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Review

SIRT2: Controversy and multiple roles in disease and physiology

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ABSTRACT

Sirtuin 2 (SIRT2) is an NAD+-dependent deacetylase that was under studied compared to other sirtuin family members. SIRT2 is the only sirtuin protein which is predominantly found in the cytoplasm but is also found in the mitochondria and in the nucleus. Recently, accumulating evidence has uncovered a growing number of substrates and additional detailed functions of SIRT2 in a wide range of biological processes, marking its crucial role. Here, we give a comprehensive profile of the crucial physiological functions of SIRT2 and its role in neurological diseases, cancers, and other diseases. This review summarizes the functions of SIRT2 in the nervous system, mitosis regulation, genome integrity, cell differentiation, cell homeostasis, aging, infection, inflammation, oxidative stress, and autophagy. SIRT2 inhibition rescues neurodegenerative disease symptoms and hence SIRT2 is a potential therapeutic target for neurodegenerative disease. SIRT2 is undoubtedly dysfunctional in cancers and plays a dual-faced role in different types of cancers, and although its mechanism is unresolved, SIRT2 remains a promising therapeutic target for certain cancers. In future, the continued rapid growth in SIRT2 research will help clarify its role in human health and disease, and promote the progress of this target in clinical practice.

1. Introduction

The sirtuin family of proteins, including seven mammalian members, are protein deacetylases that are homologous to the yeast silent information regulator 2 (Sir2) gene (Haigis and Sinclair, 2010). In eukaryotic organisms, seven sirtuin family members share highly conserved central NAD + binding and catalytic domain sequences, termed the sirtuin core domain (Frye, 2000). Sirtuins have different subcellular locations: SIRT1 is predominantly nuclear, although it can also be found in the cytoplasm (Tanno et al., 2007); SIRT2 is mainly found in the cytoplasm but can also be found in the nucleus (Vaquero et al., 2006); SIRT3, SIRT4, and SIRT5 are found in the mitochondria (Hershberger et al., 2017); SIRT6 is located in the nucleus; and SIRT7 resides in the nucleolus (Ford et al., 2006; Mostoslavsky et al., 2006). These differences in cellular localization reflect the broad range of biological functions and roles of sirtuins. SIRT2 is the only sirtuin that is mainly located in the cytoplasm. Less research has been conducted into SIRT2 compared to other sirtuins. However, in recent years, interest in SIRT2 has increased significantly, which has led to the identification of a large number of SIRT2 pathway mechanisms, a considerable number of new substrates (Table 1) and SIRT2-related proteins (Table 2). The results have been an extension of our understanding of the role of SIRT2 in physiological and pathophysiological conditions, thereby providing strong evidence for SIRT2 as a potential therapeutic target for different diseases. The purpose of this review is to summarize valuable findings regarding the potential effects of SIRT2 on physiology and disease, with a specific focus on comprehensively reviewing recent findings and conceptualizing the holistic role of SIRT2.

2. Physiological function

2.1. Functions in the nervous system

SIRT2 is highly expressed in the mammalian central nervous system (CNS), particularly in the cortex, striatum, hippocampus and spinal cord, suggesting that it may have a function in the nervous system (Maxwell et al., 2011). However, the function of SIRT2 in the nervous system remains largely unknown. Recent studies have explored several molecular mechanisms underlying the neural effects of SIRT2, improving our understanding of the functions of SIRT2 in the nervous system.

SIRT2 is crucial for myelination and is expressed principally in oligodendrocyte (OL), the myelin-producing cells of the CNS, where its expression is considerably upregulated during OL differentiation. SIRT2

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Table 1
The deacetylase substrates of SIRT2.

Substrates	Site	Mechanism	Functions	Reference
CDK9	K48	Activate	Genome integrity	Zhang et al. (2013)
PGAM2	K100	Activate	Oxidative stress	Xu et al. (2014)
AKT	–	Activate	Inactivates GSK-3β	Dan et al. (2012)
GAPDH	–	Inactivate	iPSC reprogramming	Cha et al. (2017)
PGK1	–			
ENO1	–			
ALDOA	K322			
ALDH1A1	K353	Activate	Breast cancer	Zhao et al. (2014)
PKM2	K305	Tetramerization and activate	Breast cancer	Park et al. (2016)
G6PD	K403	Dimerization and activate	Oxidative stress	Wang et al. (2014)
ATRIP	K32	Activate ATR	Genome integrity	Zhang et al. (2016)
Par-3	–	Activate aPKC	Myelin assembly	Beirowski et al. (2011)
CDH1	K69, K159	Activate APC/C	Mitotic regulation	Kim et al. (2011)
CDH2	K66			
MPK-1	–	Inactivate	I/R injury	Wang et al. (2017b)
MEK	–	Inactivate	Drug resistance	Bajpe et al. (2015)
p73	–	Inactivate	Glioblastoma	Funato et al. (2018)
Prdx-1	–	Inactivate	Breast cancer	Fiskus et al. (2016)
GKRP	K126	Inhibit glucokinase	Hepatic glucose uptake	Watanabe et al. (2018)
BubR1	K668	Increase abundance	Lifespan	North et al. (2014)
LKB1	K48	Increase abundance	Cardiac hypertrophy	Tang et al. (2017)
Slug	K116	Increase stability	Breast cancer	Zhou et al. (2016)
PEPCK1	K70, K71,K594	Increase stability	Gluconeogenesis	Jiang et al. (2011)
ACLY	K540, K546, K554	Degradate	Lung cancer	Lin et al. (2013a,b)
NRF2	K506, K508	Degradation	Iron homeostasis	Yang et al. (2017)
AMPAR	K813,K819, K822, K868	Degradation	Synaptic plasticity	Wang et al. (2017a)
HIF-1α	K 709	Degradation	Hypoxic response	Seo et al. (2015)
Skp2	–	Degradation	NSCLC	Li et al. (2016b)
p65	K310	Cytosolic localization	NF-κB-dependent gene expression	Rothgiesser et al. (2010)
PR-Set7	K90	Chromatin localization	Mitosis regulation	Serrano et al. (2013)
CNK1	K414	Plasma membrane localization	ERK signaling	Fischer et al. (2017)
eIF5A	K47	Cytosolic localization	–	Ishfaq et al. (2012)
FOXO1	–	Inhibit phosphorylation	Adipocyte differentiation	Jing et al. (2007)
MARCKS	–	Inhibit phosphorylation	Maternal diabetes-induced NTDs	Yang et al. (2019)
STAT3	–	Phosphorylate	Angiogenesis	Hu et al. (2018)
α-syn	K6, K10	Aggregate	Neurotoxicity	de Oliveira et al. (2017)
Keratin 8	K207	Solubility	Filament organization	Snider et al. (2013)
FOXO1	K262, K265, K274	Unbound to ATG7	Autophagy	Zhao et al. (2010a,b,c)
FOXO3a	–	Enhance bound to DNA	Oxidative stress	Wang et al. (2007)
TUG	K549	Redistributed GLUT4 to plasma membrane	Insulin sensitivity	Belman et al. (2015)
ATG5	–	–	Mitophagy	Liu et al. (2017)
α-tubulin	K40	–	–	North et al. (2003)
Histone3	K56	–	–	Das et al. (2009)
Histone3	K18	Transcriptional reprogram	Bacterial infection	Eskandarian et al. (2013)
Histone4	K16	–	Mitosis regulation	Vaquero et al. (2006)

Table 2
The function of non-classical deacetylase activity of SIRT2.

Protein	Mechanism	Functions	Reference
K-Ras4a	Defatty-acylation K182/184/185	Cellular transforming activity	Jing et al. (2017)
HOXA10	Partner	–	Bae et al. (2004)
AKT	Partner	Inactivate GSK-3β	Ramakrishnan et al. (2014)
ARRDC3	Lower the acetylation level of promoter region	Breast Cancer	Soung et al. (2014)
JMJD2A	Lower the acetylation level of promoter region	Lung cancer	Xu et al. (2015)
NEDD4	Lower the acetylation level of promoter region	Myc stabilition	Liu et al. (2013)

has emerged as a major component of the myelin proteome (Dugas et al., 2006; Ji et al., 2011; Li et al., 2007; Werner et al., 2007). Similar to myelin basic protein (MBP) expression, SIRT2 expression increases gradually after birth until adulthood. In the quest to understand this phenomenon, different research groups have offered conflicting explanations. For example, one study showed that SIRT2 protein expression marks the immature stage of OL differentiation, and suppresses MBP protein expression to control OL over differentiation using primary cell cultures (Li et al., 2007). However, another study showed that SIRT2 enhanced MBP expression and facilitated CG4 cell differentiation (Ji et al., 2011). Moreover, SIRT2 has also been identified as a presumptive myelination-associated protein in the peripheral nervous system as its expression is similar to that of mRNA encoding structural myelin proteins during myelin formation in Schwann cells (SCs) (Nagarajan et al., 2002). Later studies showed that SC-specific SIRT2 ablation in mice delayed developmental myelination and postinjury remyelination. This function was mechanistically attributed to SIRT2 regulation with the deacetylation of polarity protein Par-3 in SCs and subsequent alteration of atypical protein kinase C (aPKC) activation during developmental myelination and postinjury remyelination in mice (Beirowski et al., 2011). Whether oligodendrocytes also regulate myelin differentiation through this pathway needs to be further studied.

