamily are transactivators that share functional similarities and participate in crosstalk with p53 (Pinkston-Gosse and Kenyon, 2007). FOXOs induce the transcription of genes involved in stress responses and survival, including DNA repair (*GADD45*), oxidative stress (*MnSOD*), cell-cycle arrest (*p27kip1*), and apopotsis (*BIM*). Depending on the promoters, the effects of SIRT1 on FOXO-induced gene expression range from activation to repression. In general, SIRT1 appears to shift FOXO-induced responses away from death by inhibiting apoptotic genes (*BIM*) and toward survival by promoting the expression of GADD45, p27kip1, and manganese superoxide dismutase (MnSOD) (Brunet et al., 2004). The intricate crosstalk between sirtuins and FOXO-dependent pathways needs to be re-examined in postmitotic neurons, since most related studies were performed in cell lines. Surprisingly, SIRT1 sensitizes neurons to oxidative damage (Li et al., 2008). SIRT1 inhibition is associated with resistance to oxidative damage. Deleting SIRT1 also lowers the levels of oxidized proteins and lipids in the brain. These studies suggest that mammalian sirtuins can play both protective and pro-aging roles under different pathophysiological conditions.

4.3 Mitochondrial functions

Various factors contribute to mitochondrial dysfunction in neurodegenerative diseases (Lin and Beal, 2006). Remarkably, in a proteomic survey of proteins acetylated on lysine residues, more than 20% were mitochondrial proteins involved in longevity regulators and metabolism (Kim et al., 2006), suggesting important modulatory roles for sirtuin deacetylases. For example, as one of the major sirtuins located in the mitochondrial matrix, SIRT3 modulates mitochondrial intermediary metabolism and fatty-acid use during fasting (Hirschey et al., 2010). In addition, SIRT1 directly deacetylates and activates peroxisome proliferator-activated receptor gamma (PPARγ) coactivator 1α (PGC-1α), a master regulator of mitochondrial number and function (Rodgers et al., 2005). Mutant huntingtin, the culprit in Huntington's disease (HD), inhibits expression of PGC-1α, leading to impairment of mitochondrial function (Cui et al., 2006). In transgenic mouse models of HD, genetic deletion of PGC-1α exacerbates the degeneration of striatal neurons and motor abnormalities. In contrast, overexpression of PGC-1α protects striatal neurons against mutant huntingtin in these models and in cell culture. Furthermore, activation of SIRT1 prevented polyglutamine-induced cell death in striatal neurons derived from HdhQ111 knock-in mice (Parker et al., 2005). These findings suggest that SIRT1 counteracts HD-related mitochondrial impairments by activating PGC-1α.

5 Sirtuins modulate aging-associated inflammation

5.1 NF-κB signaling in aging

Aging is associated with an upregulation of genes involved in inflammatory responses in the human brain (Lu et al., 2004; Franceschi et al., 2007). On the other hand, CR, which activates sirtuin pathways, attenuates aging-induced upregulation of inflammatory genes (Cao et al., 2001). These findings highlight an intriguing connection between the anti-inflammatory function of sirtuins and their potent anti-aging effects. Although the molecular mechanisms of age-related inflammation remain unclear, potential mechanisms include the activation of redox-sensitive transcription factors by the cumulative effects of oxidative damage during aging. For example, increased production of reactive oxygen species during aging is associated with upregulation of nuclear factor κB (NF-κB) (Kabe et al., 2005). Activation of NF-κB, in turn, induces the expression of proinflammatory genes, including cytokines, growth factors, and chemokines (Mattson and Meffert, 2006). Since some of the NF-κB-induced proteins are also potent NF-κB activators, the resulting vicious cycle may contribute to the establishment of a chronic inflammatory state and related pathologies.

Indeed, bioinformatics analyses identified the NF-κB binding domain as the motif most strongly associated with the aging process (Adler et al., 2007). In the skin of aged mice, genetic blockade of NF-κB reversed the global gene expression program and tissue characteristics to those of young mice (Adler et al., 2008). Moreover, a recent study linked hyperactive NF-κB signaling with shortened life span and an aging-like phenotype in SIRT6-deficient mice (Kawahara et al., 2009). SIRT6 interacts with the NF-κB RELA subunit and deacetylates histone H3 lysine 9 (H3K9) at NF-κB target gene promoters. In SIRT6-deficient cells, hyperacetylation of H3K9 at these target promoters is associated with increased RELA promoter occupancy and enhanced NF-κB-dependent modulation of gene expression, apoptosis, and cellular senescence. These studies provide strong evidence that continued NF-κB activation is required to enforce many features of aging.

5.2 NF-κB in innate immune responses

Innate immune responses, including prominent activation of microglia and astrocytes, are prolonged in various neurodegenerative diseases. In primary neuronal cultures, Aβ1-42 oligomers elicit cell death only in the presence of microglia. Constitutive inhibition of NF-κB signaling in microglia by expression of a nondegradable inhibitor κBα (IκBα) super-repressor blocked this neurotoxicity, indicating a critical role for microglial NF-κB signaling in Aβ-dependent neurodegeneration (Chen et al., 2005b). Notably, NF-κB-dependent transcription can be repressed by SIRT1, which deacetylates RelA/p65 at lysine 310 (Yeung et al., 2004). Increased expression of SIRT1 or treatment with resveratrol markedly reduced Aβ-dependent NF-κB activation in microglia and neuronal loss, suggesting that sirtuins block neuropathogenic inflammatory loops (Chen et al., 2005b).

