Sirtuins in neurodegenerative diseases: an update on potential mechanisms

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INTRODUCTION

The past decade has seen an explosion of studies of sirtuins in health and disease. The founding member of the sirtuin gene family Sir2 was originally found in yeast, but others have since been found in many organisms (Kaeberlein et al., 1999). Mammalian sirtuins have seven homologs (SIRT1–7) that share a conserved catalytic core domain as class III histone deacetylases (HDACs) but exhibit different enzymatic activities in distinct subcellular localizations. Unlike class I and II HDACs, which require only zinc as a cofactor, sirtuins depend on NAD+ for activity. In the presence of NAD+, sirtuins catalyze the conversion of an acetylated substrate to a deacetylated substrate with O-acetyl-ADP-ribose and nicotinamide as side products.

SIRT1 shares the greatest homology with yeast Sir2 (Frye, 2000). In addition to histones, SIRT1 catalyzes deacetylation of a large number of non-histone substrates in the nucleus and cytoplasm. It is involved in diverse cellular functions, including maintaining genomic stability, suppressing inflammation, enhancing synaptic plasticity, and protecting against neurodegeneration. Like SIRT1, SIRT2 is a strong deacetylase with some common substrates in the cytoplasm and nucleus (Doutremepuich and Outeiro, 2013). SIRT3–5 are localized mainly in the mitochondria. SIRT3 is the major mitochondrial deacetylase with a broad range of substrates (Newman et al., 2012). SIRT4 is a mitochondrial ADP-ribosyltransferase without any recognized deacetylase activity, and SIRT5 is both an NAD+-dependent deacetylase and deacetylase (deamidase and desuccinylase; Du et al., 2011). Localized exclusively in the nucleus, SIRT6 is a chromatin-bound NAD+-dependent deacetylase and an ADP-ribosyltransferase. SIRT7 is localized to the nucleolus and regulates ribosomal DNA gene expression (Ford et al., 2006; Jia et al., 2012; Table 1).

Sirtuins have potential mechanisms that promote free radicals and provide key factors that regulate protecting against neurodegenerative diseases.

Keywords: SIRT1, neurodegeneration, amyloid-β, tau, inflammation, NF-κB, mitochondria, epigenetic regulation

TABLE 1

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Alzheimer’s disease (AD) is the most common dementia in the elderly population. Aβ peptides are believed to be a key culprit in AD (Hardy and Selkoe, 2002). Although amyloid plaques are well-recognized pathological hallmarks in AD brains, specific types and forms of soluble Aβ oligomers have been implicated as the earliest triggers in the amyloid toxicity pathway (Klein, 2002; Lesne et al., 2006; Querfurth and LaFerla, 2010). The amyloid hypothesis is strongly supported by human genetic analyses: the vast majority of familial mutations that cause early-onset AD are associated with increased production of Aβ peptides, leading to imbalance in homoeostatic control of protein levels (Tanzi and Bertram, 2005). In contrast, a coding mutation that protects against AD and cognitive decline also reduces the production of Aβ by 40% (Jonsson et al., 2013). SIRT1 lowers Aβ levels by reducing its production from amyloid precursor protein (APP). Cleavage of APP by α-secretase results in production of non-amyloidogenic fragments, and cleavage by β- and γ-secretases results in various Aβ and C-terminal fragments (Hardy and Selkoe, 2002). In cultured cells, SIRT1 enhances α-secretase activity via inhibiting the Rho-associated, coiled-coil-containing protein kinase 1 (ROCK), and reduces Aβ production (Figure 1; Qin et al., 2006). A more recent study showed that SIRT1 also enhances the transcription of ADAM10, a

| Subcellular localization | Catalytic activity  |
|--------------------------|---------------------|
| SIRT1 Nucleus, cytoplasm  | Deacetylase         |
| SIRT2 Nucleus, cytoplasm  | Deacetylase         |
| SIRT3 Mitochondria       | Deacetylase         |
| SIRT4 Mitochondria       | ADP-ribosyltransferase |
| SIRT5 Mitochondria       | Deacetylase, deacetylase |
| SIRT6 Nucleus            | Deacetylase, ADP-ribosyltransferase |
| SIRT7 Nucleolus          | Deacetylase         |

