



Will Sirtuin 2 Be a Promising Target for Neuroinflammatory Disorders?

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Neuroinflammatory disorder is a general term that is associated with the progressive loss of neuronal structure or function. At present, the widely studied diseases with neuroinflammatory components are mainly divided into neurodegenerative and neuropsychiatric diseases, namely, Alzheimer's disease, Parkinson's disease, depression, stroke, and so on. An appropriate neuroinflammatory response can promote brain homeostasis, while excessive neuroinflammation can inhibit neuronal regeneration and damage the central nervous system. Apart from the symptomatic treatment with cholinesterase inhibitors, antidepressants/anxiolytics, and neuroprotective drugs, the treatment of neuroinflammation is a promising therapeutic method. Sirtuins are a host of class III histone deacetylases, that require nicotinamide adenine dinucleotide for their lysine residue deacetylase activity. The role of sirtuin 2 (SIRT2), one of the sirtuins, in modulating senescence, myelin formation, autophagy, and inflammation has been widely studied. SIRT2 is associated with many neuroinflammatory disorders considering it has deacetylation properties, that regulate the entire immune homeostasis. The aim of this review was to summarize the latest progress in regulating the effects of SIRT2 on immune homeostasis in neuroinflammatory disorders. The overall structure and catalytic properties of SIRT2, the selective inhibitors of SIRT2, the relationship between immune homeostasis and SIRT2, and the multitasking role of SIRT2 in several diseases with neuroinflammatory components were discussed.

Keywords: sirtuin 2 (SIRT2), deacetylation, neuroinflammatory disorders, inflammatory, neuroprotection, promising target

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Abbreviations: CNS, central nervous system; SIRT2, sirtuin 2; NAD, nicotinamide adenine dinucleotide; HDACs, histone deacetylases; AADPR, the 2'-O-acetyl-ADP-ribose; PEPCK1, phosphoenolpyruvate carboxykinase 1; DCA, dichloroacetic acid; PDHA1, pyruvate dehydrogenase α 1; OCR, oxygen consumption rate; ROS, reactive oxygen species; OXPHOS, oxidative phosphorylation; LPS, lipopolysaccharide; TNF- α , tumor necrosis factor- α ; PGE2, prostaglandin E2; α -syn, α -synuclein; FOXO3a, forkhead box O3; MAPK, mitogen-activated protein kinase; HBV, hepatitis B virus; HSPA5, heat shock protein family A (Hsp70) member 5; IL-1 β , interleukin-1 β ; GFAP, glial fibrillary acidic protein; SAMP8, senescence accelerated mouse prone 8; NMDA, N-methyl-D-aspartic; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; Foxp3, forkhead box P3; NF- κ B, nuclear factor-kappa B; AQP4, aquaporin 4; MMP-9, matrix metalloproteinases 9; TBI, traumatic brain injury; CXCL1, chemokine (C-X-C motif) ligand 1; MCP1, metaphase chromosome protein 1; CCL28, CC-chemokine ligand 28; LIF, leukemia inhibitory factor; MORC2, microorchidia 2; NO, nitric oxide; MKP-1, MAPK phosphatase-1; AD, Alzheimer's disease; A β , β -amyloid; LTP, long-term potentiation; PD, Parkinson's disease; DAT, dopamine transporter; MPP+, neurotoxin 1-methyl-4-phenylpyridinium; CMS, chronic mild stress; AKT, protein kinase B.

INTRODUCTION

With aging populations worldwide, the central nervous system (CNS) diseases associated with aging have been on the rise (Hou et al., 2019). Neurological diseases such as depression and stroke have also been increasing in young and middle-aged people (Pascoe and Parker, 2019; Putaala, 2020). Recent studies have found that the occurrence and development of these diseases have a common feature related to neuroinflammation, which generally refers to the noxious effects caused by immunological activation of microglia and astrocytes in various diseases of the CNS (Kwon and Koh, 2020; Griiciuc and Tanzi, 2021). It is a physiological response of the immune system to harmful stimuli (Akbari et al., 2020; Jia et al., 2021). In response to harmful stimuli, neutrophils, monocytes/macrophages, different subtypes of T cells, and other inflammatory cells are commonly activated to maintain the immune system's balance (Maida et al., 2020). An appropriate neuroinflammatory response can promote brain homeostasis, while excessive neuroinflammation can inhibit neuronal regeneration (Yang B. M. et al., 2019). An immune imbalance has been considered to be the mechanism of the deterioration of a variety of CNS diseases, including Alzheimer's disease (AD) (Armstrong, 2019), Parkinson's disease (PD) (Schonhoff et al., 2020), depression (Hayley et al., 2021), stroke (Iadecola et al., 2020), and so on. Thus, restoring the balance of the immune homeostasis has been suggested as a new treatment approach for diseases with neuroinflammatory components. These biologic molecules of immune regulation have moved toward the focus of research. Based on the specific effects on inflammatory factors, sirtuin 2 (SIRT2) has attracted much academic attention. We further reviewed the specific and detailed role of SIRT2 in neuroinflammatory disorders in the CNS.

Sirtuin 2 is predominantly found in the cytoplasm of cells in the (CNS), where it balances the whole immune homeostasis *via* the nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylases (HDACs) (Gu et al., 2020; Hong et al., 2020; Zhang et al., 2021a; **Figure 1**). SIRT2 has a generic catalytic core domain like other Sirtuin family members and unique N-terminal and C-terminal sequences (Yang et al., 2020). Substrate and the catalytic core domain are vital during SIRT2 deacetylation (Minten et al., 2021). Therefore, SIRT2 participates in many biological processes by catalyzing the deacetylation of various substrates, such as senescence, myelin formation, autophagy, and inflammation (Puigoriol-Illamola et al., 2020; Lu et al., 2021). Yet, the exact role of SIRT2 in the immune regulation of neuroinflammatory disorders is still not fully understood. This review summarized the latest advances in SIRT2 in neuroinflammatory disorders, and the role of SIRT2 in balancing the immune homeostasis and inflammation in the CNS.

STRUCTURE AND FUNCTION OF SIRTUIN 2

Sirtuin 2, an NAD⁺ dependent protein deacetylase, is the only sirtuin protein that is predominantly found in the cytoplasm.

Yet, SIRT2 is also found in the mitochondria and nucleus (Lin et al., 2021).