Dopaminergic (DA) neurons play a prominent role in several major functions of the CNS, and DA neuron dysfunction is implicated in

several neurological diseases including Parkinson's disease (PD). SIRT2 is robustly upregulated during the differentiation of human embryonic stem cells (hESCs) into midbrain DA neurons (Cha et al., 2017). Moreover, SIRT2 knockout (Sirt2−/−) mice showed fewer DA neurons and less dense striatal fibers in the substantia nigra, and the SIRT2 inhibitor AK–7 could also decrease the ratio of DA neurons in primary midbrain cultures (Szego et al., 2017). Mechanistically, SIRT2 has been reported to interact with protein kinase B (AKT) *via* the glycogen synthase kinase 3 (GSK–3β)/β-catenin pathway, subsequently modulating the differentiation of DA neurons (Szego et al., 2017). These results suggested that the deacetylase activity of SIRT2 plays an important role in the differentiation and survival of DA neurons and that SIRT2 inhibition or knockout inhibits this differentiation.

SIRT2 gene knockout affects the normal behavioral function of the nervous system. Adult Sirt2−/− mice showed aberrant synaptic plasticity accompanied by impaired learning and memory. As SIRT2 may act as an α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor (AMPAR) deacetylase, regulating AMPAR trafficking and proteostasis and contributing to synaptic plasticity and cognitive function (Wang et al., 2017a). In another study, middle-aged Sirt2−/− mice exhibited locomotor dysfunction due to axonal degeneration, while this effect was not present in young (3.5 months) Sirt2−/− mice (Fourcade et al., 2017), which is consistent with the result from Wang et al., in which the locomotor dysfunction were also not observed in young (8–15-week-old) mice (Wang et al., 2017a). SIRT2 plays a role in both cognition and locomotion with existing literature suggesting that this role may be age-dependent.

We know that SIRT2 plays important roles in mitochondrion function in the CNS but our understanding is not complete. Recent studies show that SIRT2 is localized in the mitochondrial intima in the mouse brain. The loss of SIRT2 changes the morphology of mitochondria making them rounder and smaller relative to controls in the cortex of Sirt2−/− mice (Liu et al., 2017). A critical role of the mitochondria is to generate adenosine triphosphate (ATP) from adenosine diphosphate (ADP). The striata of mice lacking SIRT2 exhibit decreased ATP levels (Liu et al., 2017). This is consistent with the result from another study, in which ATP levels in the spinal cord were significantly reduced in Sirt2−/− mice (Fourcade et al., 2017). Meanwhile, mitochondrial DNA (mtDNA) levels are lower in both the spinal cord and cortex of middle aged Sirt2−/− mice (Fourcade et al., 2017).

In summary, the *in vivo* and *in vitro* evidence presented above suggest that SIRT2 is a crucial regulator of neurological function in the differentiation and survival of different nerve cells. SIRT2 knockout has a injurious effect on the normal function of the nervous system that may be associated with age (Fig. 1). Additional *in vivo* research examining the conditional knockout of SIRT2 in different nerve cells of mice will further our understanding of its function in the nervous system.

2.2. Mitosis regulation and genome integrity

The role of SIRT2 in mitotic regulation was the earliest SIRT2 functional discovery. SIRT2 was always thought to be cytoplasmic until it was found to be enriched in the nucleus during G2/M transition of growing Saos2 cells (Dryden et al., 2003). Further research showed that SIRT2 could rapidly accumulate in the nucleus in normal human fibroblasts after treatment with a nuclear export inhibitor, suggesting that nucleocytoplasmic shuttling may contribute to the nuclear enrichment of SIRT2 (Inoue et al., 2007). Moreover, overexpression of SIRT2 increased multinucleation and prolonged the mitotic phase of the cell cycle *in vitro* (Dryden et al., 2003; North and Verdin, 2007a) and Sirt2−/− mice exhibited increased levels of mitotic regulators, which impacted centrosome amplification, aneuploidy and mitotic cell death (Kim et al., 2011). These results suggest that SIRT2 is enriched in the nucleus during mitosis to maintain normal mitotic processes.

In terms of mechanism, SIRT2 regulates mitosis *via* its deacetylation activity with several mitosis-related proteins. SIRT2 deacetylates histone methyltransferase PR-Set7, modulating its chromatin localization, thereby decreasing the overall mitotic deposition of H4K20me1 (Serrano et al., 2013). H4K16Ac is the acetylated substrate of SIRT2 and when SIRT2 is localized on chromatin, the level of H4K16Ac also decreases during the mammalian cell cycle (Vaquero et al., 2006). SIRT2 also modulates the activity of the anaphase-promoting complex/cyclosome (APC/C) *via* the deacetylation of the coactivator proteins CDH1 and CDC20, regulating their interaction with CDC27 and ultimately contributing to the maintenance of mitosis (Kim et al., 2011).

Replication stress refers to the slowing or stalling of replication fork progression and/or DNA synthesis, which is caused by an increasing number of different cellular perturbations and has serious implications for genome stability (Manic et al., 2018; Zeman and Cimprich, 2014). Studies have also shown that SIRT2 likely regulates acetylome networks involved in maintaining genome integrity in response to replication stress through the deacetylation and activation of CDK9, a protein required for recovery from replication arrest, or deacetylation of the ataxia telangiectasia-mutated and Rad3-related (ATR)-interacting protein (ATRIP), driving ATR activation, facilitating recovery from replication stress, and ultimately maintaining the genome integrity (Zhang et al., 2016, 2013).

2.3. Cell differentiation

Among the sirtuin family, SIRT2 is the most conspicuously expressed sirtuin at the mRNA level in both adipose tissues and adipocytes (Jing et al., 2007; Wang et al., 2007), and SIRT2 decreases during the differentiation of 3T3-L1 preadipocytes (Jing et al., 2007; Wang and Tong, 2009). Overexpression of SIRT2 inhibits 3T3-L1 preadipocytes differentiation and *vice versa* (Wang et al., 2007). Forkhead box O (FOXO) transcription factors can be phosphorylated leading to inhibition of their transcriptional activity by remaining in the cytosol (Nakae et al., 2003). SIRT2 deacetylates FOXO1 and decreases phosphorylation of FOXO1, which, in turn, promotes the activity of FOXO1, thereby preventing the differentiation of preadipocytes. On the other hand, as α-tubulin is a classic deacetylated substrate of SIRT2 (North et al., 2003), the expression of a mutated acetylation-resistant α-tubulin significantly inhibits adipogenesis (Yang et al., 2013), which is also consistent with the decrease in SIRT2 during adipocyte differentiation. These findings suggest that the regulation of SIRT2 activity may play a regulatory role in increased fat content.

SIRT2 is also associated with pluripotent differentiation. Some evidence suggests that SIRT2 plays a key role in inducing pluripotent stem cells through the deacetylation of glycolysis-related proteins. A switch from oxidative phosphorylation (OXPHOS) to glycolysis occurs during the conversion of somatic differentiated cells into induced pluripotent stem cells (iPSC) and reflects metabolic reprogramming (Ito and Suda, 2014). SIRT2 is downregulated in primed human pluripotent stem cells (hPSCs) during the reprogramming process (Cha et al., 2017). It is worth noting that SIRT2 is downregulated in hPSCs compared to human fibroblasts. In line with this, knockdown of SIRT2 in human fibroblasts results in a significant decrease in OXPHOS and an increase in glycolysis *in vitro*. Five glycolytic enzymes, pyruvate kinases M1/2 (PKM), aldolase (ALDOA), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), phosphoglycerate kinase (PGK1), and enolase (ENO1) are highly acetylated and their activation accompanies SIRT2 suppression in hPSCs. SIRT2 can deacetylate and decrease the enzymatic activities of four of these glycolytic enzymes (Cha et al., 2017). Taken together, SIRT2 regulates the activity of metabolic enzymes and then directs hPSCs functions, as well as the balance between pluripotency and differentiation (Liu and Shyh-Chang, 2017). However, the authors did not determine the relationship between SIRT2 and activity of PKM directly further but this was confirmed to be deacetylation and activated by SIRT2 in a different study (Park et al., 2016).

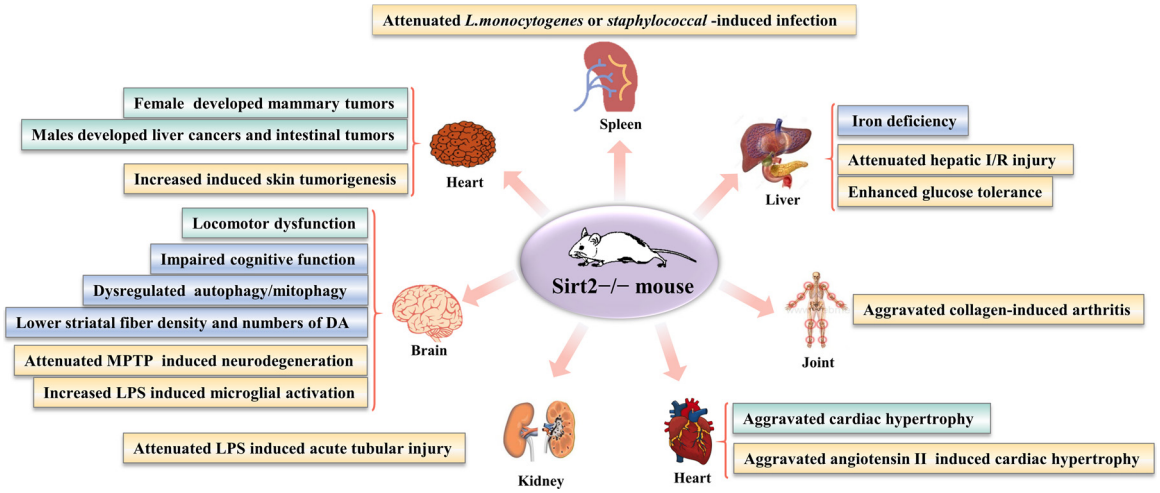

Fig. 1. The *in vivo* study of the physiological function and the disease-induced model in SIRT2−/− mice. SIRT2 gene deletion affected several important physiological functions *in vivo*, causing impaired cognitive function, dysregulated autophagy/mitophagy, iron deficiency and neurological injury. With aging, SIRT2−/− mice displayed locomotor dysfunction, female mice developed mammary tumors, and male mice developed liver cancers and intestinal tumors. SIRT2−/− mice also showed aggravated cardiac hypertrophy with aging. In different disease models, SIRT2−/− mice had aggravated arthritis, cardiac hypertrophy, tumor formation, and microglial activation. SIRT2−/− mice had attenuated hepatic I/R injury and acute tubular injury, enhanced glucose tolerance and reduced infection. The blue text box represents the effects of physiological function in SIRT2−/− mice, the green text box represents the SIRT2−/− mice that were used in ageing-related research and the yellow text box represents the SIRT2−/− mice that were under disease induction.