FIGURE 1 | Protective mechanisms of SIRT1 in AD. SIRT1 deacetylates tau protein at multiple residues, and enhances tau polyubiquitination and subsequent proteasomal degradation. Overexpression of SIRT1 deacetylates retinoic acid receptor (RAR) β and activates ADAM10, a component of the α-secretase, which processes APP along an anti-amyloidogenic pathway that decreases formation of toxic Aβ species. SIRT1 was also shown to enhance α-secretase cleavage via a mechanism involving reducing ROCK1, which suppresses α-secretase cleavage.
AD, the number and extent of neurofibrillary tangles are the best late stages of tauopathies (Min et al., 2010; Cohen et al., 2011; Irwin). Indeed, tau was acetylated in the early and deacetylates tau, and its deficiency results in enhanced levels of acetylated tau and phosphorylated tau (Min et al., 2010; Cohen et al., 2011; Irwin et al., 2012; Grinberg et al., 2013). SIRT1 deacetylates tau, and its deficiency results in enhanced levels of acetylated tau and phosphorylated tau (Min et al., 2010; Figure 1).

SIRT1 has been implicated in several neurodegenerative diseases, including dementia with Lewy bodies, Parkinson's disease (PD), and multiple system atrophy (Goedert et al., 2013). SIRT1 suppresses the formation of α-synuclein inclusions in Caenorhabditis elegans (van Ham et al., 2008). Treatment with resveratrol, an indirect activator of SIRT1, protected cells of the human neuroblastoma line SK-N-NE against toxicity induced by expression of α-synuclein carrying familial PD mutation (AMBP; Albani et al., 2009). This protective mechanism depends on SIRT1; treatment with arsinol, a specific inhibitor of SIRT1, restored toxicity. SIRT1 reduced the number of α-synuclein aggregates in the brains of mice expressing A35T α-synuclein. SIRT1 deacetylates heat shock factor-1 (Westerheide et al., 2009), resulting in an increased expression of Hsp70, a molecular chaperon that could serve as a protective mechanism against α-synuclein toxicity (Donmez et al., 2012). In contrast, inhibiting SIRT2 rescued α-synuclein-mediated toxicity and modified aggregation in models of PD in vitro (Ortiz et al., 2007). The opposing effects of SIRT1 and SIRT2 on synucleopathies could reflect their distinct subcellular localizations and substrates.

In mammalian cells, misfolded proteins can be removed by the proteasome or the autophagy–lysosomal pathways. Since acetylation and ubiquitination both occur at lysine residues, acetylation often interferes with polyubiquitination, which is required for proteasome-mediated degradation. Thus, lack of SIRT1 induces hyperacetylation of the substrate proteins, which preclude them from the polyubiquitination process, resulting in increased steady-state protein levels. For example, inhibition of SIRT1 blocks tau polyubiquitination and tau turnover, likely via increased acetylation of tau on lysine residues that are also subject to polyubiquitination (Min et al., 2010).

SIRT1 deacetylates autophagy gene products 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). Autophagy induced by SIRT1 activation prevented neurotoxicity by prion protein fragment (106–126) in a neuronal cell line (Jeong et al., 2013). Degradation of α-synuclein was also enhanced by SIRT1 activator via autophagy induction in α-synuclein-expressing PC12 cell lines (Wu et al., 2011). In agreement with these findings in mammalian cells, Sir2 promotes both autophagy and mitophagy in Saccharomyces cerevisiae (Sampaio-Marcues et al., 2012). In contrast to the autophagy-enhancing effects of SIRT1, SIRT2 inhibits the autophagy-mediated degradation of protein aggregates in neuronal cell lines (Gal et al., 2012). In a neuronal cell line, overexpression of SIRT2 inhibits lysosome-mediated autophagic turnover of protein aggregates and exacerbates toxicity induced by AB (Gal et al., 2012).