Overall Structure of Sirtuin 2

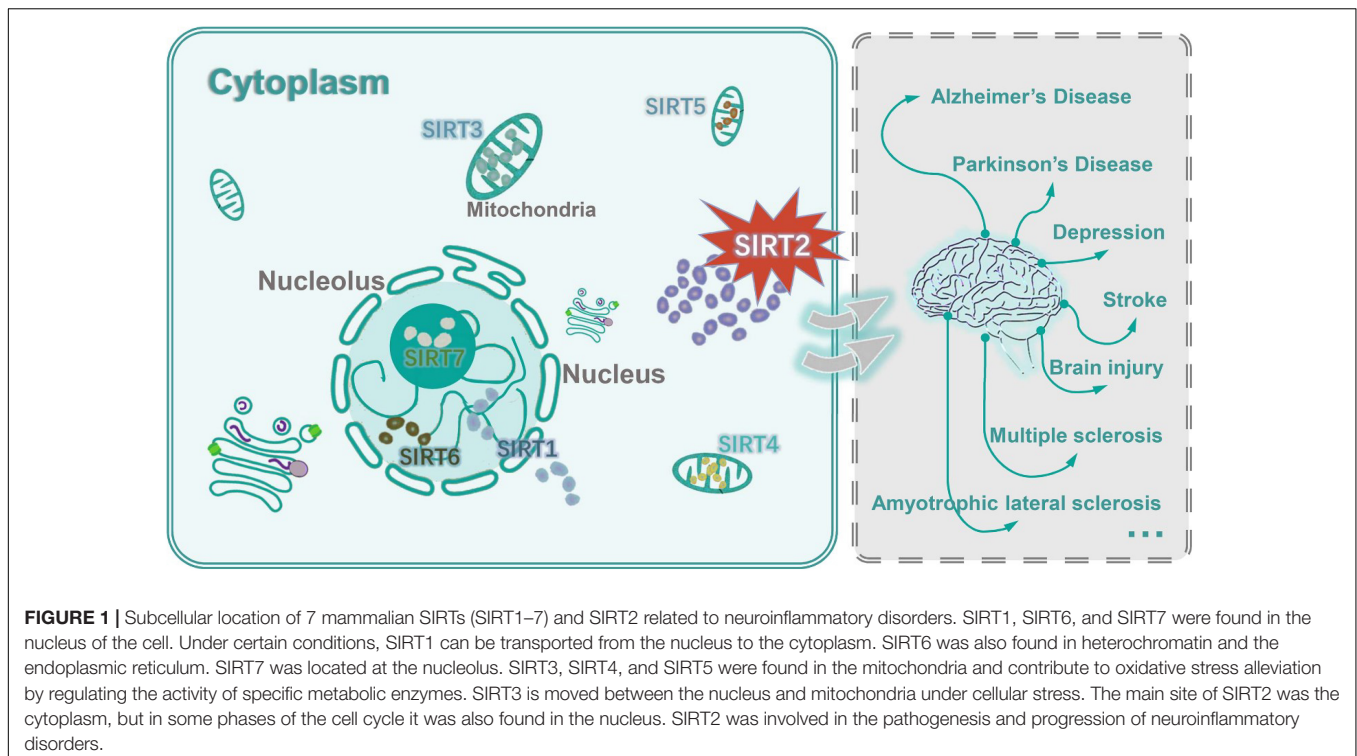
The human SIRT2 gene, mapped at chromosome 19q13.2, is composed of 16 exons and spans a region of 20,960 bp (Yang W. T. et al., 2017; Yang Y. et al., 2017). SIRT2 has a 323 amino acid catalytic core, which is flanked by a 19-residue N-terminal and a C-terminal helical extension (Li et al., 2015; **Figure 2B**). Two isoforms of the SIRT2 protein are encoded: a 389-aa protein with a predictive molecular weight of 43.2 kDa and an isoelectric point of 5.22 is encoded by isoform 1, a 352-aa protein with a predictive molecular weight of 39.5 kDa, and an isoelectric point of 6.05 is encoded by isoform 2, which lacks the first three exons (Alcaín and Villalba, 2009).

The catalytic core has an elongated shape containing two domains, namely, a larger domain (residues 53–89, 146–186, and 241–356) and a smaller domain (residues 90–145 and 187–240) (Finnin et al., 2001). The former is a variant of the Rossmann fold, which is present in many diverse NAD(H)/NADP(H) binding enzymes (Hou et al., 2014). And the latter is composed of a helical module and a zinc-binding module (Carafa et al., 2012; Karaman et al., 2018). The two domains are connected by a hinge region that consists of four crossovers of the polypeptide chain (Finnin et al., 2001). At the interface of the two domains, the four crossovers and three loops of the large domain form a large groove (Liu Y. M. et al., 2019; **Figure 2C**).

The larger domain consists of six β strands and eight α helices (North and Verdin, 2004). The β strands form a parallel β sheet, and the α helices pack against the β sheet (Finnin et al., 2001). The Rossmann fold contains various features of a typical NAD⁺ binding site, such as a conserved Gly-X-Gly sequence important for NAD⁺ phosphate binding, a charged amino acid residue responsible for ribose group binding, and a small pocket to accommodate an NAD⁺ molecule (Satoh et al., 2011; Zhang X. et al., 2021; **Figure 2C**).

The smaller domain contains two structural modules that stem from two insertions in the Rossmann fold of the large domain (North and Verdin, 2004). The first insertion comprises four α helices that fold to form the helical module (Finnin et al., 2001). The second insertion consists of a β sheet, an α helix, and a zinc atom coordinated by four Cys residues (Finnin et al., 2001). A pocket in the helical module lines with hydrophobic residues and could intersect with the large groove between the larger and smaller domains, which is a class-specific binding site for proteins. The zinc-binding module has a topology, that mediates the interactions between protein and protein in diverse proteins (**Figure 2C**).

The SIRT2 enzymatic reaction consists of three sequential steps. Two of them are reversible, and one, the final step, is irreversible. The enzyme catalyzes the deacetylation of an acetylated substrate with the NAD⁺. The Acetyl Lys protein is an acetylated substrate. These three steps are involved in the binding of NAD⁺ and an acetylated lysine substrate; the formation of an enzyme-ADP-Ribose (ADPR)-acetylated lysine (AcLys-protein) intermediate (enzyme-ADPR-AcLys-protein) with the release of nicotinamide (Nic); and at last, 2'-O-acetyl-ADP-ribose



(AADPR) and the deacetylated protein release. The reversibility of the second step is the basis of the NER assay, as only in this way the excess of labeled nicotinamide can reverse the reaction, and the labeled NAD⁺ can be produced *de novo* (Figure 2D).