5.3 Other inflammatory pathways

SIRT1 deacetylates and positively regulates liver X receptors (LXRs), which have emerged as integrators of lipid metabolism and inflammation (Li et al., 2007). Activation of LXRs inhibits NF-κB-dependent induction of inflammatory genes in macrophages/microglia (Joseph et al., 2003), and LXR signaling lowers Aβ levels in hAPP transgenic mice. One likely pathway is through engagement of the direct transcriptional target of the LXR, ATP-binding cassette transporter A1, in neuronal cells (Sun et al., 2003). More recent data suggest that LXR activation may also lower Aβ levels by promoting the phagocytic ability of microglia (Zelcer et al., 2007). Because of the prominence of microglial activation in diverse neurodegenerative conditions, these anti-inflammatory effects of sirtuins and LXRs could have broad relevance.

6 Compounds modulating sirtuin activities

6.1 Inhibitors of sirtuins

Structural and mechanistic insights into NAD$^+$-dependent deacetylation provide important information for developing compounds to selectively modulate sirtuin activities. Nicotinamide, a direct product of SIRT1 deacetylation, is a potent physiological inhibitor of SIRT1. It has been proposed that nicotinamide acts as a classical noncompetitive product inhibitor by intercepting an ADP-ribosyl-enzyme-acetyl peptide intermediate during regeneration of NAD$^+$. A nicotinamide analogue, isonicotinamide, antagonizes the inhibition of Sir2 *in vitro*, resulting in increased Sir2 deacetylation activity. Other SIRT1 inhibitors have been developed, including sirtinol, salermide, and EX-527 (Solomon et al., 2006). All three compounds are potent SIRT1/2 inhibitors, but only EX-527 has high specificity for SIRT1 but not SIRT2 (Peck et al., 2010).

6.2 Activators of sirtuins

In earlier studies, several putative yeast and human sirtuin-activating compounds were identified with a high-throughput screen. These compounds included several plant polyphenols. Among them, resveratrol (3,5,4'-trihydroxystilbene), a compound found in red wine, emerged as the most potent of 18 inducers of deacetylase activity. In addition, resveratrol was found to extend lifespan in yeast, *C. elegans*, and flies — but only if Sir2 was present. Resveratrol was also found to reduce insulin resistance, increase mitochondrial function, and prolong survival in mice fed a high-fat diet (Baur et al., 2006; Lagouge et al., 2006). Other putative SIRT1 activators that are structurally unrelated to resveratrol, including SRT1720, appear to improve whole-body glucose homeostasis and insulin sensitivity in mouse models related to type 2 diabetes (Milne et al., 2007).

However, more recent studies provided strong evidence that SRT1720, the structurally related compounds SRT2183 and SRT1460, and resveratrol do not lead to apparent activation of SIRT1 with native peptide or full-length protein substrates (Pacholec et al., 2010). Further analyses revealed that they activate SIRT1 with peptide substrate containing a covalently attached fluorophore, most likely by direct interaction with fluorophore-containing peptide substrates (Pacholec et al., 2010). These findings are consistent with an earlier observation that activation of SIRT1 by resveratrol *in vitro* appears to require a covalent attachment of a fluorophore at the carboxy group of the acetyl-lysine residue (Borra et al., 2005). Thus, developing authentic small-molecule sirtuin activators for native substrates remains a pressing challenge.

7 Conclusion

Tremendous progress has been made in identifying downstream effectors of sirtuins, which exert diverse anti-aging effects. Sirtuins block several processes that may contribute to age-dependent neuronal injury, including the abnormal aggregation and accumulation of misfolded proteins, the engagement of cell-death pathways, and mitochondrial dysfunction. By enhancing stress resistance and promoting repair processes, sirtuins can counteract the results of increasing oxidative damage. Besides protecting neurons directly, sirtuin activators also repress pathogenic inflammatory responses of glial cells. Thus, sirtuin modulators may provide new therapeutic avenues for preventing or delaying aging-related ailments, including neurodegenerative diseases.

It is important to recognize that the effects and regulation of sirtuins are extremely complex. Broad activation of sirtuins will lead to deacetylation of histones and various nonhistone proteins, which may affect diverse cellular functions. For example, SIRT1 and SIRT2 appear to have opposite effects on the aggregation of misfolded proteins. Moreover, depending on the cell type and pathophysiological circumstances, activation of a given sirtuin may have divergent outcomes. For example, SIRT1 appears to exert both protective and proaging roles under different pathophysiological conditions (Chen et al., 2008).

From a therapeutic perspective, it is promising that the activities of some sirtuins and of some of their downstream mediators, such as LXR receptors (Joseph et al., 2003), can be enhanced by small-compound activators. However, direct activation of SIRT1 by small molecules, such as resveratrol and SRT1720, has been called into question. More studies will be needed to develop new SIRT1 activators. Furthermore, it will be important to assess their ability to pass the blood–brain barrier and their effects on brain functions in behavioral assays.

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