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Review

Regulation of SIRT3 on mitochondrial functions and oxidative stress in Parkinson's disease

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ABSTRACT

Sirtuin-3 (SIRT3) is a NAD^+-dependent protein deacetylase that is located in mitochondria, regulating mitochondrial proteins and maintaining cellular antioxidant status. Increasing evidence demonstrates that SIRT3 plays a role in degenerative disorders including Parkinson's disease (PD), which is a devastating nervous system disease currently with no effective treatments available. Although the etiology of PD is still largely ambiguous, substantial evidence indicates that mitochondrial dysfunction and oxidative stress play major roles in the pathogenesis of PD. The imbalance of reactive oxygen species (ROS) production and detoxification leads to oxidative stress that can accelerate the progression of PD. By causing conformational changes in the deacetylated proteins SIRT3 modulates the activities and biological functions of a variety of proteins involved in mitochondrial antioxidant defense and various mitochondrial functions. Increasingly more studies have suggested that upregulation of SIRT3 confers beneficial effect on neuroprotection in various PD models. This review discusses the mechanism by which SIRT3 regulates intracellular oxidative status and mitochondrial function with an emphasis in discussing in detail the regulation of SIRT3 on each component of the five complexes of the mitochondrial respiratory chain and mitochondrial antioxidant defense, as well as the pharmacological regulation of SIRT3 in light of therapeutic strategies for PD.

1. Introduction

PD is a complicated and multifactorial neurodegenerative disorder with its clinical key features manifested as the triad of motor symptoms including resting tremor, bradykinesia, and rigidity caused by neurodegeneration and loss of dopaminergic neurons [1]. Epidemiological investigation has shown that the morbidity of PD is more than 1% of the population over the age of 60 years and more than 4% of the population by the age of 85 years [2,3]. The prevalence rate has been increasing with each passing year recently, which calls for more research on the pathological features and etiology of PD [4].

Pathologically, the hallmark characteristic of PD is the progressive loss of central dopaminergic neurons in the substantia nigra and the occurrence of Lewy bodies, which are cytoplasmic eosinophilic inclusions composed of abnormal protein aggregates of presynaptic protein α-synuclein (α-syn) [5]. Although the cause of PD is not known, evidence shows that the etiology of PD is caused by multiple factors. Both genetic and environmental factors are deemed to be etiological elements of PD [6]. Over the last few decades studies have identified several proteins that are unequivocally linked to PD, including SNCA (PARK1), LRRK2 (PARK8), Parkin (PARK2), PINK1 (PARK6), DJ-1 (PARK7), and ATP13A2 (PARK9). Mutations in these PD proteins are closely related to mitochondrial impairments and cellular oxidative stress leading to neuronal damage, which has been extensively studied in various in vitro and in vivo experiments, as well as in human cells [7,8]. However, genetic forms of PD only take up about 10 % of PD cases, and the majority of sporadic PD has a much lower connection with single-gene mutations that are easily identified by specific protein dysfunction [9]. On the other hand, environmental exposure has been recognized as an important contributing factor to the development of idiopathic PD. Epidemiological investigation has identified that exposure to several environmental factors including pesticides and heavy metals has been positively associated with increased risk of developing PD [10]. Of the pesticides, the most studied are rotenone and paraquat that have been found to cause increased PD risk and PD-like neuropathology, supported by experimental evidence that administration of

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these chemicals induces PD symptoms in various animal models. The pathogenesis of environmental chemicals induced idiopathic PD involves a complicated mechanism that has yet to be fully investigated. Nevertheless, the loss or degeneration of dopaminergic (DA) neurons is the key in the course of the pathogenic progression of this disorder. It has been proposed that mitochondrial dysfunction and oxidative stress may play a central role in the neurodegeneration or death of the DA neurons caused by exposure to pesticides. Interestingly, rotenone, a classic inhibitor of mitochondrial complex I, when administrated in rodents, produces some features of PD symptoms shared by neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) that has been reported to induce Parkinsonism in drug abusers [11]. Although the detailed mechanism may differ, MPTP is also an inhibitor of mitochondrial complex I that causes mitochondrial impairment and increased oxidative stress in neurons [12]. Over the last decades, the study of mitochondrial malfunction and oxidative damage has been an active area understating the pathogenic mechanism and exploring treatment strategies for the Parkinson's disease [1,13,14].