Catalytic Properties of Sirtuin 2

The sirtuin family is an NAD⁺ dependent HDACs family, which has been highly conserved during its evolution (Dai et al., 2018). SIRT2 is a member of the Sirtuin family that mediates transcriptional silencing at telomeres, mating-type loci, and ribosomal gene clusters (Finnin et al., 2001). Its major characteristic is that it can realize deacetylation of acetyllysine substrate (Wang et al., 2019). NAD⁺ is the basis of this catalytic reaction. Moreover, it influences the direct response of SIRT2 to the changes in intracellular metabolism (Jěško et al., 2017). As a redox-active metabolite, NAD⁺ can be converted from NADH or into NADH. Thus, the ratio of NAD⁺/NADH affects the activity of SIRT2 (Ren et al., 2020). In addition, the activity of SIRT2 is also influenced by nicotinamide, which is the product of the deacetylation process (Ma et al., 2014; Li et al., 2018).

During the deacetylation reaction mediated by SIRT2, NAD⁺, SIRT2, and acetyllysine substrate interact to produce three products, i.e., the nicotinamide, the deacetylated substrate, and AADPR (Sedlackova and Korolchuk, 2020). The detailed steps of the NAD⁺ dependent deacetylation are roughly divided into three parts (Tatone et al., 2015; Grabowska et al., 2017; Carafa et al., 2019; Lewis et al., 2019): (1) the first part is mediated by NAD⁺, where SIRT2 recognizes and binds to the substrate; during this process, the NAD⁺, SIRT2, and substrate can form a ternary complex. Also, the combination between NAD⁺ and

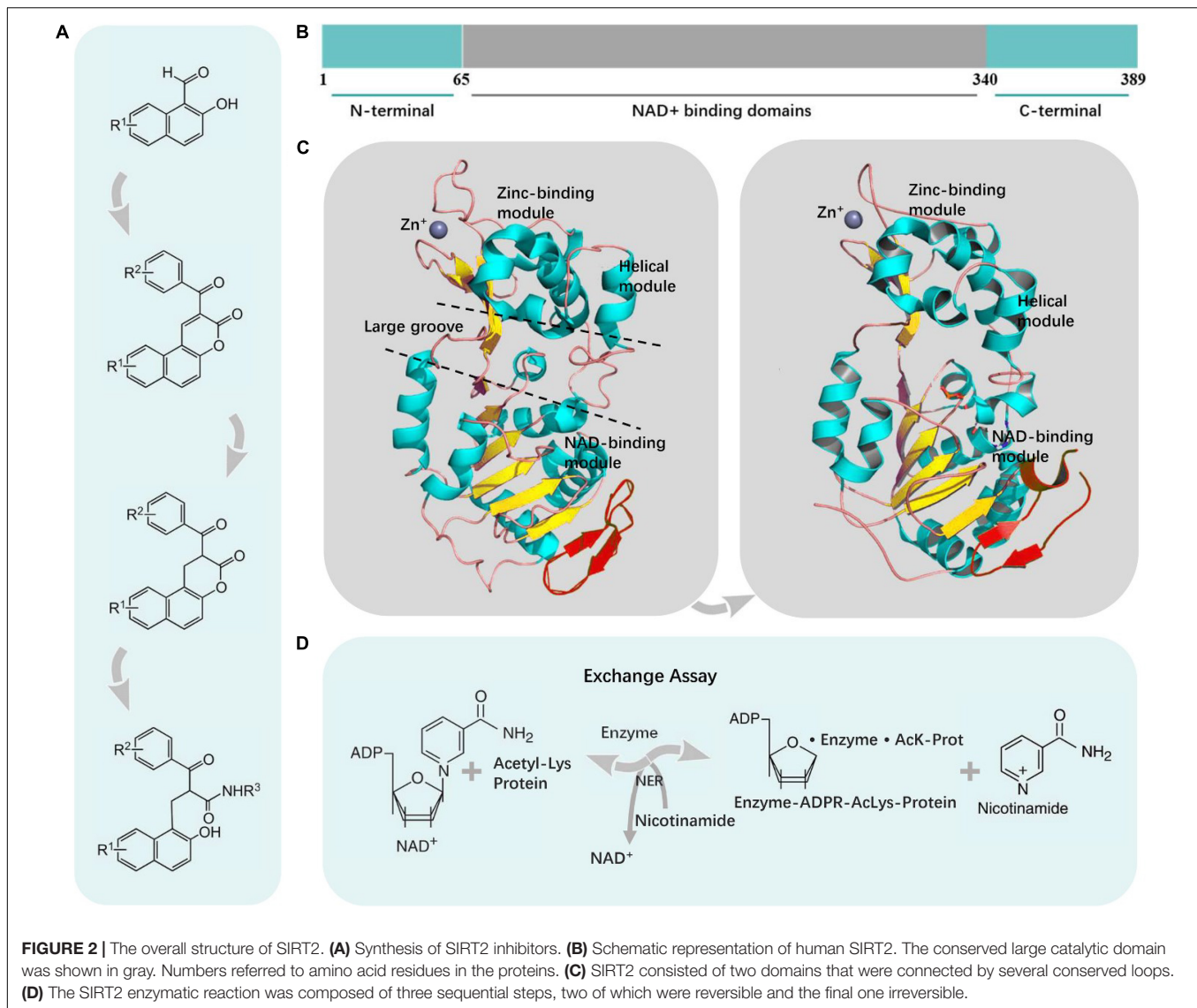
SIRT2 is related to the NAD⁺ binding site on the Rossmann fold of SIRT2; (2) the second part mainly includes NAD⁺ releasing the free nicotinamide and the activated ADP-ribose, which is realized by SIRT2 cleaving the glycosidic bond between nicotinamide and ADP-ribose of NAD⁺; and (3) the third part, the acetyl group of the substrate is transferred to the ADP-ribose *via* SIRT2 catalysis, after which two products (the deacetylated substrate and the AADPR) are obtained.

EMERGING REGULATOR

The benefits of SIRT2 modulation by small molecules have been demonstrated in cancer (Chen et al., 2020) and various metabolic (Yang P. H. et al., 2019) and neurodegenerative disorders (Zhang et al., 2020). Gradually, the potential of the unexplored regulator scaffolds in developing SIRT2 ligands has been rationalized. The regulator scaffolds of SIRT2 include two main modes, namely, the activators and inhibitors (Villalba and Alcaín, 2012). Almost all sirtuin activators are described for SIRT1 (Villalba and Alcaín, 2012), while SIRT2 is rarely involved (Dai et al., 2018). However, the inhibitors of SIRT2 have been widely studied.

