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Paths of Convergence: Sirtuins in Aging and Neurodegeneration

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Abstract

Members of the sirtuin family of protein deacetylases support and promote longevity in diverse organisms and can extend life span when upregulated. Sirtuin pathways also modulate fundamental mechanisms in aging-related neurodegenerative diseases, including protein aggregation, stress responses, mitochondrial homeostasis, and inflammatory processes. In this minireview, we will discuss how progress in understanding the neurobiology of sirtuins is shedding light on the pathogenesis of these devastating conditions. We will also examine the potential and challenges of targeting sirtuin pathways therapeutically.

With the rapid growth of aging populations worldwide, age-associated neurodegenerative diseases pose major medical and economic challenges to modern societies. Indeed, the increasing prevalence of these disorders threatens to overwhelm our healthcare systems. Although significant progress has been made in deciphering the molecular mechanisms underlying these conditions, there is an urgent need for better strategies to stall, reverse, and prevent them.

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 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. This is where sirtuins may come into play.

Sirtuins–A Family of Histone Deacetylases

Sirtuins were first identified in *Saccharomyces cerevisiae* as silence information regulators (*SIRs*), from which the family derives its name (Rine and Herskowitz, 1987). These class III histone deacetylases (HDACs) consume one nicotinamide adenine dinucleotide (NAD^+) for every acetyl group they remove from a protein substrate (Landry et al., 2000). Their activities produce deacetylated proteins, nicotinamide, and O-acetyl-ADP-ribose (OAADPr)

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(Tanner et al., 2000). Sirtuins are dependent on the relative levels of NAD^+ and NADH and are thus uniquely responsive to the redox and metabolic states of a cell.

Sirtuins are phylogenetically conserved from bacteria to humans and regulate cell functions by deacetylating both histone and nonhistone targets. Sir2 in *S. cerevisiae* is the founding member of the sirtuin gene family, and its deacetylase activity is required for chromatin silencing at mating-type loci, telomeres, and the ribosomal DNA locus (Buck et al., 2004). There are seven human homologs (SIRT1–7), which are divided into four classes according to phylogenetic analysis (Frye, 2000) (Table 1). 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. SIRT1 is the most studied among mammalian sirtuins. Many of its nonhistone substrates have been identified, including p53, NF-κB, forkhead transcription factor (FOXO), Ku70, peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), and liver X receptor (LXR) (Li et al., 2007b; Motta et al., 2004; Nemoto et al., 2005; Rodgers et al., 2005; Vaziri et al., 2001; Yeung et al., 2004). SIRT2, which resides mostly in the cytoplasm, is involved in mitosis and differentiation of oligodendrocytes, likely through deaceylation of tubulins (Li et al., 2007a; North et al., 2003). Because SIRT3, SIRT4, and SIRT5 are localized in mitochondria, they may play a role in energy metabolism and responses to oxidative stress.

In this review, we will focus on SIRT1 and, to a lesser extent, SIRT2, because these sirtuins play important roles in aging and neurodegeneration and because next to nothing is known about the roles of the other sirtuins in the central nervous system.

The Pleiotropic Antiaging Effects of Sirtuins and Caloric Restriction

In organisms ranging from protozoa to metazoa, activation of sirtuins delays the aging process. The replicative life span of *S. cerevisiae* is shortened by the deletion of *SIR2* and lengthened by the overexpression of Sir2 (Kaeberlein et al., 1999). In *Caenorhabditis elegans*, life span extension induced by Sir-2.1 (the Sir2 ortholog) is mediated through activation of 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 life span considerably (Rogina and Helfand, 2004). The SIRT1 agonist resveratrol extends the life span of mice fed a high-caloric diet (Baur et al., 2006). However, whether increased SIRT1 activity promotes longevity also in mammals fed a normal diet has not yet been reported.

The most studied nongenetic strategy to extend life span is caloric restriction (CR), which activates sirtuin pathways (Kenyon, 2001). However, the link between CR-induced longevity and sirtuin activation remains somewhat tenuous. There is evidence that CR extends life span 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). However, under certain conditions, CR can also extend life span in *S. cerevisiae* in a Sir2-independent manner (Kaeberlein et al., 2004). CR increases SIRT1 expression in various rat tissues, but whether CR-induced life span extension in mammals is mediated by SIRT1 remains unknown. 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 wild-type mice, but not in SIRT1 knockout mice (Chen et al., 2005a). Some of the beneficial effects found in CR wild-type mice have also been observed in SIRT1-overexpressing transgenic mice on a regular diet (Bordone et al., 2007). These findings raise the possibility that in mammals at least some of the beneficial effects of CR are mediated by sirtuins.