The acetylation/deacetylation of mitochondrial proteins represents a mechanism by which mitochondrial functions are regulated to adapt to various cellular stress and other metabolic challenge [15]. Among the seven sirtuins including SIRT1-SIRT7, SIRT3 is located in mitochondria where it modulates mitochondrial functions via modification of proteins participating in the regulation of cell survival under various physiological and pathological conditions [16–18]. SIRT3 is expressed at relatively high levels in tissues with high oxidative capacity including brain tissues. Studies have found that the expression of SIRT3 is maintained in the brain from early development through elderly stages [19]. This persistent expression of SIRT3 provides a possibility to modulate the biological functions in the brain throughout various developmental stages of life by targeting SIRT3. Given the important role of mitochondria in neural development, regulation of mitochondrial function and cellular oxidative defense system through modulation of SIRT3 is thus a unique niche for the therapeutic strategy for neurodegenerative disorders including PD. Indeed, increasing evidence demonstrates that upregulation of SIRT3 confers neuroprotective effects in PD and other neurodegenerative disorders [20,21]. Our recent studies found that activation of SIRT3 by icariin (ICA), a natural flavonoid glucoside isolated from the herb Epimedium, exerts neuroprotective effects on dopaminergic neuronal cell loss in the rotenone-induced PD rat and cell models [22]. In this review, we will summarize the research progress on the role of SIRT3 in relation to PD. Our review will emphasize the mechanistic regulation of SIRT3 on mitochondrial functions and oxidative stress, and the implication of genetic and pharmacological upregulation of SIRT3 in the intervention and treatment for Parkinson's disease.

2. Structure and biology of SIRT3

SIRT3 is a mitochondrial NAD^+-dependent protein deacetylase that is encoded by the nuclear genome. The structure of SIRT3 consists of a highly conserved catalytic core of ~275 amino acids that is flanked by N and C terminal extensions [23]. There are two forms of SIRT3 in human and mice, a full-length protein of 44 kDa and a 28 kDa short form that localizes exclusively in mitochondria [24,25]. Whereas there have been reports showing nuclear and cytoplasmic localization of SIRT3, accumulating studies have established that endogenous SIRT3 is mainly localized in mitochondria where it functions as a deacetylase enzyme regulating a broad range of mitochondrial functions [18]. In mitochondria, SIRT3 catalyzes the deacetylation of mitochondrial proteins in a NAD^+ dependent manner. The deacetylation activity of SIRT3 is highly dependent on the NAD^+ and is affected by the NAD^+/NADH ratio (Fig. 1). NAD is a cofactor essentially involved in several redox reactions and other signaling and regulatory pathways. Accumulating evidence has demonstrated that cellular NAD^+ levels in various organs including human brain decline during chronological aging [26–28]. Interestingly,

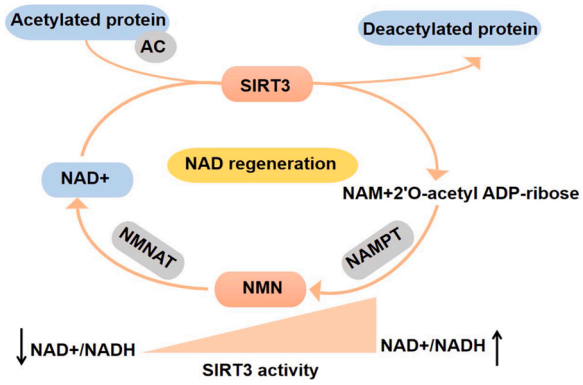

Fig. 1. SIRT3 catalyzed deacetylation of proteins and its regulation by NAD^+/NADH. Increase in the NAD^+ level or NAD^+/NADH ratio may enhance the activity of SIRT3, while a decrease in the NAD^+/NADH ratio suppresses SIRT3 activity.