The core scaffolds of SIRT2 inhibitors are synthesized by morpholine-catalyzed Knoevenagel condensation/lactonization of hydroxy naphthaldehydes with β -keto esters (Figure 2A).

In view of the variety of SIRT2 functions in cells, they are a druggable class of enzymes that have beneficial effects on various human diseases when selectively activated or inhibited by different molecules. This review focuses on those compounds that act as sirtuin inhibitors, which are potentially useful as therapeutic agents. Several specific inhibitors have been



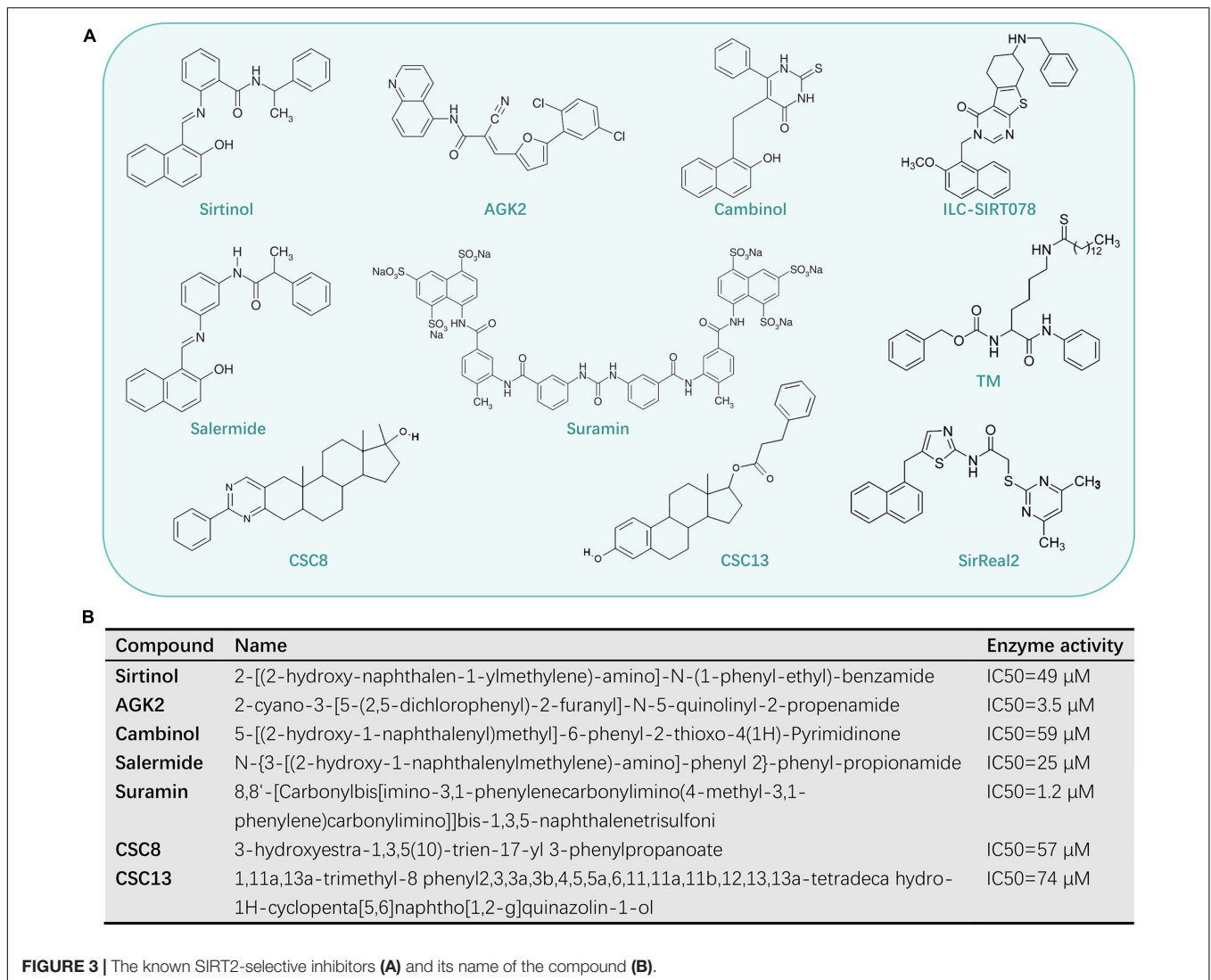
described, including sirtinol (Zhang M. M. et al., 2021), AGK2 (Yu et al., 2018), cambinol (Mahajan et al., 2014), salermide (Mu et al., 2019), suramin (Trapp et al., 2007), CSC8, and CSC13 (Schlicker et al., 2011; **Figure 3**).

Sirtinol

Sirtinol is a widely used sirtuin inhibitor that affects the activation of both yeast Sir2p and human SIRT2 *in vitro* (Grozinger et al., 2001; Alcaín and Villalba, 2009). Sirtinol has an IC₅₀ of 38 μ M against SIRT2 in an *in vitro* assay, which shows only approximately threefold weaker potency against SIRT1 (Schlicker et al., 2011). Two further analogs, m- and p-sirtinol, have been demonstrated to be more potent than sirtinol against human SIRT2 (Villalba and Alcaín, 2012).

Sirtuin 2 has an important role in deacetylating phosphoenolpyruvate carboxykinase 1 (PEPCK1), a critical enzyme for gluconeogenesis (Jiang et al., 2011; Knyphausen et al., 2016). Also, sirtinol has been previously used

to treat type II diabetes (Zhang M. M. et al., 2021). Zhang M. M. et al. (2021) have demonstrated that sirtinol has anti-diabetic effects on cell gluconeogenesis *in vivo* and *in vitro*. In SIRT2-knockdown cells, sirtinol exerts little influence on endogenous PEPCK1 levels (Zhang M. M. et al., 2021). Thus, SIRT2 may be a key target for cetirizine in the treatment of diabetes. In addition, sirtinol administration has also been reported to effectively kill cancer cells when combined with dichloroacetic acid (DCA) and another SIRT2 inhibitor, AGK2 (Ma et al., 2018). AGK2 and sirtinol increase the lysine-acetylation and decrease the serine-phosphorylation of pyruvate dehydrogenase α 1 (PDHA1). Also, the two inhibitors synergize with DCA to further activate PDHA1, which further decreases glucose consumption and lactate production, and increases oxygen consumption rate (OCR) and reactive oxygen species (ROS) generation, which is the function of oxidative phosphorylation (OXPHOS) (Ma et al., 2018). Furthermore, a recent study has demonstrated that lipopolysaccharide (LPS)-stimulated production of tumor



necrosis factor- α (TNF- α) and prostaglandin E2 (PGE2) in HAPI rat microglial cells can be inhibited by sirtinol, which protects SH-SY5Y cells from excessive inflammation (Zhang Y. Q. et al., 2021). This research provides theoretical support for further investigation of the therapeutic effect of SIRT2 regulators on LPS-induced neuroinflammation and neurodegeneration.