**NEUROPLASTICITY**

Regulation of the formation and maintenance of memory involves epigenetic mechanisms, such as post-translational modifications of histone tails, DNA methylation, and non-coding RNA (Fischer et al., 2007; Day and Sweatt, 2011; Wang et al., 2012). Brain-specific SIRT1 knockout mice showed deficits in learning and memory, supporting the importance of SIRT1 in maintaining neural plasticity (Gao et al., 2010). Whether and how other sirtuins might regulate neural plasticity remains to be determined.

Brain-derived neurotrophic factor (BDNF), which plays a critical role in neural plasticity (Lipsky and Marini, 2007), is enhanced by SIRT1 (Gao et al., 2010). Specifically, it increases the number of dendritic spines, neuronal connectivity, and memory function. SIRT1 deficiency reduces BDNF expression by upregulating the microRNA miR-134 (Gao et al., 2010). SIRT1 forms a repressor complex with the transcription factor YY1 to suppress miR-134 expression (Gao et al., 2010). Another mechanism by which SIRT1 regulates BDNF involves deacetylation of methyl-CpG binding protein 2 (MeCP2). This action allows MeCP2 to be released from the methylated CpG sites within the BDNF exon 4 promoter, resulting in increased BDNF transcription in hippocampus (Zocchi and Sassone-Corsi, 2012).

The importance of cAMP response element-binding protein (CREB) as a crucial regulator for learning and memory process is conserved from mollusk neurons in culture to complex behaviors in mammals (Bliss and Collingridge, 1993; Alberini et al., 1994). Like BDNF, SIRT1 enhances CREB expression through the miR-134 pathway (Gao et al., 2010). SIRT1 directly deacetylates CREB and modulates its activity in liver (Qiang et al., 2011) but not in brain (Pascos et al., 2012). CREB is involved in the brain’s response to CR, which upregulates SIRT1 levels. Increased SIRT1 levels, in turn, enhance CREB-dependent expression of genes involved in neuronal metabolism, survival, and plasticity (Pascos et al., 2012). Although the exact molecular mechanism underlying the CREB–SIRT1 axis is unknown, these findings highlight a unique molecular network at the crossroad of energy metabolism, metabolic diseases, and brain aging.

**MITOCHONDRIAL FUNCTIONS**

Mitochondria are critical regulators of neuronal survival and death. They produce energy in response to nutrient availability and are the main contributors of oxidative stress. Accumulating lines of evidence suggest that disruption of mitochondrial processes leads to neurodegenerative diseases (Lin and Beal, 2006). In a proteomic survey of lysine acetylation, more than 20% of mitochondrial
proteins are acetylated on their lysine residues (Newman et al., 2012). This study supports the importance of modulatory role of sirtuins as deacetylases in the maintenance of mitochondrial functions. Most studies focused on SIRT1 and SIRT3 as the primary regulators of mitochondrial biology via deacetylation (Brenneman and Hoeflich, 2013). SIRT1 and SIRT3 are also localized in mitochondrial cristae. However, SIRT4 has only weak ADP ribosyltransferase activity (Verdin et al., 2010), and SIRT5 regulates malonylation and succinylation (Du et al., 2011). Indeed, SIRT3 knockout mice display remarkable increases in the acetylation levels of mitochondrial proteins, whereas no mitochondrial hyperacyetylation was observed when the two other mitochondrial sirtuins, SIRT4 and SIRT5, were deleted (Lombard et al., 2007).