there is a similar aging related decrease in the expression and activity of SIRT3 in the brain and other tissues that have been reported in various models [29]. As illustrated in Fig.1, the activity of SIRT3 is modulated by NAD^+ or NAD^+/NADH ratio [30], yet the exact mechanism behind remains to be fully elucidated. Of the several sirtuins, SIRT3 appears to be the only one that is able to slow down the aging related decline of physiological functions, and to modulate longevity and pathogenesis of neurodegeneration [31,32]. All these argue for a critical role of SIRT3 in the regulation of physiology and pathological process, suggesting that SIRT3 may be a potential target for the intervention and treatment of neurogenerative disorders.

3. SIRT3 and mitochondrial function

Mitochondria are essential organelles in eukaryotic cells, being the central site of principal cellular functions including adenosine triphosphate (ATP) generation, cellular Ca^{2+} homeostasis, and modulation of ROS status [33]. ATP is produced in the cell involving in oxidation of the substrate in cytosol glycolysis, the tricarboxylic acid cycle, pyruvate decarboxylation, and oxidative phosphorylation (OXPHOS) in mitochondria [34,35]. OXPHOS is the major source of ATP in aerobic organism, which is critical, particularly to the cells with high energy demand as neurons [36]. Meanwhile, during the process of OXPHOS, the electron transport chain located on the inner mitochondrial membrane produces ROS, which is a major source of intracellular ROS generation. The imbalance between the ROS generation and ROS scavenging is detrimental to the cells [37]. Impaired mitochondrial respiratory chain (MRC) and dysfunctional mitochondria have been well documented to be present in the substantia nigra of PD patients as well as in various animal models [38]. Because of adverse effects of ROS overproduction and insufficient energy supply to neurons [39–41], therefore, maintaining the execution of MRC and the physiological function of mitochondria is crucial for delaying the pathological process of PD.

Previous studies have shown that SIRT3, as a reversible protein deacetylase, regulates the post-transcriptional modification of critical proteins and thus participates in characteristic mitochondrial processes [25]. Recent studies have demonstrated that upregulation of SIRT3 maintains mitochondrial homeostasis and may be a potential therapeutic target for many diseases including neurodegenerative disorders and PD [42–44]. On the one hand, SIRT3 regulates MRC and reduces oxidative stress, thus preventing degeneration of dopaminergic neurons in the substantia nigra pars compacta via strengthening the functional capacity of mitochondria [45]. On the other hand, SIRT3 also participates in the regulation of a wide range of mitochondrial functions including modulating mitochondrial biogenesis, and maintaining mitochondrial dynamics and mitochondrial genomic integrity, etc. [44]. The

deficits in mitochondrial respiration and increased oxidative stress are two central events underlying the pathogenesis of PD. In this review we discuss in details on the research advance and evidence on the regulation of SIRT3 on the each component complex of the MRC that is closely related to the mitochondrial bioenergetics, and on the oxidative stress, with regards to the mechanistic understanding of the pathogenesis of neurodegeneration and exploring of a potential therapeutic target of the treatment of PD.

3.1. SIRT3 modulates mitochondrial respiratory chain in relation to PD

MRC consists of four protein complexes (complexes I-IV) that are associated with mitochondrial electron transport and ATP synthase (complex V) that utilizes proton-motive force to generate ATP from adenosine diphosphate (ADP) and an inorganic phosphate (Pi) through OXPHOS [34]. As illustrated in Fig. 2, OXPHOS produces ATP through two electron transfer paths: (1) NADH transports electrons to oxygen via complex I, coenzyme Q, complex III, cytochrome C, and complex IV, and (2) electron enters the respiratory chain from succinate via complex II, eventually forming an electron gradient to drive ATP synthase to produce ATP [46]. Due to both nuclear and mitochondrial genetic origins, the complexes of MRC must be tightly regulated to maintain the important structure and function of the MRC. Post-translational modifications have been described in the regulation of the components of MRC [47]. The acetylation/deacetylation regulation presents one of the post-translational modifications, which plays a critical role in regulating mitochondria enzymatic activities. SIRT3 is increasingly recognized as an important deacetylase involved in the regulation of all the complexes of MRC (Fig. 2), which is essential in modulating or improving mitochondrial bioenergetic failure that is implicated in the pathological process of neurodegeneration in PD.