2.4. Cell homeostasis

The liver serves as the major site for maintaining blood glucose levels by activating *de novo* gluconeogenesis during states of limited energy availability, and by reducing glucose surges during feeding cycles by promoting glycogen synthesis while inhibiting gluconeogenesis (Biddinger and Kahn, 2006; Lin and Accili, 2011; Petersen et al., 2017). Phosphoenolpyruvate carboxykinase (PEPCK1) catalyzes the first committed and rate-limiting step of gluconeogenesis, and the acetylation of PEPCK1 under high glucose levels is associated with a decrease in protein stability (Zhao et al., 2010a). Furthermore, SIRT2 can deacetylate and stabilize PEPCK1 under conditions of glucose deprivation (Jiang et al., 2011), suggesting a potential mechanism by which SIRT2 enhances gluconeogenesis, particularly during times of energy restriction. SIRT2 is also associated with insulin sensitivity. Under standard nutrient conditions, SIRT2 overexpression enhances insulin-induced activation of AKT and the downstream GSK-3β phosphorylation *in vitro*. Pharmacological or genetic inhibition of SIRT2 causes the opposite effect, ameliorating the reduced activity of AKT and increasing insulin-stimulated glucose uptake in insulin-resistant neuro-2a cells and skeletal muscle cells (Arora and Dey, 2014, 2016; Ramakrishnan et al., 2014). Insulin mobilizes glucose transporter 4 (GLUT4) transporters into a cell surface-recycling pathway to accelerate glucose uptake (Bogan, 2012). The tether containing a UBX domain for the GLUT4 (TUG) protein regulates this process by acetylation. In this way acetylation is increased, and glucose disposal is enhanced during insulin-stimulated glucose tolerance in Sirt2−/− mice (Belman et al., 2015). Together, these findings suggest that SIRT2 may negatively influence glucose uptake under insulin-resistant conditions. However, recently, contradictory results have reported that SIRT2 is downregulated in insulin-resistant hepatocytes and liver tissues, and that SIRT2 overexpression improves insulin sensitivity in insulin-resistant hepatocytes (Lemos et al., 2017). Nevertheless, the full role of SIRT2 in glucose homeostasis is yet to be clarified. With regard to iron homeostasis, SIRT2 deletion reduces cell viability in response to iron deficiency. SIRT2 maintains cellular iron levels by deacetylating nuclear factor erythroid-derived 2-related factor 2 (NRF2), reducing the total and nuclear levels of NRF2, which subsequently reduces ferroportin 1 (FPN1) expression resulting in decreased cellular iron export (Yang et al., 2017).

2.5. Aging

Growing evidence suggests that sirtuin is an attractive antiaging target because of its interaction with molecules in diverse biological processes (Lee et al., 2019). SIRT2 mRNA and protein expression is upregulated in the occipital lobe in rats of different ages but does not change significantly in other brain regions (Braidy et al., 2015). However, a specific isoform of SIRT2, SIRT2.3, accumulates in the CNS of aging mice (Braidy et al., 2015; Maxwell et al., 2011). Moreover, the latent role of SIRT2 in aging is also supported by the association between human longevity and potential functional polymorphisms of the SIRT2 gene (Crocco et al., 2016). The lifespan-modulating cell-cycle checkpoint kinase, benzimidazole-related 1 (BubR1), could be deacetylated by SIRT2, and the loss of budding uninhibited by BubR1 is observed in aging muscle due to a decline in NAD+ (Baker et al., 2013; North et al., 2014). This suggests that SIRT2 may be a potential longevity modulator along with BubR1, although it does not seem to be the sole factor that regulates BubR1 (Cosentino and Mostoslavsky, 2014). Moreover, SIRT2 has recently been reported to play a role in the aging of hematopoietic stem cells (HSCs). With aging, HSCs are more sensitive to mitochondrial stress, and the NLRP3 inflammasome is aberrantly activated in HSCs, which is due to the repressed expression of SIRT2. Moreover, SIRT2 overexpression could repress the activation of the NLRP3 inflammasome and reverse HSC aging (Luo et al., 2019). Overall, the current research on SIRT2 and aging is not systematic, and the role of SIRT2 in aging needs to be further explored.

2.6. Infection and inflammation

During infection, pathogens dramatically affect the transcriptional machinery of the host cell for their own benefit. However, in most cases, the underlying mechanisms of this alteration remain elusive. During infection with the bacterium *Listeria monocytogenes*, the host SIRT2 translocates to the nucleus and deacetylates H3 K18, which associates with a subset of genes that are repressed during infection. Bacterial infections are significantly impaired when SIRT2 activity is blocked in Sirt2−/− mice (Eskandarian et al., 2013). Bacterial infection has been shown to specifically induce dephosphorylation of S25, an event that is essential for the association of SIRT2 with chromatin (Pereira et al., 2018). SIRT2 may also participate in the response to

infections by other bacteria. SIRT2 gene expression is increased in the gastric epithelial cells of gastritis patients with *Helicobacter pylori* infection (Zandi et al., 2018). Moreover, SIRT2 deficiency increases the survival of mice with chronic *staphylococcal* infection (Ciarlo et al., 2017). For viruses, the regulation of viral inclusion body (IB) fusion by acetylated α-tubulin is critical for viral replication, and knockdown of histone deacetylase 6 (HDAC6) and SIRT2 or the expression of α-tubulin acetyltransferase 1 (α-TAT1) results in the fusion of small IBs into large IBs, promoting effective viral replication (Zhang et al., 2017b).

Since SIRT2 was found to deacetylate p65 and regulate the expression of specific NF-κB-dependent genes (Rothgiesser et al., 2010), a growing number of studies have begun to examine the relationship between SIRT2 and inflammation. Sirt2−/− mice show morphological changes in microglia, an increase in proinflammatory cytokines and hyperacetylation of NF-κB following intracortical injection of lipopolysaccharide (LPS), indicating that SIRT2 may be a gatekeeper that prevents excessive microglial activation through NF-κB deacetylation (Pais et al., 2013). Other studies have shown that silencing SIRT2 decreases microglial activation in LPS-induced BV2 cells (Chen et al., 2015a). Additionally, another study verified the above results *in vivo* using a mouse model of neuroinflammation and confirmed that SIRT2 is required for LPS-induced neuroinflammation, brain injury, and microglial activation (Wang et al., 2016a). In macrophages, NF-κB activation and nitric oxide synthase were also significantly decreased in SIRT2-deficient macrophages after LPS stimulation (Lee et al., 2014). To summarize, the presence of SIRT2 seems to be important for inflammation, but the related mechanism is not fully understood.

2.7. Oxidative stress

Under oxidative stress, SIRT2 plays a key role in maintaining cellular redox potential and protects cells from oxidative damage by maintaining NADPH homeostasis. Phosphoglycerate mutase 2 (PGAM2) is a glycolytic enzyme that plays a role in NADPH production. A key enzyme in the pentose phosphate pathway (PPP) is 6-phosphogluconate dehydrogenase (6PGD), which is required to maintain cellular NADPH levels (Salati and Amir-Ahmady, 2001). Notably, SIRT2 has been reported to deacetylate and activate PGAM and 6PGD leading to an increase in NAPDH levels during increased oxidative stress (Xu et al., 2014). FOXO regulates oxidative response genes by activating manganese superoxide dismutase (MnSOD), inducing the cell cycle inhibitor p27kip1 and the proapoptotic factor Bim (Burgering and Kops, 2002; Dijkers et al., 2000; Kops et al., 2002). SIRT2 is reported to be upregulated in response to oxidative stress, deacetylated FOXO3, and increases in the expression of genes targeted by FOXO3a, such as p27kip1, MnSOD, and Bim, consequently reduce cellular reactive oxygen species (ROS), ultimately influencing cellular responses to oxidative stress (Wang et al., 2007).

2.8. Autophagy

Some SIRT2 functions are related to autophagy, although they are not as well studied as the autophagy-related functions of SIRT1. However, reports of the relationship between SIRT2 and autophagy have been inconsistent and unclear. A reduction in SIRT2 levels leads to an increase level of autophagy in normal HCT116 cells (Inoue et al., 2014). However, impaired autophagy/mitophagy processes have been observed in Sirt2−/− mouse (Liu et al., 2017). The selective SIRT2 inhibitor AGK2 has been shown to exacerbate H_2O_2-induced decreases in intracellular ATP and increase necrosis of PC12 cells without affecting autophagy (Nie et al., 2011). SIRT2 overexpression inhibits lysosome-mediated autophagic turnover by interfering with aggresome formation in SN56 cells and SH-SY5Y cells (Gal et al., 2012).