Sirtuins Regulate the Aggregation and Removal of Misfolded Proteins

Abnormal accumulation of misfolded proteins appears to play a pivotal role in diverse neurodegenerative diseases (Figure 1). Pertinent molecules include Aβ peptides and tau in AD, α-synuclein in Parkinson's disease (PD), TDP-43 in frontotemporal dementia, and mutant huntingtin in Huntington's disease (HD) (Muchowski and Wacker, 2005).

Why do all the resulting proteinopathies typically emerge late in life? Recent studies suggest that aging promotes the accumulation of pathogenic protein assemblies and that this process might be counteracted by antiaging pathways (Figure 1). 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 life span (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).

Interestingly, formation of large and less toxic α-synuclein aggregates in a cellular model of PD was enhanced by inhibition of SIRT2 (Outeiro et al., 2007). Specific SIRT2 inhibitors also reduced α-synuclein-dependent neuronal deficits in primary neuronal midbrain cultures expressing a mutant form of α-synuclein and in a *Drosophila* model of PD (Outeiro et al., 2007). The findings that activation of the SIRT1 pathway and inhibition of the SIRT2 pathway had similar effects on the aggregation of misfolded proteins may be due to the distinct subcellular localization of these sirtuins and/or to differences in their substrates.

Sirtuins may also regulate the steady-state levels of misfolded proteins by blocking their production or facilitating their removal. In mammalian neurons, increased expression of SIRT1 prevented Aβ production by promoting the antiamyloidogenic cleavage of APP by α-secretase, a process that involved inhibition of ROCK1 expression (Qin et al., 2006). In cultured human embryonic kidney cells, the Aβ-reducing effect of resveratrol was mediated by proteasome-dependent intracellular Aβ degradation (Marambaud et al., 2005). Recent evidence also suggests that SIRT1 deactylates 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). Defining the precise roles of sirtuins in the production, assembly, and degradation of pathogenic proteins may help elucidate the etiology of neurodegenerative diseases and open up new avenues for therapeutic intervention.

Sirtuins Regulate Stress Responses and Cell Survival

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

In response to DNA damage and oxidative stress, SIRT1 directly deacetylates p53, repressing p53-dependent apoptosis (Luo et al., 2001; Vaziri et al., 2001)(Figure 1). Treatment with resveratrol resulted in deacetylation of p53, reduced neuronal loss, and improved associative learning in p25 transgenic mice, which 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 protected against neurodegeneration induced by a mutant form of superoxide dismutase I in a model of amyotrophic 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 Ku70 to interact with Bax, which prevents Bax from interacting with mitochondria and inducing apoptosis (Cohen et al., 2004).

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 a variety 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 (Figure 1). In general, SIRT1 appears to shift FOXO-induced responses away from death by inhibiting apopototic genes (*BIM*) and toward survival by promoting the expression of GADD45, p27kip1, and MnSOD (Brunet et al., 2004). Interestingly, SIRT2-mediated deacetylation of FOXO3a elevates the expression not only of p27kip1 and MnSOD, but also of Bim, a proapoptotic factor. Consequently, SIRT2 decreases cellular levels of reactive oxygen species but promotes cell death when cells are under severe stress (Wang et al., 2007), highlighting the complexity of sirtuins in the cellular stress response. However, because some related studies were performed in nonneuronal transformed cell lines, many aspects of the intricate crosstalk between sirtuins and FOXO-dependent pathways need to be re-examined in postmitotic neurons.

Sirtuins may also play a role in axonal degeneration, although this area is quite controversial. For example, it has been debated whether SIRT1 is responsible for the delay in injury-induced axonal degeneration in Wld^{S} mutant mice (Fainzilber and Twiss, 2006).

The Wld^S mutant protein consists of the N-terminal 70 amino acids of the Ube4b ubiquitination assembly factor fused with full-length nicotinamide mononucleotide adenyltransferase-1 (Nmnat1). Opinions are divided as to whether the protection is mediated by (1) a dominant-negative effect of Ube4b, (2) an increase in Nmnat, an essential enzyme in the biosynthesis pathway leading to NAD, which in turn is required for SIRT1 activation, or (3) the effects of regulatory regions outside the two open reading frames (Fainzilber and Twiss, 2006). Even among the studies supporting a protective role of increased Nmnat activity, the involvement of SIRT1 is controversial. For example, SIRT1 was required for the delay of injury-induced axonal degeneration in Wld^S mice (Araki et al., 2004) but not in a model in which NAD was applied locally (Wang et al., 2005). This discrepancy might be explained by the different time frames studied (12–72 hr in the former study and 4–12 hr in the latter). Intriguingly, in Wld^S mice, tubulin is hyperacetylated, and overexpression of SIRT2 led to tubulin deacetylation and reversed the delay in injury-induced axonal degeneration in Wld^S granule cells, suggesting that inhibition of SIRT2 is protective via regulating microtubule acetylation and stability (Suzuki and Koike, 2007). Sorting out the complex roles of sirtuins in axonal degeneration remains a challenging objective.