SIRT1 deacylates and activates PGC-1α, a transcriptional coactivator that regulates several key mitochondrial processes, including mitochondrial biogenesis and oxidative phosphorylation (Rodríguez et al., 2005). SIRT1 also enhances transcription of PGC-1α gene via interaction with Mysod, which binds to the PGC-1α promoter (Amat et al., 2009). PGC-1α is required for the induction of reactive oxygen species (ROS)-detoxifying enzymes. PGC-1α null mice show high degree of sensitivity to the neurodegenerative effects of oxidative stressors (St-Pierre et al., 2006). In models of Huntington’s disease (HD), transcription of PGC-1α is repressed by mutant huntingtin, the protein that causes HD. PGC-1α knockout exacerbates neurodegeneration and motor abnormalities in the HD knockin mice. Conversely, PGC-1α expression ameliorates, in part at least, mitochondrial dysfunction and neuronal toxicity induced by mutant huntingtin (Cui et al., 2006). Elevating SIRT1 activity ameliorated neuronal dysfunction induced by mutant polyglutamines in C. elegans (Jiang et al., 2012). Polyglutamine cytotoxicity is prevented by SIRT1 activation in neurons derived from HdhQ111 KI mice (Parker et al., 2012). This study supports the importance of modulatory role of sirtuins and their potent anti-aging effects. In addition, many age-related neurodegenerative diseases, such as AD, frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and PD, exhibit prolonged inflammatory responses (Glass et al., 2010). Thus, anti-inflammatory effects of sirtuins could have broad relevance in aging and neurodegeneration.

Nuclear factor kappa B (NF-kB) is a master regulator of immune response and inflammation (Hayden and Ghosh, 2012). Bioinformatics analyses identified the NF-kB 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-kB reversed the global gene expression program and tissue characteristics to those of young mice (Adler et al., 2008). The mechanism might involve activation of redox-sensitive transcription factors by the cumulative effects of oxidative damage during aging. For example, the increased production of ROS during aging is associated with upregulation of NF-kB (Kabe et al., 2005). Activation of NF-kB, in turn, induces the expression of proinflammatory genes, including cytokines, growth factors, and chemokines (Matsui and Meffert, 2006). Since some of the NF-kB-induced proteins are also potent NF-kB activators, the resulting vicious cycle may contribute to establishment of a chronic inflammatory state and related pathologies.

NF-kB is also important in modulating cellular senescence. Genetic reduction of p53 subunit or pharmacological inhibition of NF-kB delayed the onset of progeroid symptoms in accelerated aging mouse model caused by a defect in DNA repair (Tlsty et al., 2012). In human fibroblasts, senescence induced by activation of p16 and p53 resulted in global regulation of NF-kB pathways; silencing of NF-kB overcame senescence (Rovillain et al., 2011). Senescence is also suppressed by overexpressing SIRT1, which was downregulated in the senescent cells (Rovillain et al., 2011). Thus,
the beneficial effects of SIRT1 on senescence are likely mediated by inactivation of NF-κB pathways.

NF-κB-dependent transcription is repressed by SIRT1, which deacetylates p65/RelA at lysine 310 (Young et al., 2004; Figure 2). Macrophages derived from myeloid cell-specific SIRT1 knockout mouse model had higher levels of proinflammatory cytokines that are associated with NF-κB hyperacetylation (Schug et al., 2010). In primary cortical cultures, microglial NF-κB activation played a critical role in Aβ-mediated neuronal death (Chen et al., 2005). Increased expression of SIRT1 or treatment with resveratrol markedly reduced Aβ-dependent NF-κB activation in microglia and neuronal loss, suggesting that SIRT1 blocks the neuropathogenic inflammatory loops (Benes, 2012). It consumes NAD+ in the process of forming (ADP-ribose) polymers on target proteins (Canto et al., 2013). In cardiomyocytes, SIRT1 interacts and deacetylates PARP-1, resulting in reduced PARP-1 activity (Rajamohan et al., 2009). SIRT1 is also capable of suppressing the activity of the PARP-1 gene promoter, leading to decreased PARP-1 protein synthesis (Rajamohan et al., 2009). As PARP-1 is required and sufficient for specific transcriptional activation of NF-κB, it is thus conceivable that SIRT1 could suppress NF-κB signaling by reducing PARP-1 (Figure 2). Further studies will be needed to establish the causative link. On the other hand, since PARP-1 uses NAD+ as a substrate to synthesize PAR, excessive PARP-1 activation could deplete NAD+ levels, resulting in SIRT1 inhibition and NF-κB activation (Figure 2). In primary astrocyte cultures, activation of PARP-1 with N-methyl-N-nitro-N-nitrosoguanidine resulted in sustained acetylation of p65 and NF-κB activation, likely by inhibiting SIRT1 due to depleted NAD+ levels (Kauppinen et al., 2013). Consistent with this notion, addition of exogenous NAD+ led to p65 deacetylation and inhibition of NF-κB signaling (Kauppinen et al., 2013). In contrast, inhibition of basal PARP-1 activity in myotubes and in muscle raised NAD+ levels and enhanced SIRT1 activity. This correlative evidence supports that the increased NAD+ availability might be a key mechanism by which PARP deficiency activates SIRT1 (Bai et al., 2011). However, more studies are needed to establish direct regulation of SIRT1 activity by the relatively small magnitude changes in cytosolic NAD concentrations that occur under physiological conditions.