AGK2

AGK2, a selective SIRT2 inhibitor, has a calculated IC50 for SIRT2 of 3.5 μ M (Alcaín and Villalba, 2009). AGK2 can enter cells easily and act on endogenous SIRT2 in its natural environment. Even at the higher compound concentrations, AGK2 shows only minimal toxicity (Alcaín and Villalba, 2009).

AGK2 reduces the α -synuclein (α -syn) toxicity of dorsomedial dopamine neurons (Outeiro et al., 2007; Suresh and Manjithaya, 2019). Treatment with AGK2 leads to C-6 glioma cell apoptosis via the caspase-3-dependent pathway (He et al., 2012; Qin et al., 2014). AGK2 also downregulates the forkhead box O3 (FOXO3a) and mitogen-activated protein kinase (MAPK)

signaling pathways, which confer neuroprotection in ischemic stroke (She et al., 2018). In addition, AGK2 treatment decreases the RNAs of hepatitis B virus (HBV), the replication of intermediates, and the secretion of HBeAg and HBsAg, which inhibits HBV replication (Yu et al., 2018). Furthermore, AGK2 reduces the expression of Evans blue pigmentation by inhibiting mast cell activation and lung barrier dysfunction by inhibiting inflammatory responses (Kim Y. Y. et al., 2020).

Cambinol

Cambinol, a chemically stable compound, shares a β -naphthol pharmacophore with sirtinol (Heltweg et al., 2006; Medda et al., 2009). It is a dual SIRT1/SIRT2 inhibitor, which inhibits the activity of human SIRT2 deacetylase *in vitro* with an IC50 value of 59 μ M (Alcaín and Villalba, 2009).

Cambinol has cytotoxic activity against cancer cells *in vitro*. Other studies have shown that cambinol induces apoptosis through the hyperacetylation of BCL6 and p53, which inhibits the growth of Burkitt lymphoma xenografts (Chen, 2011;

Chowdhury et al., 2020). Besides, cambinol affects the survival and migration of cellular through modulating the acetylation of p53 and FoxO1 in HepG2 and Huh7 cells. Furthermore, it has been confirmed that SIRT2 activity blockage can be beneficial during hepatocellular carcinoma therapy (Ceballos et al., 2018).

Salermide

Salermide, a reverse amide compound histone deacetylase inhibitor (HDACI), has a strong inhibitory effect on SIRT2. For example, salermide inhibits 80% of SIRT2 activity in an *in vitro* assay at 25 μ M (Trapp et al., 2007). Also, *in vivo* studies suggest that salermide is well-tolerated by mice at concentrations up to 100 μ M (Alcaín and Villalba, 2009).

Moreover, studies have found that inhibition of SIRT2 can induce apoptosis in cancer cells, having a multifaceted role in regulating autophagy (Kim et al., 2011). Salermide upregulates heat shock protein family A (Hsp70) member 5 (HSPA5) acetylation and induces pro-survival autophagy *via* the ATF4-DDIT4-mTORC1 axis in human lung cancer cells (Mu et al., 2019). In addition, salermide induces cell death and p53 acetylation by targeting SIRT2 (Peck et al., 2010).

Suramin

Suramin is a potent inhibitor of SIRT2 NAD⁺ dependent deacetylase activity, with an IC₅₀ value for SIRT2 of 1.15 μ M (Trapp et al., 2007). It is also a polyanionic naphthylurea with antiproliferative and antiviral activity (Alcaín and Villalba, 2009). Nevertheless, the severe neurotoxicity and other systemic side effects of suramin seriously hinder its application in therapeutic treatment (Peltier and Russell, 2002).

CSC8 and CSC13

CSC8 and CSC13 are SIRT2 inhibitors. The virtual docking of the compound library into the peptide-binding pockets of SIRT2 crystal structures is exploited, which yields compounds discriminating between different isoforms. In activity assays, two compounds show the largest effects in the screen for further characterization. The compounds CSC8 and CSC13 inhibit SIRT2 to ~80% in the screen (Schlicker et al., 2011). So, CSC8 and CSC13 with micromolar potency and high specificity for SIRT2 are the novel sirtuin inhibitors that were developed based on structure (Botta et al., 2012).

INFLAMMATORY FACTORS WITH NEUROINFLAMMATION

Neuroinflammation is considered a critical factor in the progression of multiple neurological diseases (Bai et al., 2021). The inflammatory factors can rapidly activate inflammatory cells and promote the infiltration of inflammatory cells in the injured area, which aggravates brain damage and advances disease progression (Jayaraj et al., 2019).

Sirtuin 2 protects the CNS by reducing excessive inflammation. A previous study found that SIRT2 regulators effectively inhibited LPS (5 ng/mL)-stimulated TNF- and PGE2 production in HAPI rat microglial cells and protected SH-SY5Y