In terms of mechanism, current studies suggest that SIRT2 affects autophagy mainly by regulating autophagy-related microtubules (MTs) and autophagy-related proteins. Autophagic flux is highly dependent on the MT network (Kochl et al., 2006). The effect of SIRT2 on autophagy through MTs has mainly been studied in neurodegenerative diseases. Inhibition of SIRT2 by AK1 or SIRT2 knockout recovers MT stabilization and improves autophagy, favoring cell survival through the elimination of toxic Aβ oligomers (Esteves et al., 2019; Silva et al., 2017). AK1 also prevents tubulin acetylation, MT assembly and improves autophagic turnover in sporadic PD patient-derived cybrid cells (Esteves et al., 2018). Long-term vitamin E-deficient mice also exhibit decreased SIRT2 mRNA expression and show alterations in microtubule-related proteins and autophagy, leading to axonal injury (Fukui et al., 2014). For the second mechanism, in response to oxidative stress or serum starvation, FOXO1 could be acetylated by dissociating from SIRT2 and binding to autophagy protein 7 (ATG7), eliciting the autophagic process in tumors (Zhao et al., 2010b,c). Another autophagy-related protein, autophagy protein 5 (ATG5), acetylation was significantly reduced in Sirt2−/− mice suggesting that SIRT2 can interact with and deacetylate ATG5 directly (Liu et al., 2017). Regardless of whether SIRT2 disturbance in autophagy has different results under different pathological process or stimuli, the acetylation function of SIRT2 certainly has a specific role in the maintenance of autophagy, and future in-depth mechanistic research is required.

2.9. Lysine fatty acylation

SIRT2 has been shown to have a nonclassical function as a lysine defatty-acylase. SIRT2 facilitates K-Ras4a endomembrane localization by removing the fatty acylation on lysine residues, enhancing the interaction with A-Raf and promoting cellular transforming activity. Moreover, this study revealed the first lysine defatty-acylation substrate for SIRT2 and uncovered the physiological relevance of SIRT2 as a lysine defatty-acylase (Jing et al., 2017). The biological function of protein lysine fatty acylation remains unclear, and further study regarding the regulatory role of SIRT2 *in vivo* as a lysine defatty-acylase is needed.

2.10. Molecular regulation and modification of SIRT2

The activity and expression of SIRT2 can be regulated under extensive physiological or pathological conditions, suggesting that SIRT2 is involved in complex biological processes. Gene silencing by histone deacetylation is associated with SIRT2 downregulation in glioma cells (Inoue et al., 2007). The transcription factor NK2 homeobox 2.2 (Nkx2.2) can bind to the SIRT2 promoter in the rat CG4 cell line and attenuate SIRT2 expression *via* histone deacetylase 1 (HDAC-1) (Ji et al., 2011). Hypoxia-inducible factor 1α (HIF1α) can also inhibit Sirt2 gene transcription *via* an interaction with the evolutionarily conserved hypoxia response element (HRE) in the SIRT2 promoter (Krishnan et al., 2012).

At the posttranscriptional level, RNA-binding protein, quaking (QKI), can promote the expression of SIRT2 mRNA and protein in myelinating OLs by directly binding to the 3′ untranslated region (UTR) of SIRT2 mRNA (Thangaraj et al., 2017). Moreover, multiple microRNAs have been shown to negatively regulate the expression level of SIRT2 (Cha et al., 2017; Li et al., 2016a; Wang et al., 2015, 2018). Avian myelocytomatosis viral oncogene cellular homolog (Myc) oncoproteins upregulate the expression of SIRT2 posttranscriptionally, possibly by enhancing SIRT2 protein synthesis (Liu et al., 2013a). Furthermore, SIRT2 can be regulated by posttranslational modification. SRC proto-oncogene, nonreceptor tyrosine kinase (C-Src) phosphorylates SIRT2 at Tyr104 and regulates the stability of SIRT2 (Choi et al., 2014b). Cyclin-dependent kinases (CDKs) can phosphorylate SIRT2 at Ser331 and inhibit catalytic activity (Pandithage et al., 2008). In addition, extracellular signal-regulated protein kinase-1 and extracellular signal-regulated protein kinase-2 (Erk1/Erk2) have been reported to enhance the deacetylase activities of SIRT2, although the residues that are phosphorylated are not known (Choi et al., 2013). CDK-1 was reported to phosphorylate SIRT2 at Ser368 and regulate its function

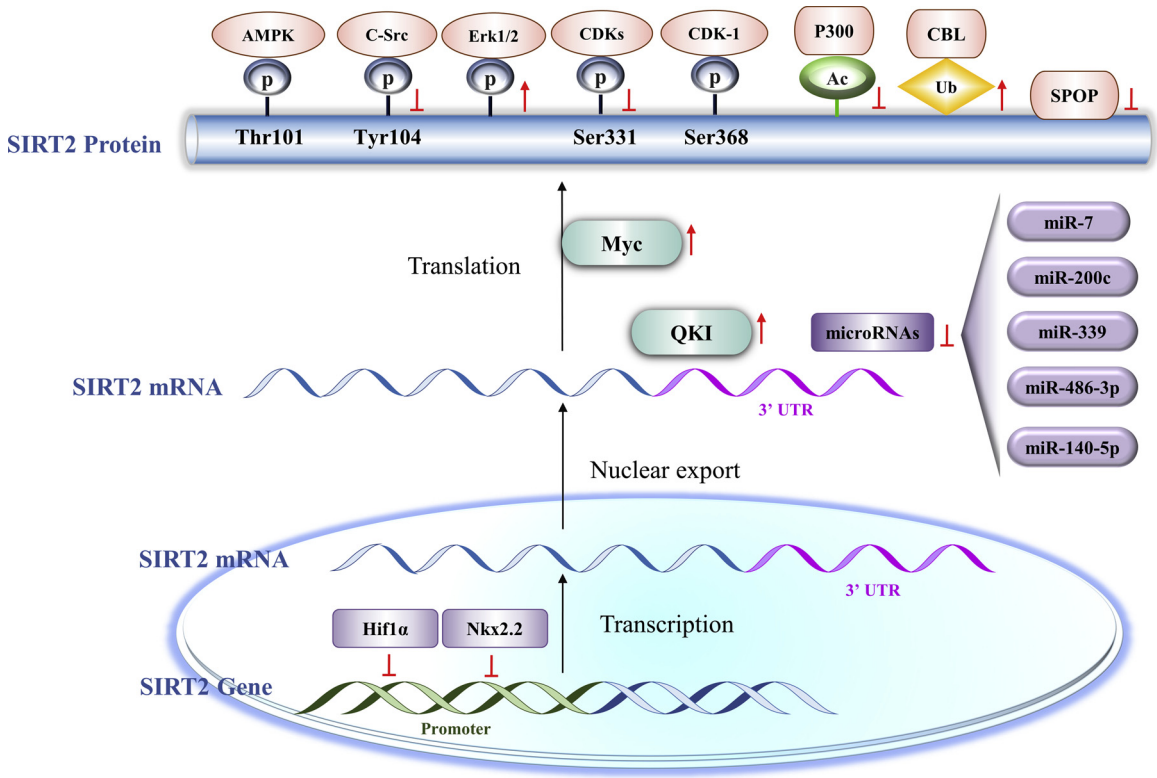

Fig. 2. Molecular regulation of SIRT2 at different levels. At the transcriptional level, the transcription factors Nkx2.2 and HIF1α bind to the SIRT2 promoter and negatively regulate SIRT2 expression. At the posttranscriptional level, QKI binds the 3′UTR of SIRT2 mRNA and increases its stability. Some miRNAs can also bind to the 3′UTR of the SIRT2 gene and have opposite effects, resulting in the degradation of SIRT2 mRNA. Myc upregulated the expression level of SIRT2 through increasing its translation. At the posttranslational level, SIRT2 can be phosphorylated by different phosphokinases at various sites, and phosphorylated SIRT2 may have changed stability, activity or binding ability with other partners. Moreover, SIRT2 can also be regulated by other posttranslational modifications, such as acetylation and ubiquitination.

during mitosis (North and Verdin, 2007b). Furthermore, Thr101 of SIRT2, a novel phosphorylation site, can be regulated by catalytic subunit of AMP-activated protein kinase (AMPK) (Ramakrishnan et al., 2014). Casitas B-lineage lymphoma (CBL) increases the protein levels and stability of SIRT2 *via* ubiquitination (Choi et al., 2014a), and P300 can inactivate SIRT2 by acetylation (Han et al., 2008) (Fig. 2).

2.11. Summary

A number of studies have described the mechanisms of SIRT2 function, from development and differentiation to the maintenance of normal physiological functions in cells, under different physiological conditions, suggesting a complex, multilevel regulation similar to that of the other well-studied members of the sirtuin family. Although the profile of the physiological functions of SIRT2 is still vague and undefined, our understanding of SIRT2 functions is improving.

3. SIRT2 and neurological diseases

SIRT2 is associated with several nervous system disorders, such as PD, Alzheimer's disease (AD), Huntington's disease (HD) (Fig. 3), depression (Erburu et al., 2017; Munoz-Cobo et al., 2017) and ischemic stroke (Xie et al., 2017). This suggests that SIRT2 has a critical role in neurological diseases and may therefore be a potential therapeutic target for these diseases.