**FIGURE 2** Anti-inflammatory mechanisms of SIRT1. SIRT1 deacetylates p65 and blocks the transactivation of NF-κB-dependent gene expression. SIRT1 suppresses the activity of PARP-1, a coactivator of NF-κB-dependent transcription, by deacetylation and by inhibiting its expression. PARP-1 activation could deplete NAD+, resulting in inhibition of SIRT1 and NF-κB activation. On the epigenetic level, SIRT1 represses NF-κB-dependent inflammatory gene expression by deacetylating H4K16 and also by recruiting more components of repressor complexes. SIRT1 deacetylates and activates histone methyltransferase SUV39H1, which suppresses expression of inducible inflammatory genes. DNA methylation is associated with suppressed expression. Whether SIRT1 could inhibit expression of inflammatory genes by enhancing promoter methylation remains to be determined.
Inflammatory responses are regulated by epigenetic changes (Medzhitov and Horng, 2009), which are defined as mitotically and meiotically heritable changes in gene function that do not depend on DNA sequence (Bernstein et al., 2007). SIRT1 deacetylates and inactivates the transcriptional state of p65, deacetylates specific lysines on histone H3 and H4, H1 nucleosome linker, and histone methyltransferase, and suppresses expression of SIRT1 (Hashimoto et al., 2013). Since SIRT1 also modulates the activities of DNA CpG methyltransferases (McCalm et al., 2011), it is possible that SIRT1 could deacetylate and inactivate p300/CBP, a critical coactivator of NF-κB-dependent expression of inflammatory genes (Chen and Greene, 2003). A number of epigenetic mechanisms are involved in SIRT1-mediated regulation of inflammatory responses (Figure 2).

HISTONE ACETYLATION

SIRT1 might repress inflammatory responses by combining deacetylation of histones and recruitment of non-histone proteins, such as p65/RelA (Liu et al., 2011). During endotoxin tolerance when transition from hyperinflammation to hypo-inflammation occurs, SIRT1 deacetylates H4K16 to terminate NF-κB-dependent transcription. SIRT1 represses gene expression by deacetylating histones and also by remaining bound to TNFα and IL-1β promoter regions to recruit more components of repressor complexes, such as histone H1, Rb, and methyltransferases (Liu et al., 2011; Figure 2).

HISTONE METHYLATION

Unlike histone acetylation, which is associated with active transcription, histone methylation is often associated with transcriptional repression (Bernstein et al., 2007). SIRT1 could suppress expression of inflammatory genes by enhancing the activities of histone methyltransferases. For example, SIRT1 deacetylates and activates histone methyltransferase SuV1H (H3K4 methyltransferase) (Fig. 2), which suppresses expression of inducible inflammatory genes (Saccani and Napol, 2002; Figure 2).

DNA METHYLATION

Inflammatory gene expression could be regulated by methylation of CpG sites on the promoter region, which is often associated with transcriptional repression (Harrinert and Ligan, 2012). For example, DNA methylation of IL-1β inversely correlated with the levels of mRNA (Hashimoto et al., 2013). Since SIRT1 also modulates the activities of DNA methyltransferases (Prig et al., 2013), it remains to be determined if SIRT1 suppresses inflammatory responses via increasing methylation of promoter regions of inflammatory genes (Figure 2).