human neuroblastoma cells from excessive inflammation (Zhang Y. Q. et al., 2021). In non-neuronal cells, SIRT2 has been shown to function as a tubulin deacetylase and a key regulator of cell division and differentiation. Moreover, the distribution and function of the SIRT2 microtubule (MT) deacetylase are related to the differentiation of cells (Maxwell et al., 2011). Studies have also demonstrated that isoform 3 of SIRT2 is an age-dependent accumulation protein in the CNS (Sola-Sevilla et al., 2021). Also, a preclinical study found a significant increase in the pro-inflammatory cytokine interleukin-1 β (IL-1 β) in the model mice overexpressing SIRT2.3 (Sola-Sevilla et al., 2021). The most recent study discovered that reduced levels of the intermediate filament protein glial fibrillary acidic protein (GFAP), IL-1 β , IL-6, and TNF- α indicated that early SIRT2 inhibition prevents neuroinflammation, which explains the improvement in cognitive deficits shown by 33i-treated senescence accelerated mouse prone 8 (SAMP8) mice (Diaz-Perdigon et al., 2020). Moreover, SIRT2 in microglia can prevent N-methyl-D-aspartic (NMDA)-mediated excitotoxicity in hippocampal slices by resisting the inflammatory signal from LPS (Sade Almeida et al., 2020). In addition, a study found that AGK2 suppresses the expression of inflammatory cytokines like inducible nitric oxide synthase (iNOS), TNF- α , and IL-1 β in BV2 mouse microglial cells induced with LPS (Jiao et al., 2020). Also, the same study indicated that AGK2 could reduce the increase of phosphorylation p38, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK) (Jiao et al., 2020). Besides, AK7, an inhibitor of SIRT2, can inhibit sevoflurane (3%)-induced neuroinflammation and microglial activation by switching microglia from the M1 to M2 phenotype (Wu et al., 2020). The expression of forkhead box P3 (Foxp3), immunosuppression-associated molecules in Treg cells, can be promoted by inhibiting the activity of SIRT2 (Shu et al., 2019). Also, the anti-inflammatory effect of Treg cells on pro-inflammatory macrophages is weakened by SIRT2 using a lentiviral system (Shu et al., 2019). The nuclear factor-kappa B (NF- κ B) drives the transcription of pro-inflammatory mediators involved in the terminal effector pathways (Liu X. X. et al., 2019). SIRT2 inhibition increases acetylation and nuclear translocation of NF- κ B p65 protein, resulting in the up-regulation of NF- κ B targets such as aquaporin 4 (AQP4), matrix metalloproteinases 9 (MMP-9), pro-inflammatory cytokines and chemokines, which exacerbates neuroinflammation (Yuan et al., 2016; Zhang and Chi, 2018). Therefore, the overexpression of SIRT2 alleviates neuroinflammation through the deacetylation of NF- κ B.

Sirtuin 2 protects against traumatic brain injury (TBI) by regulating chemokines. Studies have found that secondary injury occurs after TBI, resulting in chronic and progressive neurodegenerative changes (Thapa et al., 2021). These mechanisms are strongly related to microglial-mediated neuroinflammation (Aires et al., 2021). In the patients with severe TBI under neurointensive care, high levels of endothelial chemokine (C-X-C motif) ligand 1 (CXCL1), CXCL10, metaphase chromosome protein 1 (MCP1), MCP2, and IL-8, as well as low levels of the chemokine CC-chemokine ligand 28 (CCL28) and MCP4 have been found (Dyhrfort et al., 2019). Besides, cross-correlation analysis revealed that leukemia

inhibitory factor (LIF) and CXCL5 have a central role in the inflammatory cascade (Dyhrfort et al., 2019). Whether SIRT2 can regulate these chemokines and participate in the secondary injury of neuroinflammation after TBI should be addressed by future studies (Dyhrfort et al., 2019).

Sirtuin 2 protects spinal muscular atrophy and Charcot-Marie-Tooth disease by regulating the deacetylation of microorchidia 2 (MORC2), an effector of epigenetic silencing. Missense mutations in MORC2 cause neuropathies, including spinal muscular atrophy and Charcot-Marie-Tooth disease (Douse et al., 2018). In addition, SIRT2 is also the main deacetylase of MORC2 deacetylation (Liu et al., 2020). Knock-down of SIRT2 using siRNAs resulted in an increase in k767AC of MORC2, which further suggested that ectopic expression of SIRT2 reduces the k767AC of MORC2 (Liu et al., 2020). Also, the deacetylase activity of SIRT2 is necessary for the deacetylation of MORC2 (Liu et al., 2020). Therefore, SIRT2 has a potential role in the deacetylation of MORC2 to protect against the excessive neuroinflammation-related diseases.

SIRTUIN 2 AND MICROGLIA PHYSIOPATHOLOGY

Microglial cells, which are the immunocompetent cells and specific to the CNS, have emerged as crucial players in neuroinflammatory conditions (Rodrigues et al., 2018; Ahmad et al., 2022). In addition, studies have shown that the deacetylases SIRT2 can exert its neuroprotective effects through the reduction in neuroinflammation in the CNS, attenuating the microglial response, and releasing pro-inflammatory cytokines (Zhang Y. Q. et al., 2021).

Sirtuin 2 has an important role in the LPS-induced activation of BV2 microglia (Chen et al., 2015; Belarbi et al., 2020). The treatment of BV2 microglia with LPS increases nitric oxide (NO), iNOS, TNF- α , and IL-6 expression, indicating that microglia are activated. SIRT2 silencing significantly reversed this process in microglia cells (Chen et al., 2015). Besides, it was found that SIRT2 mediates the significant increase of the intracellular ATP level and the Akt phosphorylation in BV2 microglia induced by NAD and NADH, while SIRT2 siRNA and the SIRT2 inhibitor AGK2 can reverse this process (Zhang et al., 2018).

Similar research found that the administration of SIRT2 deacetylase inhibitors (AGK2, AK-1, or AK-7) significantly promotes the dectin-induced expression of proinflammatory genes in mouse microglia (Sun et al., 2021). SIRT2 modulators (sirtinol, AGK2) reduce LPS-induced excessive inflammation in HAPI microglial cells and protect SH-SY5Y neuronal cells *in vitro* (Zhang Y. Q. et al., 2021). In addition, the SIRT2 inhibitor AGK2 alleviates LPS-induced neuroinflammation by regulating MAPK phosphatase-1 (MKP-1) in BV2 microglial cells (Jiao et al., 2020). AK7, an inhibitor of SIRT2, attenuates sevoflurane-induced learning and memory deficits in developing rats *via* modulating neuroinflammation and microglial activation (Wu et al., 2020).

It was also observed that SIRT2 protein was mainly expressed in the cytoplasm of neurons but not in astrocytes and microglia

(Xie et al., 2017). In this regard, future studies are needed to further explore the role of SIRT2 in microglia physiopathology.

SIRTUIN 2 AND NEUROINFLAMMATORY DISORDERS

The nervous system is known as one of the most complex systems in the human body (Aslani et al., 2021). Lesions of the nervous system seriously affect the quality of life in humans (Fang et al., 2020). With the development of neurobiology, the role of neuroinflammation in nervous system disorders has been widely investigated. Studies have shown that neuroinflammation has a critical role in the pathogenesis of neurological disorders (Jayaraj et al., 2019; Mukhara et al., 2020; de Brito Toscano et al., 2021). SIRT2, a type of NAD⁺ dependent deacetylases, is predominantly expressed in the cytoplasm of cells in the mammalian CNS (Ma et al., 2020; Chen et al., 2021), which suggests that SIRT2 has a significant role in diseases with neuroinflammatory components (Wang et al., 2016, 2020; Figure 4 and Table 1).