Sirtuins Modulate 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% of them were mitochondrial proteins involved in longevity regulators and metabolism (Kim et al., 2006). This study supports the importance of sirtuin-mediated deacetylation in the maintenance of mitochondrial functions during aging. Particularly interesting in this regard is PGC-1α, a master regulator of mitochondrial number and function, which is directly deacetylated and activated by SIRT1 (Rodgers et al., 2005) (Figure 1). It exerts robust protection against neuronal injury induced by hydrogen peroxide, the excitotoxin kainic acid, and the PD-related neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (St-Pierre et al., 2006). Mutant huntingtin 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 (Cui et al., 2006). In contrast, overexpression of PGC-1α protects striatal neurons against mutant huntingtin in these models and in cell culture (Cui et al., 2006). Furthermore, activation of SIRT1 prevented polyglutamine-induced cell death in striatal neurons derived from HdhQ111 knockin mice (Parker et al., 2005). These findings suggest that SIRT1 counteracts HD-related mitochondrial impairments by activating PGC-1α.

Sirtuins as Anti-inflammatory Mediators

Aging is associated with an upregulation of genes involved in inflammatory responses in the human brain (Lu et al., 2004). CR, which activates sirtuin pathways, attenuates this upregulation (Cao et al., 2001), suggesting an intriguing connection between the anti-inflammatory function of sirtuins and their potent antiaging effects.

The molecular mechanisms of age-related inflammation are 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 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). Because 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.

Prolonged innate immune responses, including prominent activation of microglia and astrocytes, are seen in various neurodegenerative diseases (Figure 1). In cell culture, Aβ1–42 oligomers elicit the death of primary neurons only in the presence of microglia. Constitutive inhibition of NF-κB signaling in microglia by expression of a nondegradable 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)(Figure 1).

The discovery that SIRT1 deacetylates and positively regulates LXRs further highlights the anti-inflammatory function of sirtuins (Li et al., 2007b)(Figure 1). Originally identified as key regulators of lipid metabolism, LXRs have emerged as integrators of lipid metabolism and inflammation. 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.

Conclusions and Perspectives

Activation of sirtuin signaling pathways has diverse antiaging effects and may provide new therapeutic avenues for preventing or delaying aging-related ailments, including neurodegenerative diseases. By identifying downstream effectors of sirtuins, recent studies have unraveled some of the mysteries underlying the pleiotropic antiaging effects of sirtuin activation (Figure 1). Sirtuins can block several processes that may contribute to aging-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.

From a therapeutic perspective, it is promising that the activity 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. Activation of SIRT1 by the non-specific sirtuin activator resveratrol reduces insulin resistance, increases mitochondrial function, and prolongs survival in mice fed a high-fat diet (Baur et al., 2006; Lagouge et al., 2006). Highly potent and much more specific SIRT1 activators that are structurally unrelated to resveratrol improve whole-body glucose homeostasis and insulin sensitivity in mouse models related to type-2 diabetes (Milne et al., 2007). However, it remains to be determined if these SIRT1 activators can pass the blood–brain barrier and how they may affect brain functions in behavioral assays.

It is also important to note 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 activation in primary cells that have wild-type p53, FOXO, and DNA damage promotes cell-cycle arrest and survival by inhibiting apoptosis. In tumor cells that have DNA damage but lack wild-type p53 or FOXO, SIRT1 activation can promote tumorigenesis by allowing cells to proliferate without arresting or repair (Saunders and Verdin, 2007). It is likely that much more information will need to be gathered about this intriguing network of antiaging molecules before it can be harnessed pharmacologically and effectively engaged in the fight against neurodegenerative disorders.