Complex I, NADH dehydrogenase, is a multi-subunit protein of the MRC embedded in the inner membrane of the mitochondria [48]. Impaired mitochondrial complex I and oxidative stress play central roles in the loss of DA neurons during the progression of PD. Studies have demonstrated that complex I inhibitors such as MPTP and pesticides paraquat and rotenone cause parkinsonism and are widely used as classic neurotoxicants for various PD models [12,49]. The activity of complex I is subjected to the modifications caused by acetylation and deacetylation. While the acetylation of mitochondrial proteins is cell-intrinsic, and occurs primarily through the non-enzymatic mechanism owing to the high abundance of acetyl-CoA in the matrix, deacetylation in mitochondrial proteins is mainly regulated through SIRT3 [50]. Previous studies have demonstrated that SIRT3 directly interacts with two subunits of complex I, NDUFA11 and NDUFS8, and mediates its activity through deacetylation [17]. In the brain, it has been reported that several subunits of complex I are hyperacetylated, accompanied by a compromised mitochondrial respiration, in SIRT3 deficient mice [51]. On the other side, in SH-SY5Y human neuroblastoma cells, studies have demonstrated that complex I activity is enhanced by nicotinamide N-methyltransferase (NNMT) through SIRT3 [52]. Interestingly, SIRT3 function may in turn be regulated by complex I through the NAD^+-SIRT3 pathway. As NADH is dehydrogenized to form NAD^+ by complex I in the respiration chain, the resultant ratio of NAD^+/NADH thus directly affects the activity of SIRT3 [48,53]. It is worthy of noting here that although the inhibition of complex I has been implicated in the mechanism of neurodegeneration induced by MPTP, paraquat, and rotenone as mentioned above, the mode of actions of these classic Parkinsonism-causing compounds appears to be quite distinct in terms of action sites and the affinity on complex I [54,55]. Nonetheless, one of the common consequences of the inhibition of complex I by these neurotoxicants is the reduction of NADH oxidation, resulting in a decrease in NAD^+ level and an increase in the NADH/NAD^+ ratio, which may adversely affect SIRT3 activity and thereby exacerbate mitochondrial bioenergetic deficits. In this regard, the interaction between SIRT3 and complex I may be one of the crucial mechanisms involved in the pathological progression given the fact of complex I being one of the key targets of the identified Parkinsonism-causing neurotoxicants.

Complex II, succinate dehydrogenase (SDH), plays a central role in mitochondrial metabolism, linking the tricarboxylic acid cycle and mitochondrial electron transport system. It is composed of four subunits, a flavoprotein subunit (SDHA), an Fe-S protein subunit (SDHB), and two hydrophobic membrane anchor subunits, SDHC and SDHD [47]. Deficiency in complex II has been implicated in neurodegenerative disorders [56]. For example, it has been reported that a preferential loss of two subunits SDHA and SDHB along with mitochondrial dysfunction occurred in the striatum of Huntington's disease patients, which is instrumental in the striatal degeneration [57]. In PD, a study of post-mortem brain tissues revealed that there was a dramatic decrease in complex II activity in cortical regions, which was not owing to the gene expression as there was no corresponding downregulation of complex II subunits observed [58]. The decrease in complex II activity has also been observed in the occipital lobe using frozen post-mortem brain tissues, and the measurement of the protein expression in these brain tissues revealed no changes in the complex II subunits [59]. These results suggest that a post-translational modification mechanism is involved in