3.1. Parkinson's disease

SIRT2 activity is elevated in postmortem PD brain tissue compared to control tissue (Singh et al., 2017). PD typically involves progressive loss of DA neurons in the substantia nigra and accumulation of Lewy bodies (LBs) that are mainly composed of α-synuclein (α-syn) (Mor et al., 2019). Several studies have confirmed that genetic or pharmacological inhibition of SIRT2 rescues α-syn toxicity and modifies inclusion morphology in a cellular model of PD, and that the inhibitors, AGK2 and AK-1, protected against DA cell death both *in vitro* and in a *Drosophila* model of PD. Interestingly, the authors speculate that tubulin acetylation may affect α-syn aggregation (Garske et al., 2007; Outeiro et al., 2007). Further research has found that SIRT2 modulates the acetylation of α-syn on Lys6 and Lys10, in turn influencing the α-syn inclusion bodies and autophagy, ultimately alleviating neuropathology in models of synucleinopathy (de Oliveira et al., 2017). Moreover, SIRT2 also exhibits similar protective effects in other PD models *in vitro* and *in vivo*. Chronic administration of 1-methyl-4-phenyl-1–3,6-tetrahydropyridine (MPTP) can replicate most of the clinical features of PD and produces a reliable and reproducible lesion of the nigrostriatal DA pathway and neurodegeneration. AK7, a selective brain-permeable SIRT2 inhibitor, prevents MPTP-induced dopamine depletion and DA neuronal loss *in vivo* (Chen et al., 2015b). The neurodegeneration induced by chronic administration of MPTP is reduced in Sirt2−/− mice by increasing FOXO3a acetylation, decreasing Bim levels and therefore reducing apoptosis (Liu et al., 2014). MPTP-treated Sirt2−/− mice also showed no changes in motor behavior, and the neurons showed no change in microtubule assembly after exposure to MPP (+), indicating the maintenance of normal autophagic flux (Esteves et al., 2018). However, in contrast to the previous results, an increase in acetylated α-tubulin due to a decrease in SIRT2 activity was observed in a PD mouse model induced by 6-hydroxydopamine (6−OHDA) treatment, and the restoration of tubulin deacetylase function rescued the changes in MT dynamics caused by 6−OHDA stress *in vitro* (Patel and Chu,

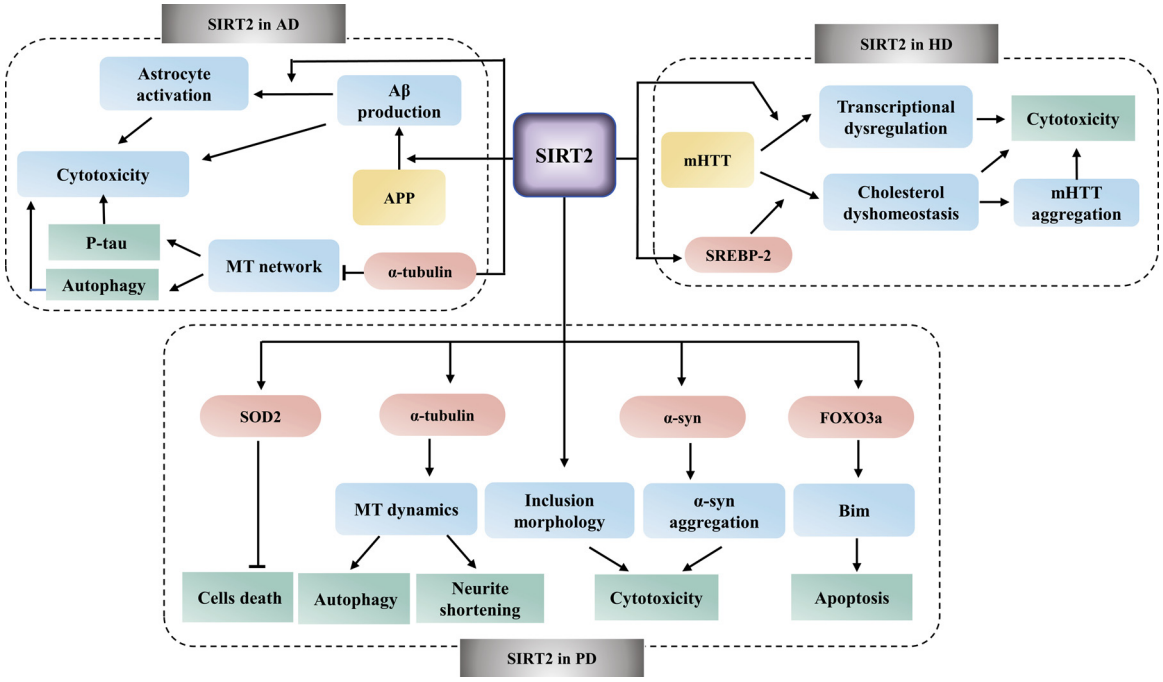

Fig. 3. SIRT2 in neurodegenerative disease. Most related studies suggest that SIRT2 has a neuroprotective role in neurodegenerative disease. In the AD model, SIRT2 influences the metabolism of Aβ, activation of astrocytes and may also be linked to mitochondrial metabolism. In the PD model, SIRT2 deacetylates α-tubulin and α-syn, in turn influencing the microtubule (MT) dynamics and contributing to abnormal autophagy and neuronal dysfunction. SIRT2 increases FOXO3a acetylation, leading to a decrease in Bim levels, thereby reducing apoptosis and ultimately contributing to PD. In the HD model, the inhibition of SIRT2 shows neuroprotection by restoring the transcriptional balance, cholesterol synthesis and reducing aggregated mHtt protein, demonstrating a beneficial effect in HD.

2014). In another PD model of rotenone or diquat treatment, elevated SIRT2 levels protected cells from death, and inhibition of SIRT2 increased cell death *in vitro*; this protection was mediated, in part, through elevated SOD2 expression (Singh et al., 2017) (Fig. 3). These inconsistent conclusions between SIRT2 and PD are due to the different disease models and the different SIRT2 interventions. Nonetheless, the vast majority of studies suggest that SIRT2 inhibition has an inhibitory effect on the pathology of PD, thereby reinforcing its potential as a target for therapeutic intervention in PD.

3.2. Alzheimer's disease

Increasing evidence confirms that SIRT1 activation plays a protective role in AD (Rizzi and Roriz-Cruz, 2018; Testa et al., 2018). One study showed that SIRT2 mRNA expression is increased in the peripheral blood of AD patients (Wongchitrat et al., 2019), and that there is an association between SIRT2 polymorphisms and AD risk, providing clinically relevant evidence of an association between SIRT2 and AD (Polito et al., 2013; Porcelli et al., 2013; Wei et al., 2014). However, to date, studies investigating the function of SIRT2 in AD have been limited.

Amyloid-β peptides (Aβ) are the most important biomarkers of AD, and the Aβ-producing amyloidogenic pathway is also the most studied target in AD (Panza et al., 2019). SIRT2 activity has been associated with Aβ and amyloid precursor protein (APP) metabolism in AD. Aβ is more cytotoxic in SIRT2-overexpressing neuronal cells (Gal et al., 2012), and the SIRT2 inhibitor AGK-2 reduces Aβ production in H4 cells expressing APP with the Swedish double mutation (H4-SW) (Biella et al., 2016). Additionally, AK-7 treatment led to a reduction in the amyloidogenic pathway and improved cognitive performance in 3xTg-AD and APP23 mouse models (Biella et al., 2016). Moreover, AGK-2 also reduced astrocyte activation as well as the proinflammatory mediators in Aβ-activated primary rat astrocytes (Scuderi et al., 2014).

Tau hyperphosphorylation is another major brain lesion in AD, which, in addition to Aβ, is emerging as a new promising therapeutic target for AD (Congdon and Sigurdsson, 2018). Nicotinamide (NAM), a pan-sirtuin inhibitor, decreases the phosphorylation of Thr231 of tau and increases acetylated α-tubulin, ultimately restoring the cognitive deficits in 3xTg-AD mice (Green et al., 2008). Further research shows that α-tubulin acetylation induced by SIRT2 inhibition is functionally associated with an improvement in microtubule dynamics determined by decreased tau phosphorylation (Esteves et al., 2019), suggesting that SIRT2 may serve as the main microtubule-associated protein (MAP), contributing to protection against AD pathology. In another tauopathy of tau-associated frontotemporal dementia (FTD), AK1, another SIRT2 inhibitor, was found to provide neuroprotection in the rTg4510 mouse model (Spires-Jones et al., 2012). These results suggest that the therapeutic benefits of SIRT2 inhibitors in AD are associated with Aβ or tau.

Multiple lines of evidence support the theory that mitochondrial dysfunction plays a major role in neurodegeneration and the etiology of AD, as well as abnormalities in the microtubule network involving tubulin and tau modifications and autophagy (Silva et al., 2011). Acetylation of Lys40 in α-tubulin reduces the disorder, thereby affecting microtubule stability and function (Eshun-Wilson et al., 2019). Increased SIRT2 levels and decreased acetylation of the Lys40 of tubulin were observed in cells containing mtDNA from AD patients as well as in AD brains. Moreover, SIRT2 dysfunction, AK1 or SIRT2 knockout can recover microtubule stabilization and improve autophagy, promoting cell survival under Aβ oligomer stress (Silva et al., 2017) (Fig. 3).

However, though the above evidence suggests that SIRT2 may contribute to protection against AD by affecting the stability of MAPs, maintaining mitochondrial function and autophagy, influencing Aβ metabolism and toxicity, an in-depth understanding of the mechanism of SIRT2 in the process of AD is still needed.