Alzheimer's Disease

Alzheimer's disease is the most common cause of dementia globally (Kim S. et al., 2020). Its incidence has been increasing over the years, especially due to the aging of the population, bringing a heavy burden to individuals and society (Soria Lopez et al., 2019). Typical characteristics of AD progress are two hallmark pathologies: β -amyloid (A β) plaque deposition and neurofibrillary tangles of hyperphosphorylated tau (Weller and Budson, 2018). Besides the two pathologies, sustained neuroinflammation is also included in the process of AD, which involves the activation of microglia and astrocytes (Laurent et al., 2018).

A previous study found that microglial SIRT2 has a protective role in amnesic deficits associated with neuroinflammation (Sade Almeida et al., 2020). *In vivo* study, LPS significantly reduced the long-term potentiation (LTP) of hippocampal slices

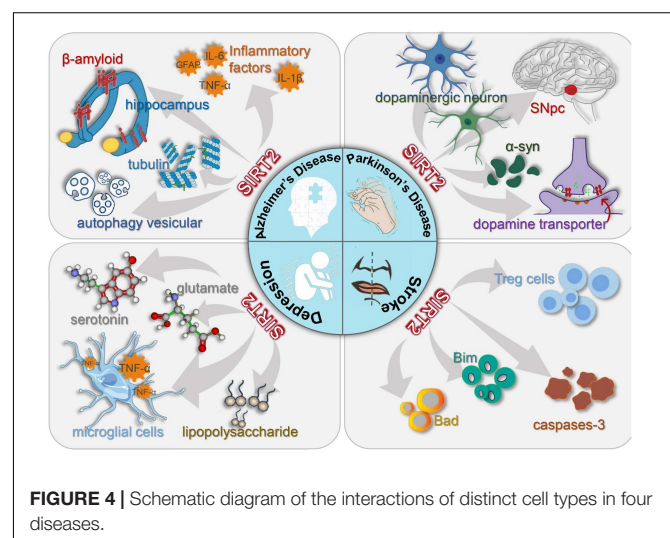


FIGURE 4 | Schematic diagram of the interactions of distinct cell types in four diseases.

TABLE 1 | The targets and function of SIRT2 involved in neuroinflammatory disorders.

Model	Inhibitor	Dose	Target	Functions	References
Alzheimer's disease	SAMP8 mouse	5 mg/kg, once/day, intraperitoneally (i.p.)	IL-1 β , IL-6, GFAP, TNF- α	Prevent neuroinflammation at early stage	Diaz-Perdigon et al., 2020
	APP/PS1 mouse	100 mg/kg, twice/day, intraperitoneally (i.p.)	-	Decrease the production of β -amyloid (A β) Induce tubulin acetylation Strengthen autophagic trafficking	Wang et al., 2020
Parkinson's disease	C57BL/6 mouse	-	LC3B, p62	Prevent the loss of dopaminergic neuron Prevent the reduction of DAT	Esteves et al., 2018
Depression	C57BL/6 mouse	5–15 mg/kg	Serotonin, GluA1, GluN2B, GluN2A	Increase the serotonin levels and glutamate receptor subunits	Erburu et al., 2017
	HAPI rat microglial cells	20, 10 μ M, 0.1 μ M	TNF- α , PGE2	Restrain the levels of TNF- α and PGE2 Control inflammation in SH-SY5Y cells	Zhang Y. Q. et al., 2021
Stroke	MCAO mouse Primary neuron-enriched cell	30 μ M, 30 μ M/1 mg/kg	Caspase-3, Bim, Bad	Attenuate the death of apoptotic cell caused by oxygen-glucose deprivation	She et al., 2018
	GFP+ Treg cells	10 μ M	HIF-1 α	Weaken the anti-inflammatory effect of Treg cells	Wu et al., 2020

in microglia-specific SIRT2 deficient mice (Sade Almeida et al., 2020), while NMDA receptor antagonists restored the LTP values. The results suggest that microglial SIRT2 can prevent NMDA-mediated excitotoxicity in hippocampal slices in response to an inflammatory signal (Sade Almeida et al., 2020).

Another study found that early inhibition of SIRT2 prevents excessive neuroinflammation by decreasing the levels of IL-1 β , IL-6, GFAP, and TNF- α , which suggests that SIRT2 is an emerging target for improving excessive neuroinflammation or AD progression (Diaz-Perdigon et al., 2020). A recent study showed that the pharmacological inactivation of SIRT2 exhibits a protective role in AD. For example, in the amyloid precursor protein/presenilin 1 transgenic mouse, the inhibitor of SIRT2 improved cognitive impairment and decreased the production of A β in the hippocampus (Wang et al., 2020). A similar protective role of SIRT2 for AD was also shown in another study (Zhang et al., 2020). AK1, an inhibitor of SIRT2, increases the acetylation level of tubulin, the completion of autophagy vesicular, and the aggregation of A β in AD cell models. It has been clarified that the inhibition of SIRT2 plays a beneficial role in inducing tubulin acetylation and strengthening autophagic trafficking (Zhang et al., 2020). Other evidence also suggests SIRT2 as a novel target for controlling AD (Jésko et al., 2017; Silva et al., 2017; Shen et al., 2020).

Parkinson's Disease

Parkinson's disease, a progressive neurodegenerative disease characterized by tremors and bradykinesia, causes heavy losses in productivity and medical resources (Hayes, 2019). The loss of dopaminergic neurons in the substantia nigra striatal pathway and the formation of neuronal inclusions are the main causes of PD (Xie et al., 2021). Yet, recent data have suggested chronic neuroinflammation as another feature of PD (Belarbi et al., 2020).

Some evidence suggests that SIRT2 is an emerging target in controlling PD by participating in the processes of PD pathogenesis, including the aggregation of α -syn, inflammation, oxidative stress, autophagy, and microtubule function (Singh et al., 2021). For example, a recent study found that SIRT2 inhibition exhibited the effects of neuroprotection and anti-inflammation *in vitro* (Liu Y. M. et al., 2019). Meanwhile, the expression level of SIRT2 in degenerating SNpc in the brain of PD was also mentioned (Liu Y. M. et al., 2019), suggesting that SIRT2 might be a potential target in treating PD.