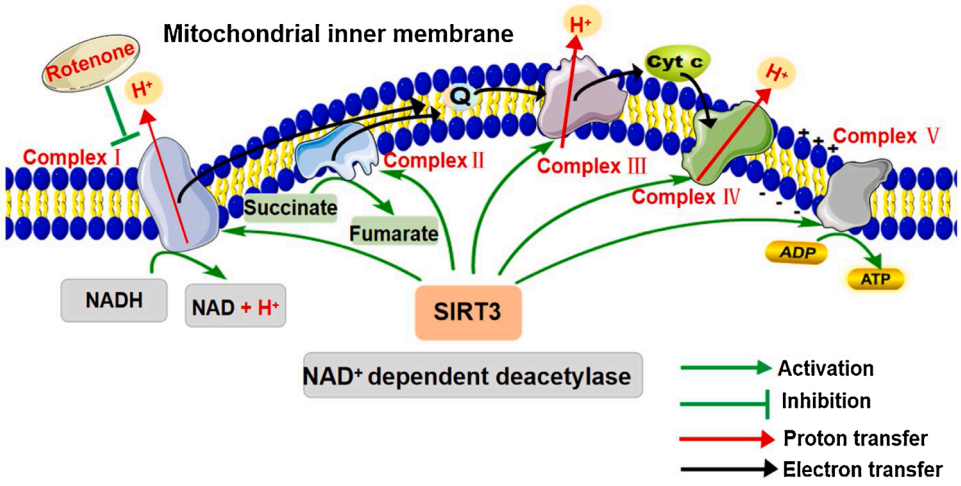

Fig. 2. Regulation of MRC by SIRT3. The MRC contains four complexes I-IV involved in the electron transport, and F1F0-ATP synthase (complex V). In the process of OXPHOS, electrons enter the chain through two paths, from NADH via complex I and from succinate via complex II. SIRT3 regulates some components of all five mitochondrial complexes.

the regulation of these protein functions. Whether acetylation/deacetylation is involved in these pathological phenomena, however, remains unknown. In fact, there have been relatively more studies showing the presence of acetylation in complex II. Indeed, it has been well demonstrated that mitochondrial complex II is subjected to the acetylation modulation by SIRT3. Through proteomic screening, Finley et al. identified two subunits SDHA and SDHB of complex II to interact specifically with SIRT3, and using mass spectrometry they further identified the acetylation sits on SDHA [60]. Moreover, they showed that the complex II activity in $SIRT3^{-/-}$ was lower than that of the $SIRT3^{+/+}$, which was attributed to the complete deacetylation of SDHA in the $SIRT3^{+/+}$ mice [60]. However, the physiological implications of deacetylation of complex II, in particular its relevance to neurodegeneration remain less studied. In addition, it has been controversial on the SIRT3-mediated regulation of complex II. For instance, studies have shown that SIRT3 deletion does not affect complex II-mediated respiration [61,62]. Therefore, the interaction between complex II and SIRT3 has yet to be further characterized. More importantly, fully exploring of the acetylation of complex II may offer new clues to mechanistic understanding of the pathological progression of neuronal cell death in PD.