3.3. Huntington's disease

HD is caused by the expansion of CAG-triplet repeats within exon 1 of the HTT gene, which is translated into the mutant huntingtin (mHTT) protein with a pathologically extended polyglutamine tract prone to

misfolding and aggregation (Snell et al., 1993). Mutant mHTT is known to markedly affect mRNA levels through direct or indirect transcriptional regulation (Benn et al., 2008). Genetic or pharmacological inhibition of SIRT2 provides neuroprotection to Htt-challenged *Drosophila*, and this effect is enhanced when Rpd3 and Sirt2 are simultaneously inhibited (Pallos et al., 2008). SIRT2 inhibitors also play a protective role *ex vivo* in the rat corticostriatal and *Drosophila* models of HD (Quinti et al., 2016). Treatment with AK1 and AGK2 in a primary neuronal model of HD significantly reduce the presence of mHTT inclusions through influence at the sterol level, *via* a decrease in nuclear trafficking of the sterol response element binding protein 2 (SREBP-2) (Luthi-Carter et al., 2010). The above study provided strong evidence that SIRT2 deletion or inhibition rescued the pathogenesis of HD *in vitro* and in the *Drosophila* model.

However, there are inconsistent reports of SIRT2 in mouse models of HD. A study investigating the *in vivo* efficacy of SIRT2 inhibition with chronic pharmacological treatment in two HD mouse models found that AK7 treatment reduced brain atrophy, improved motor function and extended survival (Chopra et al., 2012). Conversely, the genetic depletion of SIRT2 in R6/2 HD transgenic mice did not affect polyglutamine aggregation and therefore had no neuroprotective effect, showing no difference in the cholesterol biosynthesis enzyme level among the control mice, the Sirt2 −/− mice, or the SIRT2 inhibitor treated R6/2 HD mice (Bobrowska et al., 2012).

In summary, although arguments regarding the effect of SIRT2 on HD still exist, the conflicting data may be due to differences in HD models, different SIRT2 interventions or time points of assessments. Nevertheless, in light of the above studies, SIRT2 clearly plays a pivotal role in HD but more research is needed to confirm the potential of SIRT2 as a target for HD treatment (Fig. 3).

3.4. Other neurological diseases

SIRT2 has been found to be associated with ischemic stroke. The SIRT2 protein is highly expressed in myelin-rich brain regions after stroke, and Sirt2−/− mice showed fewer neurological deficits in middle cerebral artery occlusion (MCAO) models with different occlusion times (Krey et al., 2015). Similar results were reported indicating that SIRT2 is upregulated in ischemic neurons in the oxygen-glucose deprivation cell model and in the transient MCAO (tMCAO) mouse model. Furthermore, AGK2 administration and SIRT2 knockout both showed neuroprotective effects in the tMCAO model (Xie et al., 2017). With regard to other neurological diseases, SIRT2 was identified as a candidate molecular pathway that may mediate cocaine addiction (Renthal et al., 2009). Interestingly, SIRT2 knockout has also been reported to have significant effects on the brain proteome and its response to ionizing radiation (Shukla et al., 2015).

3.5. Summary

In summary, SIRT2 plays a crucial role in neurological diseases, especially neurodegenerative diseases. Most current studies suggest that SIRT2 inhibition or deletion has clear neuroprotective effects on pathological neuropathy. However, the mechanism of action of SIRT2 in different neurological diseases is far from clear. Additional conditional knockout animal models and clinical data are still needed to clarify the feasibility of SIRT2 as a therapeutic target for neurological diseases.

4. SIRT2 and cancer

Many studies have linked SIRT2 to cancers by showing that the SIRT2 expression is always disordered in cancer (Fig. 4). Studies focusing on investigating the mechanism of SIRT2 function in tumors have demonstrated that SIRT2 may suppress tumorigenesis through diverse mechanisms (Kim et al., 2011; Seo et al., 2015; Zhang et al., 2013). Data from Sirt2−/− mice supports the hypothesis that Sirt2 −/− mice develop sex-specific tumorigenesis and SIRT2 may be a tumor suppressor (Kim et al., 2011; Serrano et al., 2013) (Fig. 1). However, SIRT2 expression levels and mechanisms are diverse in different types of cancers.

4.1. Breast cancer

Breast cancer is the most common malignant cancer in women. SIRT2 has been most extensively studied in breast cancer while there is no lack of controversy about whether SIRT2 inhibits or promotes breast cancer. Female mice lacking SIRT2 developed mammary tumors in old age (Kim et al., 2011), suggesting that SIRT2 acts as a tumor suppressor in mice. This finding was also supported in human samples in which SIRT2 expression was downregulated in cancer tissues compared with normal cancer-adjacent breast tissues (Kim et al., 2011). Mechanistic evidence suggests that the loss of SIRT2 function reprograms glycolytic metabolism *via* inactivation of the PKM2, and ultimately inhibits malignant growth in mammary tumor cells (Park et al., 2016). Moreover, elevated levels of SIRT2 also sensitize breast cancer cells to ROS-induced DNA damage and cell cytotoxicity *in vitro* by deacetylating and inhibiting the activity of the antioxidant protein peroxiredoxin (Prdx-1) (Fiskus et al., 2016), all suggesting the promotion of breast cancer in the absence SIRT2.

Conflicting data has been also published, especially for basal-like breast cancer (BLBC). SIRT2 has been reported to be amplified and highly expressed in BLBC samples (Zhou et al., 2016). Several mechanistic studies also imply that the suppression of SIRT2 inhibits the development of breast cancer. Overexpression of the Snail Family Transcriptional Repressor 2 (slug) protein is common in human cancer and represents an important determinant underlying the aggressiveness of BLBC (Liu et al., 2013b). SIRT2 has been reported to deacetylate and prevent the degradation of the transcriptional repressor slug, thereby controlling BLBC malignancy (Zhou et al., 2016). Moreover, arrestin domain-containing 3 (ARRDC3) is a tumor suppressor with nonexistent or reduced expression in BLBC (Zhang et al., 2013). Genetic knockdown of SIRT2 restores ARRDC3 levels with epigenetic alterations in MDA-MB-231 cells (Soung et al., 2014). Moreover, SIRT2 inhibition also exhibits an anticancer effect by promoting c-Myc ubiquitination and degradation in a mouse model of breast cancer (Jing et al., 2016).

The above studies illustrate the inconsistencies in data related to SIRT2 breast cancer research. Notably, McGlynn et al demonstrated that low levels of nuclear SIRT2 were associated with poor outcomes in moderately differentiated Grade 2 breast tumors. Conversely, high levels of nuclear SIRT2 were associated with a shorter time of relapse and death in poorly differentiated Grade 3 tumors (McGlynn et al., 2014), suggesting temporal expression of SIRT2 in different stages of breast cancer. Overall, more clinical evidence and mechanistic studies are required to clarify the role that SIRT2 plays in breast cancer development.

4.2. Lung cancer

SIRT2 is significantly downregulated at both the mRNA and protein level in non-small cell lung cancer (NSCLC) compared with nontumor tissues or cells (Li et al., 2016b, b), and low levels of SIRT2 are associated with poor patient survival (Li et al., 2016b), while high SIRT2 expression is associated with longer overall survival time (Gong et al., 2018). SIRT2 overexpression inhibits cell proliferation and increases cell sensitivity to cisplatin treatment in lung cancer cell lines (Li et al., 2013b). Studies have found that the Jumonji domain-containing 2A (JMJD2A) protein is upregulated in NSCLC (Kogure et al., 2013), and that SIRT2 binds to the promoter region of JMJD2A and negatively regulates JMJD2A expression, ultimately contributing to NSCLC (Xu et al., 2015). SIRT2 also induces Skp2 deacetylation and subsequent degradation, abolishing the effects of Skp2 on p27, ultimately affecting NSCLC cell growth (Li et al., 2016b). Moreover, ATP-citrate lyase

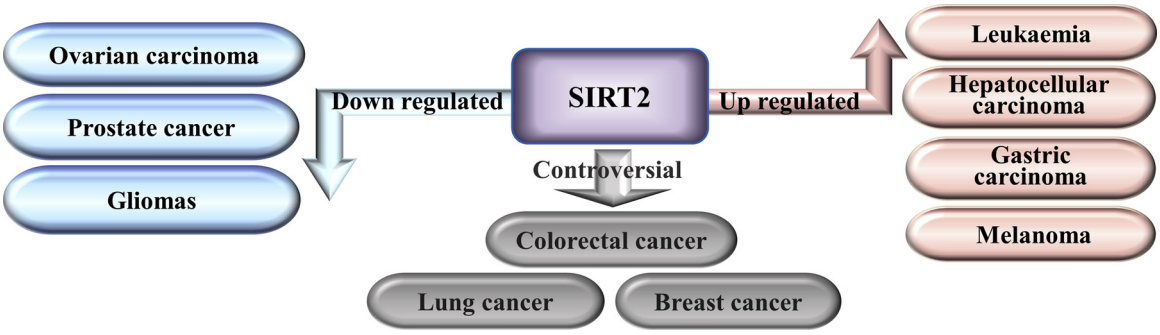

Fig. 4. SIRT2 is dysregulated in cancer. SIRT2 has been reported to be upregulated in leukemia, hepatocellular carcinoma, gastric carcinoma and melanoma and downregulated in gliomas, prostate cancer and ovarian carcinoma. Controversial reports still exist in colorectal cancer, lung cancer and breast cancer.

(ACLY) is upregulated or activated in several types of cancer, including lung cancer, and the 3 K acetylation of ACLY is also increased in human lung cancers. SIRT2 has been shown to deacetylate and destabilize ACLY, also suggesting that SIRT2 has a potential signaling role in lung cancer pathology (Lin et al., 2013b). However, conflicting data shows that the level of SIRT2 is significantly increased in NSCLC cell lines and primary tumors from cancer patients (Grbesa et al., 2015; Luo et al., 2017), and many SIRT2 inhibitors may potentially benefit NSCLC (Hoffmann et al., 2014; Lima et al., 2013; Ma et al., 2018; Yang et al., 2018).