To specifically address the role of SIRT2 in sporadic PD, a SIRT2 knock-out mouse was used to verify the pathogenic role of SIRT2. The SIRT2 knock-out mouse, which is cultured by the neurotoxin 1-methyl-4-phenylpyridinium (MPP+), induced a decrease in mitochondrial membrane potential in mesencephalic neuronal cells (Esteves et al., 2018). The knock-out of SIRT2 deacetylase enhanced α -tubulin acetylation and facilitated the trafficking and clearance of misfolded proteins (Esteves et al., 2018). These results indicated that mitochondrial, microtubule, and autophagy dysfunction are involved in neurodegeneration observed in sporadic PD.

Furthermore, studies have shown that inhibiting SIRT2 activity *via* miR-212-5p transfection can prevent dopaminergic

neuron loss and reduce dopamine transporter (DAT), implying that miR-212-5p can control PD by targeting SIRT2 (Sun et al., 2018). These studies all indicate that SIRT2 has an important role in PD.

Depression

Depression is a common mental disorder characterized by low mood, poor cognition, and anhedonia as its core symptoms (Zheng et al., 2019). Currently, depression is one of the essential contributors to disability globally and one of the leading causes of the global burden of disease (Yao et al., 2019; Sarno et al., 2021). It has been estimated that depression will become the primary factor of disability by 2030 (Subermaniam et al., 2020).

Depression, as a neuropsychiatric disease, also belongs to the category of neuroinflammatory disorders. Among the mainstream hypotheses of the cause of depression, the hypothesis of immune and inflammation has been a hot spot in studying its pathological mechanism (Sharma, 2016; Leonard, 2018; Beurel et al., 2020). Polymorphism studies have shown that SIRT2-related genes are associated with postpartum depression (Luo et al., 2020) and AD depression (Porcelli et al., 2013).

A previous study found that 33i, a selective SIRT2 inhibitor, led to the increase of serotonin levels and glutamate receptor subunits, inducing an antidepressant-like action in the chronic mild stress (CMS) model of depression (Erburu et al., 2017). Another study found that the SIRT2 inhibitors sirtinol and AGK2 significantly decrease the secretion of TNF- α and reduce the production of PGE2 in LPS-stimulated HAPI rat microglial cells (Zhang Y. Q. et al., 2021). In addition, the pretreatment of Sirtinol and AGK2 protects the cells from LPS-stimulated HAPI supernatant in differentiated SH-SY5Y cells (Zhang Y. Q. et al., 2021). SIRT2 inhibition can induce an antidepressant-like action. Moreover, as new antidepressant agents, 33i, sirtinol, and AGK2 have the therapeutic potential to treat depression.

Stroke

Stroke with a high lifelong disability and fatality rate is one of the most common diseases in modern society (Campbell and Khatri, 2020). It is an acute cerebrovascular disease, resulting in brain tissue damage due to the sudden rupture of blood vessels in the brain (hemorrhagic strokes) (Saand et al., 2019) or vascular occlusion preventing blood from flowing into the brain (ischemic strokes) (Patel et al., 2020). Ischemic stroke is the most common type of stroke (Wei et al., 2020).

Recent studies suggest that secondary neuroinflammation promotes further brain damage, leading to cell death in patients with acute stroke (Jayaraj et al., 2019; Huang et al., 2020). Conversely, the secretion of inflammatory factors is also beneficial as it promotes immune recovery (Jayaraj et al., 2019). SIRT2 has a vital role in stroke as well. It was found that the downregulation of SIRT2 protects the mouse brain against ischemic stroke (Xie et al., 2017). In addition, SIRT2 serves as a risk and prognosis marker for acute ischemic stroke in clinical practice (Zhang et al., 2021b).

Sirtuin 2 induces neuronal cell death in ischemic stroke. Previous studies reported that the SIRT2 inhibitors AK1 and AGK2 could reduce the cleaved caspase-3, Bim, and Bad,

by attenuating apoptotic cell death caused by oxygen-glucose deprivation (She et al., 2018). Moreover, the neuroprotective effect of SIRT2 inhibition on ischemic stroke is modulated *via* the downregulation of the protein kinase B (AKT)/FOXO3a axis and the MAPK pathways (She et al., 2018). Another study showed that the anti-inflammatory effect of Treg cells was weakened by SIRT2 on pro-inflammatory macrophages, which indirectly impacted the process of stroke in the model of middle cerebral artery occlusion (Shu et al., 2019).

CONCLUSION

In this review, the latest reports on the role of SIRT2 in regulating neuroinflammatory disorders were summarized and highlighted. As one of the most special sirtuins in the CNS, SIRT2 regulates multiple biological functions by NAD⁺ dependent deacetylation effects, including senescence, myelin formation, autophagy, and inflammation. We focused on the immunomodulatory effects of SIRT2 in the immunology response through molecules of immune regulation of neuroinflammatory disorders.

The immunomodulatory properties and the therapeutic potential of SIRT2 have been demonstrated *in vivo* or *in vitro* models of neuroinflammatory disorders. Moreover, previous studies have indicated that SIRT2 modulates immune balance in nervous system diseases *via* key molecules in different cellular signaling pathways. Herein, we summarized terminal effector molecules of the inflammatory response and reviewed the specific inhibitors of SIRT2, while the specific mechanisms of SIRT2 were inversely verified by relevant molecular biology experiments. Also, the regulatory details of different diseases with neuroinflammatory components, including neurodegenerative and neuropsychiatric diseases, were summed up to a certain extent.

Although the regulatory mechanism of SIRT2 in neuroinflammatory disorders has been studied, some questions still remain. First, the molecular regulating mechanism of SIRT2 has not yet been elaborated. Second, due to the lack of effective activators, it is difficult to assess the potency of SIRT2 inhibitors. Moreover, clinical evidence of immunomodulatory and immune-balancing effects of SIRT2 is lacking. Therefore, further studies should focus on investigating precise targets of SIRT2, which will contribute to developing treatment strategies for neuroinflammatory disorders.

With the state-of-art methods for studying SIRT2 that are expected to be available in the future, studies with an interdisciplinary perspective will ultimately provide a more comprehensive understanding of SIRT2 during the development of neuroinflammatory disorders. We hope this review will draw more attention to preventing and treating neuroinflammatory disorders by targeting SIRT2.

AUTHOR CONTRIBUTIONS

ZF conceived and designed the framework of the review, performed literature research and sorting, analyzed most of the data, prepared the figures, and wrote the manuscript.

LB conceived and designed the framework of the review, supervised the execution of this project, and contributed to data interpretation and manuscript preparation. Both authors read and approved the final manuscript.

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