REFERENCES

Adler, A. S., Kawahara, T. L., Segal, E., and Chang, H. Y. (2008). Reversal of aging by Nfkb-deletion blockside. Cell Cycle 7, 596–601. doi:10.4161/cc.7.5.5490

Adler, A. S., Sinha, S., Kawahara, T. L., Zhang, J. Y., Segal, E., and Chang, H. Y. (2007). Morphol- ized stop reveals enhancement of aging by continual NF-kb-knapped activity. Genes Dev. 21, 3244–3257. doi:10.1101/gad.1588507

Albini, C. M., Ghirardi, M., Metz, B., and Kandel, E. R. (1994). CREB is an immediate-early gene required for the consolidation of long-term facilitation in Aplysia. Cell 76, 1099–1114. doi:10.1016/0092-8674(94)90286-7

Albin, M. J., Plante, A., Chen, S. L., Iglou, B., Grib, M., and Villarroya, F. (2009). SIRT1 controls the transcription of the peroxisome proliferator-activated receptor-γ (PGC-1α) co-activator (PGC-1α) gene in skeletal muscle through the PGC-1α regulatory loop and interaction with MyoD. J. Biol. Chem. 284, 21877–21885. doi:10.1074/jbc.M109.022749

Anderson, Z. K. (2008). Oxidative stress in neurodegneration: cause or consequent? Nat. Med. 10(Suppl.) S51– S52. doi:10.1038/nm.1434

hyperactive NF-κB signaling in SIRT6-deficient mice is important for the premature aging phenotype (Kawahara et al., 2009). 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 (Kawahara et al., 2009). Partial inactivation of NF-κB ameliorates the premature aging in SIRT6 KO mice (Kawahara et al., 2009). Thus, continued NF-κB activation is required to enforce many features of aging. Interestingly, overexpression of SIRT6 in male mice, but not in female mice, resulted in significantly longer lifespan than wild-type mice (Kanit et al., 2012). Male mice overexpressing SIRT6 had lower serum levels of insulin-like growth factor 1 (IGF1), a key pathway for regulating lifespan (Kanit, 2010). Thus, SIRT6 could promote longevity via multiple downstream signaling pathways.

CONCLUSION AND THERAPEUTIC PERSPECTIVES

Sirtains block multiple key processes in neurodegeneration. They restore protein homeostasis by reducing accumulation of toxic protein aggregates, improve neural plasticity by elevating transcription of genes important for learning and memory, enhance mitochondrial function by reducing oxidative stress, and suppress sustained chronic inflammation via inhibiting NF-κB combined with epigenetic mechanisms.

However, 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 non-histone proteins, which may affect diverse cellular functions. For example, SIRT1 and SIRT2 appear to have opposite effects on the aggregation of misfolded proteins. Activation of a given sirtuin may have divergent outcomes, depending on pathophysiological circumstances. Nevertheless, specific sirtuin modulators could have broad therapeutic potential against various neurodegenerative diseases.

There has been an intense debate surrounding the importance of sirtuin enzymes in mediating the effects of resveratrol and other small-molecule compounds that activate SIRT1-related pathways (see Baur et al., 2012 for a comprehensive review on this topic). More studies will be needed to resolve the discrepancies and to develop new SIRT1 activators that can pass the blood–brain barrier and improve CNS functions in models of neurodegenerative diseases.

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Remote sensing of nutrient status in C. elegans. Nature 437, 821–825.

4. MicroRNAs: small RNAs with big impact. Science 326, 897–900.

5. Epigenetics. Nature 430, 376–380.

6. Sirtuins and aging: from C. elegans to humans. Cell 143, 182–195.

7. Nutrient sensing and cellular metabolism in aging. Trends Mol. Med. 16, 34–41.
Sirtuins are a family of proteins that play a crucial role in regulating cellular metabolism and aging. They have been implicated in various diseases, including Alzheimer’s disease (AD), by influencing the expression of important molecular markers. Sirtuins are NAD+-dependent deacetylases and receive substrate deacetylation via the deacetylase activity of the sirtuin protein. This process is mediated by the sirtuin family members Sirtuin 1 (SIRT1) and Sirtuin 3 (SIRT3), which are involved in the regulation of autophagy and oxidative stress, respectively.