4.3. Leukemia

Recent studies have indicated that SIRT2 is an oncogene in leukemia. SIRT2 is overexpressed in clinically acute myeloid leukemia (AML) samples (Dan et al., 2012; Xu et al., 2016). Additionally, the levels of SIRT2 are significantly elevated in patients with high-risk AML compared to lower risk patients (Dan et al., 2012). Furthermore, high SIRT2 levels are also associated with significantly lower overall survival and event-free survival compared with low SIRT2 expression in a cohort of patients with AML, suggesting that SIRT2 may be a potential biomarker for AML risk stratification (Deng et al., 2016). Moreover, SIRT2 inhibitors induces apoptosis and shows antiproliferative effects in both AML cell lines and primary cells from AML and chronic lymphocytic leukemia (CLL) patients (Bhalla and Gordon, 2016; Dan et al., 2012; Moniot et al., 2017; Rotili et al., 2012; Yoon et al., 2014). The inhibition of SIRT2 activity is also sufficient to induce cell differentiation in acute promyelocytic leukemia (APL) cell line NB4 (Sunami et al., 2013). AC93253, a SIRT2 inhibitor, shows antiproliferative and proapoptotic effects in HL60 cells, NB4 cells, and primary blasts of AML patients (Dan et al., 2012). Mechanistically, SIRT2 inhibition may acetylate and inactivate AKT, in turn influencing the activation of GSK-3β by diminishing phosphorylation, ultimately leading to the inactivation of β-catenin (Dan et al., 2012). Notably, only SIRT2 inhibitors were used as interventions in the above studies on SIRT2 function in leukemia. More *in vivo* evidence describing genetic interference should be obtained to explore the function of SIRT2 in leukemia.

4.4. Glioma

SIRT2 has been shown to be downregulated in human glioma *in vivo* and *in vitro* (Hiratsuka et al., 2003; Li et al., 2013a). However, glioblastoma patients with low nuclear SIRT2 survived significantly longer than patients with high nuclear SIRT2 (Imaoka et al., 2012). SIRT2 knockdown resulted in caspase 3-dependent apoptosis in glioma cells (He et al., 2012) and suppressed glioblastoma proliferation and survival of glioblastoma cells by deacetylating p73 C-terminal lysine residues and activating the transcriptional activity of p73 (Funato et al., 2018). Whether SIRT2 suppresses glioma cell growth or is required for glioma cell proliferation remains controversial.

4.5. Colon cancer

SIRT2 has also been shown to be upregulated in tissue samples of colorectal cancer compared to normal tissue samples. Moreover, elevated SIRT2 is associated with poor prognosis in patients with colorectal cancer (Hu et al., 2018). Tumor cells promote angiogenesis to increase the supply nutrients and oxygen by secreting a diversity of angiogenic factors, such as vascular endothelial growth factor-A (VEGFA), thereby ensuring cancer cell survival (Leite de Oliveira et al., 2011; Nowak-Sliwinska et al., 2018). Silencing SIRT2 directly inhibits the phosphorylation and nuclear translocation of signal transducer and activator of transcription 3 (STAT3) and the STAT3/VEGFA signaling pathway, resulting in colon tumor angiogenesis (Hu et al., 2018). The SIRT2 inhibitor AK1 slows proliferation, impairs wound healing activity and induces G1 arrest in HCT116 and HT-29 human colon cancer cells. Mechanistically, AK1 induces the proteasomal degradation of the snail transcription factor by inactivating the NF-κB/CSN2 pathway, which subsequently upregulates p21 (Cheon et al., 2015). The thiourea mechanism-based inhibitors of SIRT2 also show anticancer activity in an HCT116 xenograft murine model (Farooqi et al., 2019).

In contrast, SIRT2 was found to be downregulated in colon cancer biopsy samples compared to adjacent noncancerous tissues, and the overexpression of SIRT2 inhibited the proliferation and metastatic progression of SW480 cells, while blocking SIRT2 expression induced the proliferation and metastatic progression of HT29 cells (Zhang et al., 2017a). Epidermal growth factor receptor (EGFR) antibody drugs are effective in metastatic colorectal cancer. Loss of SIRT2 confers resistance to EGFR inhibitors in colon and lung cancer through the regulation of mitogen activated protein kinase kinase (MEK) activity (Bajpe et al., 2015). Overall, the current inconsistent reports still make it difficult to clarify the role of SIRT2 in colon cancer.

4.6. Other cancers

SIRT2 has been found to be upregulated in gastric cancer (GC) compared to adjacent normal tissues and is linked with reduced patient survival. An inhibitor of SIRT2 activity, SirReal2, decreased migration and invasion by the downstream target PEPCK1 in human GC cells (Li et al., 2018). SIRT2 is upregulated in melanoma (Wilking-Busch et al., 2017, 2018) and pharmacological inhibition of SIRT2 reduces melanoma cell proliferation (Karwaciak et al., 2015), while the knockdown of SIRT2 results in decreased colony formation and increased susceptibility to dasatinib in melanoma cells (Karwaciak et al., 2019; Wilking-Busch et al., 2018). SIRT2 is also upregulated in hepatocellular carcinoma, and its overexpression is associated with the presence of microscopic vascular invasion, more advanced tumor stage and lower overall survival (Chen et al., 2013), as well as tumoral progression and multidrug resistance (Ceballos et al., 2018).

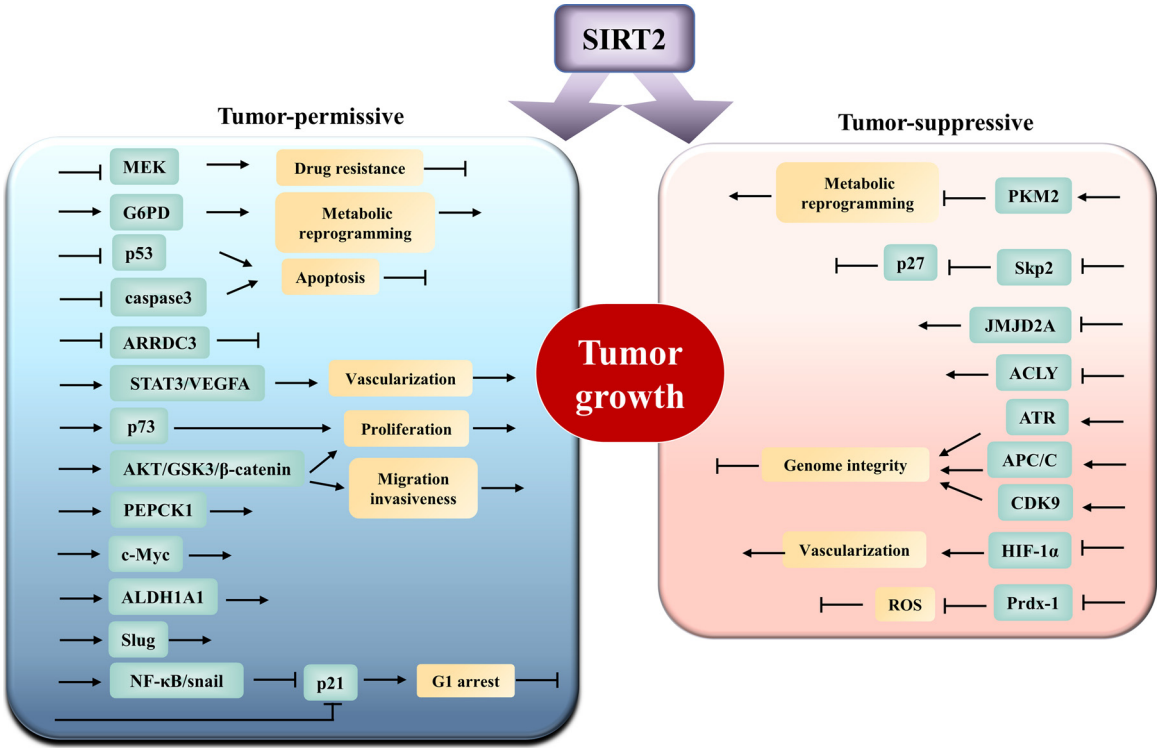

Fig. 5. SIRT2 participates in tumor inhibition and promotion. As an oncogene, SIRT2 promotes tumor growth by promoting oncogenes (*e.g.* Slug, ALDH1A1, c-Myc) and inhibits the tumor suppressor gene ARRDC3. SIRT2 deacetylates G6PD and induces metabolic reprogramming. SIRT2 increases cancer cell drug resistance through MEK. SIRT2 inhibits apoptosis by p53 and caspase 3. SIRT2 promotes tumor vascularization and proliferation by STAT3/VEGFA and p73, respectively. SIRT2 promotes tumor proliferation, migration and invasiveness by AKT/GSK3/β-catenin. SIRT2 inhibits p21 through NF-κB/snail transcription factor or other pathways. In contrast, SIRT2 inhibits tumor growth mainly through inhibiting of oncogenes (*e.g.* JMJD2A and ACLY). SIRT2 inhibits p27 through skp2. SIRT2 inhibits metabolic reprogramming through PKM2. SIRT2 maintains genome integrity *via* ATRIP and APC/C. SIRT2 prompted ROS through Prdx-1. SIRT2 inhibits vascularization through HIF-1α.

4.7. Summary

There is clear clinical evidence to suggest that SIRT2 expression is distorted in cancer. However, whether this is as a consequence or a cause of tumorigenesis has not yet been clarified, and the full profile of molecular mechanisms remains controversial and incomplete. For example, some reports show that SIRT2 is upregulated in leukemia, hepatocellular carcinoma, gastric carcinomas and melanoma, while other studies show that SIRT2 is downregulated in ovarian carcinoma (Du et al., 2017), prostate cancer (Damodaran et al., 2017) and gliomas. There are also controversial reports regarding lung cancer, breast cancer and colorectal cancer (Fig. 3). In addition, the mechanism underlying SIRT2 is currently unresolved and still controversial in different types of cancers (Fig. 5), and more clinical evidence and a better understanding of SIRT2 interactions is necessary to allow us to refine our understanding of the pivotal roles that SIRT2 plays in each cancer and to explore therapeutic tumor editing.