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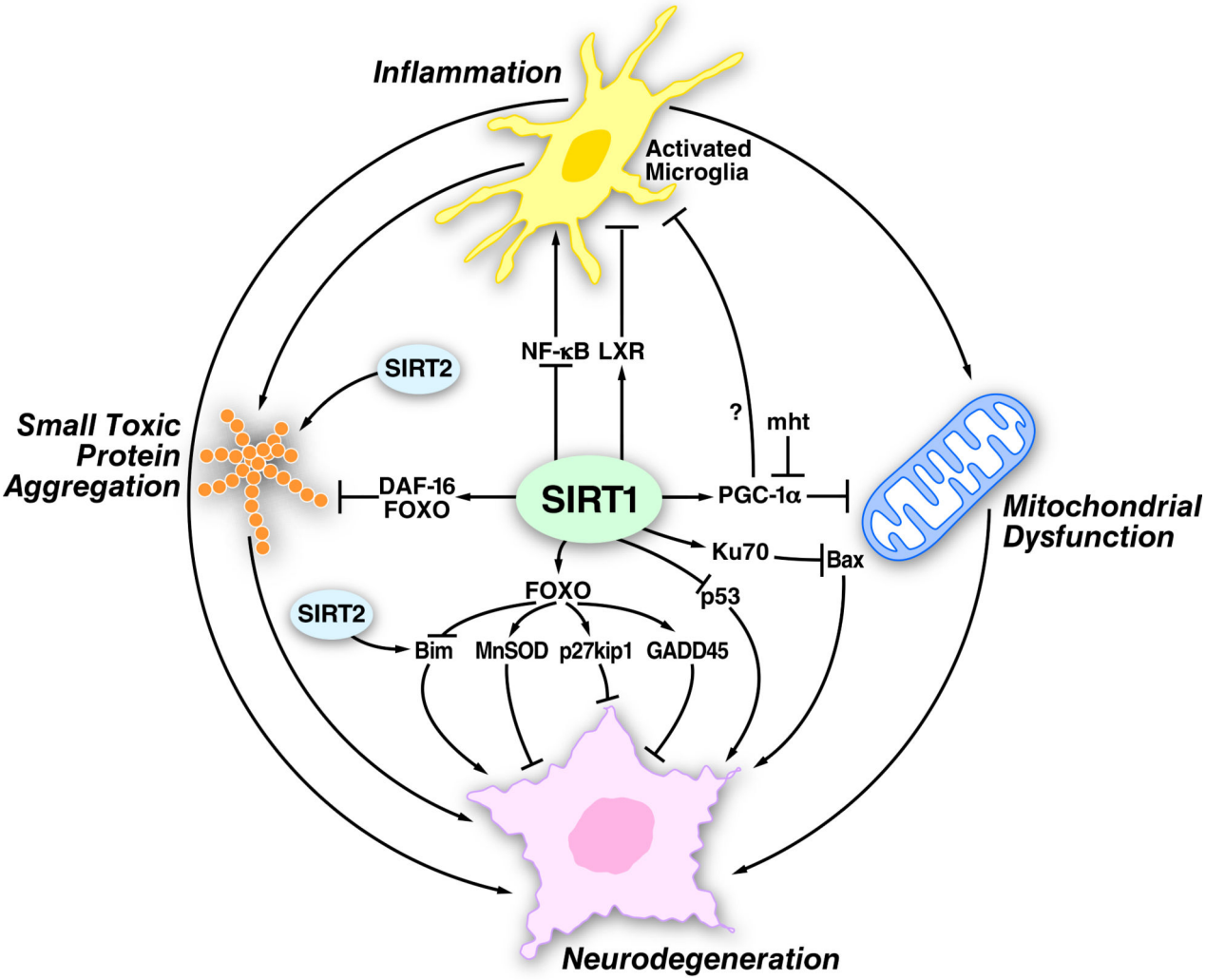

Figure 1.

Potential Roles of Sirtuins in Aging and Neurodegenerative Disease

Shown are major pathways and downstream mediators by which SIRT1 and SIRT2 may regulate aging and neurodegenerative processes, including protein aggregation (DAF-16), stress responses (FOXO, p53, Ku70), mitochondrial dysfunction (PGC-1α), and inflammation (NF-κB and LXR). Some of the downstream mediators are involved in multiple pathways. For example, FOXO transcription factors regulate genes involved in stress responses (GADD45, MnSOD, p27kip), survival (Bim), and the aggregation and degradation of proteins. In a similar vein, the processes sirtuins affect are highly interconnected. For example, abnormal protein aggregates may injury neurons directly or indirectly by activating inflammatory processes, which can further enhance protein aggregation. By intervening at one or more critical steps, sirtuins could block vicious cycles and exert broad protective effects. Arrows indicate activation; blunt arrows indicate suppression.

Table 1.

Classification of mammalian sirtuins and their orthologs

	Mammals	D. melanogaster	C. elegans	S. cerevisiae
Class I	***SIRT1***	***dSir2 (D. mel 1)***	***Sir-2.1***	***Sir2 & Hst1***
	SIRT2*/3*	*D. mel 2*	–	*Hst2*
Class II	*SIRT4*	*D. mel 3*	*C. ele 2 & 3*	–
Class III	*SIRT5*	–	–	–
Class IV	*SIRT6*	*D. mel 4*	*C. ele 4*	–
	SIRT7	*D. mel 5*	–	–

The seven mammalian sirtuins and their orthologs in other eukaryotes are classified into four classes according to phylogenetic analysis (Frye, 2000). Genes in bold are discussed in detail in this minireview. Dashes indicate that no corresponding molecules have been identified.