Complex III, ubiquinol-cytochrome C (Cyt C) oxidoreductase, is an integral part of the MRC, contributing to the generation of electrochemical potential by catalyzing the electron transfer reaction from ubiquinol to Cyt C coupled to proton translocation across the membrane [63]. The decreased activity in complex III has been well documented in the brain tissues of PD patients [58,59]. It has also been reported that a low activity of complex III occurred early in the brain and platelet of PD [64,65]. These results suggest that the decrease in complex III may contribute to the pathological progress of PD. complex III is a substrate of SIRT3 and its activity is subjected to deacetylation regulation by SIRT3 [66]. It has been shown that SIRT3 deficiency causes a dramatic reduction in the complex III activity of brain mitochondria of $SIRT3^{-/-}$ mice [51]. In addition, Kim et al. demonstrates that loss of SIRT3 alters the activity of complex III, and thus the generation of ATP by OXPHOS [67]. Interestingly, SIRT3 also regulates complex III activity in a distinct manner. In a study of brain ischemia/reperfusion, Novgorodov et al. showed that SIRT3 deacetylates ceramide synthases and increases the accumulation of ceramide that causes the inhibition of complex III leading to mitochondrial dysfunction and brain injury [68]. These differing regulation mechanisms of SIRT3-mediated regulation on complex III indicates a diverse link between SIRT3 and mitochondrial respiratory proteins. It may also suggest that the functions of SIRT3 are cell type specific, and vary depending on physiological and pathological conditions. The exact role of SIRT3 in PD pathogenesis in light of its regulation of complex III thus has yet to be fully studied. In addition, complex III is an important source of cellular ROS generation. Any changes in the activity affecting mitochondrial bioenergetics such as a compromised complex III function may also disturb cellular oxidative status, which we will discuss more in depth later on.

Complex IV, Cytochrome c Oxidase (COX), is one of the critical enzymes and the last electron acceptor of the respiratory chain, playing a key action in maintaining mitochondrial function. It has been reported that the activity of complex IV is lower in the brain of PD patients compared with that in the control [69]. Other studies have shown that the activity of complex IV is significant decreased in neuromyelitis optica patients with symptoms of loss of motor and cognitive function [70]. Importantly, complex IV can be covalently modified by acetylation, and numerous lysine acetylation sites have been identified via high-resolution mass spectrometry [71]. Earlier studies showed that there was no difference in the enzymatic activity of IV in the heart tissues between $SIRT3^{-/-}$ and WT mice exposed to ischemia-reperfusion [72]. However, in a recent study involving both in vitro and in vivo models, Tu et al. demonstrated that SIRT3 deacetylates COX-1, thereby suppressing oxidative stress induced apoptosis in neuronal cells [73]. In the same study, they also identified several acetylation sites of COX-1 in response to oxidative stress [73]. Nevertheless, the biological functions and signaling of SIRT3-mediated deacetylation of complex IV need to be further characterized despite the demonstration of the acetylation of complex IV. In particular, there have been no reports to date showing the effect of SIRT3-mediated regulation of complex IV on neurodegeneration and the implication in PD pathogenesis.

The OXPHOS system consists of the four complexes involved in mitochondrial electron transport discussed above and F_1F_0-ATP synthase, also called complex V. Complex V is composed of two multisubunit subcomplexes, F1 and FO, which use an electronic gradient to synthesize ATP from adenosine diphosphate (ADP) and Pi [74]. ATP synthase is one of the most abundant proteins located in the mitochondrial inner membrane. Although most of the cellular ATP is synthesized by ATP synthase, this enzyme is also involved in the process of hydrolysis of ATP, which is essential to cell metabolism and survival, especially under certain pathophysiological conditions [75,76]. Bioenergetic failure has been suggested to be a central player in the death of neurons involved in neurodegenerative disorders [77]. A deficit in ATP production is one of the hallmarks of PD in patients [78]. Although the depletion of ATP observed in the PD may not be attributed solely to the dysfunction of complex V, damage to other components of the MRC may cause bioenergetic failure, and in many cases it is likely a consequence of the action of multiple factors. However, a significant decrease in the expression level of ATP synthase was indeed discovered in the substantia nigra of PD models [79]. Moreover, ATP synthase has recently been found to be involved in the regulation of dopaminergic cell metabolism through the regulation of DJ-1, a well described PD protein [79,80]. The deacetylation modification of complex V components by SIRT3 has been reported in a number of studies. In human 143B cells, it has been demonstrated that knockdown of SIRT3 causes increased acetylation levels of the α and OSCP subunits of FoF1ATPase along with decreased activity [81]. The SIRT3 is also involved in the regulation of cardiac ATP production through the deacetylation of ATP synthase [82,83]. However, there have been little studies showing the deacetylation of complex V in the neuronal cells or tissues. Since neurons are highly ATP dependent, maintaining mitochondrial integrity and function is crucial. Given the abundance of complex V and high expression level of SIRT3 in the brain [84], it is likely that complex V in a neuronal setting is also subject to the deacetylation modification by SIRT3, which remains to be tested.