5. Other diseases

As well as the aforementioned diseases, SIRT2 has also been reported to be associated with several other diseases, further emphasizing the known extensive regulatory role of SIRT2 in disease. Some of the developments in recent years are illustrated below. SIRT2 levels are decreased in hypertrophic hearts induced by aging and angiotensin II (Ang II). Sirt2−/− mice show accentuated cardiac hypertrophy in aging-related and Ang II-induced models. Moreover, the cardiac-specific SIRT2 transgene also inhibits cardiac hypertrophy by activating AMPK signaling by deacetylating and activating its upstream liver kinase B1 (LKB1) (Tang et al., 2017). SIRT2 is also linked to inflammation and has been reported to play a role in many inflammatory-related diseases. SIRT2 inhibited collagen-induced arthritis, and Sirt2−/− mice showed aggravated arthritis severity (Lin et al., 2013a). LPS-treated Sirt2−/− mice exhibited reduced C-X-C motif chemokine ligand 2 (CXCL2) and C-C motif chemokine ligand 2 (CCL2) levels in proximal tubular epithelial (MPT) cells and showed infiltration of neutrophils and macrophages, acute tubular injury and a decrease in renal function compared to LPS-treated wild-type (WT) mice, showing that regulation of SIRT2 might be a therapeutic target for renal inflammatory injury (Jung et al., 2015). SIRT2 levels were increased in ob/ob mice during hypoinflammation, and SIRT-2 inhibition or knockout reversed the repression of microvascular inflammation in obese mice, significantly improving survival (Buechler et al., 2017; Wang et al., 2016b). Impaired hepatic glucose uptake (HGU) causes postprandial hyperglycemia in type 2 diabetes (Basu et al., 2001), and the depletion of Sirt2 inhibits HGU in hepatocytes derived from obese diabetic mice because SIRT2 permitted the glucose-dependent dissociation of glucokinase from glucokinase regulatory protein (GKRP) by deacetylating GKRP and glucokinase. Notably, this GKRP glucose-dependent dissociation is necessary for HGU (Watanabe et al., 2018). The acetylation of myristoylated alanine-rich C kinase substrate (MARCKS), which mediates the teratogenicity of maternal diabetes in neural tube defect (NTD) induction, is a prerequisite for self-phosphorylation; SIRT2 alleviates maternal diabetes-induced NTD *via* a mechanism that interacts with and deacetylates MARCKS (Yang et al., 2019). SIRT2 was elevated during hepatic ischemia-reperfusion (I/R) in liver tissues, and pharmacological or genetic suppression of SIRT2 attenuated hepatic I/R injury *via* the deacetylation of MKP-1, thereby interrupting MAPK signaling (Wang et al., 2017b) (Fig. 1).

6. Discussion and conclusions

In the present review, we provide an overview of SIRT2 function, revealing the current role of SIRT2 in nervous system regulation, mitotic regulation, genome integrity, cell differentiation, cell homeostasis, aging, infection, inflammation, oxidative stress and autophagy. We also condensed the current regulatory mechanism of SIRT2 and systematically summarized the identified substrates of SIRT2 (Table 1). Moreover, we provided a review of the current role of SIRT2 in neurological diseases and cancer as well as its potential as a therapeutic target.

SIRT2 is one of the least studied members of the sirtuin family in terms of physiology and disease. In recent years, increasing evidence suggests that SIRT2 plays a role in a wide range of physiological processes and diseases, similar to other sirtuin family members. The role of SIRT2 in so many physiological processes also highlights its indispensable role in the development and maintenance of normal physiological functions. Of note, although SIRT2 has been shown to have many substrates and extensive physiological functions, SIRT2 knockout mouse are able to survive and are protected against several diseases, such as some types of cancers and damaged neural pathways. The vast majority of pathological studies also reinforce the potential of SIRT2 as a therapeutic target for different diseases.

As for mechanism, in addition to the classic SIRT family deacetylation function, SIRT2 also shows several nonclassical functions, including lysine fatty acylation (Table 2). However, based on the increasing number of SIRT2 substrates identified, deacetylation is still the most important function of SIRT2 to exert its physiological and pathological effects. Moreover, SIRT2 is often reported to regulate the same substrate in different physiological processes, resulting in different physiological changes, this may be determined by cell or tissue specificity (Fig. 6). However, since SIRT2 regulates so many substrates, it may be able to regulate multiple substrates in the same physiological or pathological process. Therefore, more complete *in vivo* studies are needed to elucidate the mechanisms that play a major role in different function of SIRT2. Besides, different members of the sirtuin family sometimes regulate the same substrate, the study of the regulation of different sirtuins on the same substrate under a certain physiological or pathological condition will be more helpful to understand the function of SIRT2.

Remarkably, SIRT2 knockout seems to have negative effects on nerves under normal conditions in an age-dependent manner while various inhibitors of SIRT2 almost show a clearly protective effect on injured nerves or neurological diseases. Such conflicting data is not surprising. It is thought that although SIRT2 knockout is not lethal, it does play an important role in the development of nerves such as myelin or DA neurons and show the synaptic damage and behavioral cognitive impairment in the old age of mouse model, but the various inhibitor of SIRT2 activity does protect the injured nervous system in major neurological diseases just in mature animal models of diseases, the process of intervention does not involve neurodevelopment in infancy or cumulative damage in old age with the SIRT2 gene knockout. So currently SIRT2 is still believed to be a promising target for the treatment of neurological diseases. Furthermore, it is not just SIRT2 in neurological function, some conclusions from several studies with SIRT2 knockout are also not consistent with conclusions reached using various SIRT2 inhibitors under physiological and pathophysiological conditions. This is not surprising as in addition to the developmental effects of SIRT2, it may also be related to the compensatory effect of SIRT2 function or the specificity, dosage of SIRT2 inhibitor or even due to different phenotypes of the same disease, the mechanism of SIRT2 in different pathological processes should be examined separately. Furthermore, developing accurate disease models and inhibitors that are specific to not only SIRT2 but also SIRT2 substrates will aid our understanding of the roles of SIRT2 under different conditions and the detailed mechanisms underlying these roles.

In brief, current research has consistently shown that SIRT2 plays a wide range of roles in extensive biological processes and diseases, acting as a promising therapeutic target for many diseases. The continued rapid growth in SIRT2 research in the future will help us better understand the functions of this protein, clarifying the role of SIRT2 in human health and disease and promoting the progress of the application of SIRT2 as a therapeutic target the clinic.

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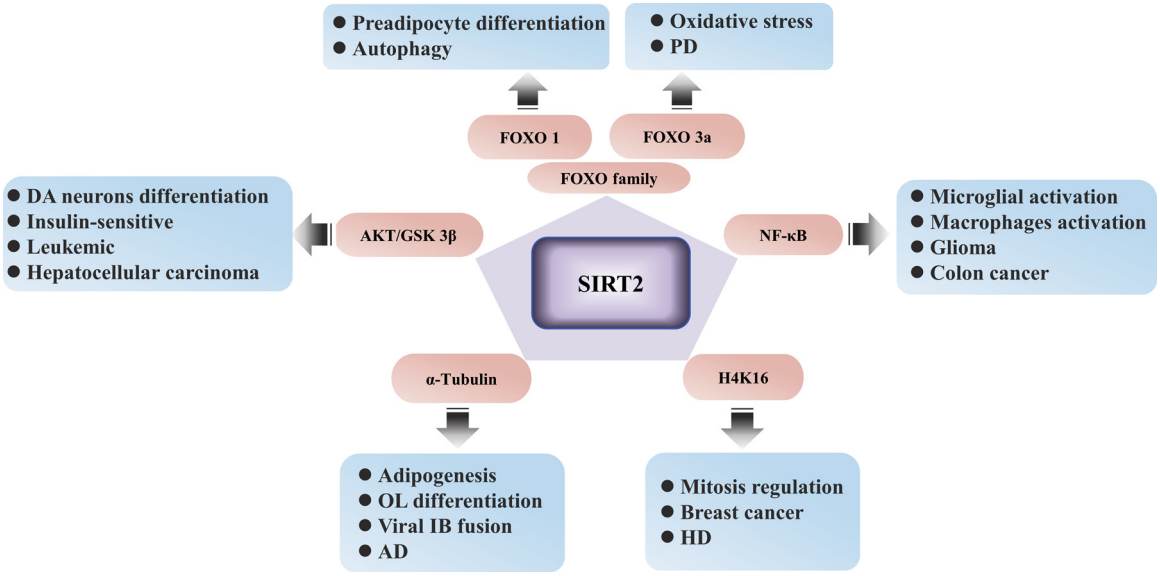

Fig. 6. The shared substrate regulation of SIRT2 in different physiological and disease processes. SIRT2 deacetylates FOXO1 during preadipocyte differentiation and autophagy. SIRT2 deacetylates FOXO3a in oxidative stress and PD. SIRT2 is involved in DA neuron differentiation, insulin-sensitive, leukemic, and hepatocellular carcinoma through the AKT/GSK 3β pathway. SIRT2 influences α-tubulin acetylation in viral IB fusion, adipogenesis, OL differentiation and AD. SIRT2 participates in colon cancer, microglial activation, macrophage activation and glioma *via* NF-κB. SIRT2 deacetylates H4K16 and participates in breast cancer, mitotic regulation, and HD.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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