Sirtuins have been shown to have a direct effect on the β-amyloid accumulation in the brain, which is a hallmark of AD. Studies have demonstrated that the overexpression of sirtuins can reduce the toxic effects of β-amyloid, while the loss of function is associated with increased AD pathology.

In a recent study, the researchers explored the role of sirtuins in modulating the inflammatory response in AD. They found that sirtuins act as a neuroprotective mechanism by inhibiting the inflammatory cascade and reducing the production of pro-inflammatory cytokines.

Another study reported that the activation of SIRT1 is a novel mechanism underlying the prevention of Alzheimer disease amyloid neuropathology by calorie restriction. This finding suggests that the activation of SIRT1 can have a therapeutic potential in the treatment of AD.

In summary, sirtuins are crucial in the regulation of various processes, including metabolism, cell survival, and inflammation. Their role in the development of AD is further supported by the fact that sirtuin activation can reduce the expression of inflammatory markers and modulate the inflammatory response in the brain. These findings highlight the potential of sirtuins as therapeutic targets for the treatment of AD.
Someya, S., Yu, W., Hallows, W. C., Xu, J., Yoon, J. M., Leuvenhoek, C., et al. (2010). Sirt1 mediates reduction of oxidative damage and prevention of age-related hearing loss under caloric restriction. Cell 143, 802–812. doi: 10.1016/j.cell.2010.10.002

Tis Park, J., Dreno, S., Uldry, M., Silvaggi, J.-M., Bibo, J., Jaziri, S., et al. (2009). Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. Cell 127, 397–408. doi: 10.1016/j.cell.2006.09.074

Tannir, R. E., and Bertram, L. (2005). Twenty years of the Alzheimer’s disease amyloid hypothesis: a genetic perspective. Cell 120, 545–555. doi: 10.1016/j.cell.2005.02.008

Törönen, W., and Guarente, L. (2001). Increased dosage of a sir-2 gene extends lifespan in Caenorhabditis elegans. Nature 410, 669–675. doi: 10.1038/sj.emboj.7602851

Tso, S. W., and Guarente, L. (2011). Regulation of Caenorhabditis elegans lifespan by sir-2.1 transgenes. Nature 477, E1–E2. doi: 10.1038/nature10440

Wang, W., Keen, E. L., and Tsai, L. H. (2012). MicroRNA in learning, memory, and neurological disorders. Learn. Mem. 19, 259–268. doi: 10.1101/lm.024915.112

Weir, H. J., Murray, T. K., Kohse, P. G., Love, S., Verdin, E. M., O’Neill, M. J., et al. (2012). CNS SIRT5 expression is altered by reactive oxygen species and in Alzheimer’s disease. PLoS ONE 7:e48225. doi: 10.1371/journal.pone.0048225

Westerheide, S. D., Ankkari, J., Stevens, S. M. Jr., Sistonen, L., and Morimoto, R. I. (2009). Stress-inducible regulation of heat shock factor 1 by the deacetylase SIRT1. Science 325, 1061–1066. doi: 10.1126/science.1169446

Wu, Y., Lu, X., Zhu, J. X., Xia, W., Lü, W., Fan, Z., et al. (2011). Renovirally activated AMPK/SIRT1/autophagy in cellular models of Parkinson’s disease. Neuroreport 19, 165–174. doi: 10.1097/WNR.0b013e3281e4c97b

Yang, F., Hofer, J. F., Ramsey, C. S., Kilbride, M. D., Jones, D. R., Pesc, R. A., et al. (2004). Modulation of NF-κB-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J. 23, 2369–2380. doi: 10.1038/sj.emboj.7602448

Zocchi, L., and Sassone-Corsi, P. (2012). SIRT1-mediated deacetylation of Mi2ε contributes to RNF1 expression. Epigenetics 7, 493–500. doi: 10.4161/epi.20773

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