Taken all together, the five complexes of OXPHOS are directly under regulation of deacetylation modification by SIRT3, which is critical in maintaining mitochondrial homeostasis. Therefore, SIRT3/complex (I–V) axis may act as potential therapeutic targets for PD.

3.2. *Role of SIRT3 in the regulation of mitochondrial ROS generation*

Mitochondria are the main source of cellular ROS due to the leaking of electrons from the electron transport chain (ETC), which interact with oxygen to form superoxide anion (O_2^-) or hydrogen peroxide (H_2O_2) [85,86]. It has been established that the mitochondrial ROS can be produced at sites of complex I, II, and III, while complex IV is less prone to generate ROS at a sufficient level of physiological and pathological significance [87,88]. It is estimated that approximately 90 % of cellular ROS are produced in the mitochondria [89]. Complex I has been demonstrated to be the major contributor to the mitochondrial ROS production that is associated with a variety of pathogenesis, in particular, in DA neuronal degeneration of PD, although the ROS level associated with complex I may vary dramatically depending on pathological conditions. Since the enzymatic activities of mitochondrial complexes I, II, and III are suppressed in the brain of PD [12,58,59,64], in addition to the collapse in bioenergetics, deficits in the functions of these important proteins may hinder the mitochondrial electron transfer, and thus cause excessive ROS production. Therefore, the deacetylation regulation of these complexes by SIRT3 not only improves mitochondrial bioenergetics, but it also directly modifies the production of mitochondrial ROS at these target sites. Rotenone is an environmental neurotoxin and classic inhibitor of mitochondrial complex I, which has been

demonstrated to cause characteristic loss of DA neurons in various animal models of Parkinson's disease [22,90]. In rotenone-induced human neuroblastoma SH-SY5Y cells, it was clearly demonstrated that treatment of rotenone caused increased ROS generation, while upregulation of SIRT3 enhanced cell survival with protection of mitochondrial membrane potential and at the same time decreased ROS generation [91]. In recent studies we also showed that treatment of rotenone causes an over two-fold increase in ROS generation in PC12 cells, which was further exacerbated in the presence of 3-(1H-1,2,3-triazol-4-yl) pyridine, an inhibitor of SIRT3. On the contrary, upregulation of SIRT3 significantly reduced ROS generation and ameliorated oxidative stress in both rotenone-treated cells and rat models [22,92]. These studies clearly demonstrate that there is a close association of mitochondrial bioenergetic collapse with increased oxidative stress, and that SIRT3-mediated deacetylation is directly involved in the regulation of mitochondrial ROS production. However, this raises an important question on how to evaluate the contributions toward improved cellular oxidative stress from the perspective of reducing oxygen free radicals in the scenario of SIRT3-mediated neuroprotection because SIRT3 also has a robust effect on mitochondrial antioxidant systems through the deacetylation modulation of its target antioxidant proteins, thus directly impacting the overall oxidative status. SIRT3 mediated antioxidant defense will be discussed in more details in the next section.

In addition to the effect on ROS generation through regulation of the complexes of ETC, SIRT3 also modulates mitochondrial ROS level via regulating the subunits of TCA cycle enzymes pyruvate dehydrogenase (PDH) and aconitase, both of which are associated with increased production of mitochondrial ROS [93]. Despite the fact that the MRC is a major ROS producer in mitochondria under resting conditions, these proteins are able to produce a significant amount of O_2^- and H_2O_2 under stress [94,95]. PDH is a gatekeeper enzyme complex of TCA cycle and OXPHOS involved in the generation of ATP [96]. With isolated rat and mouse brain mitochondria, Starkov et al. demonstrated that pyruvate dehydrogenase complex is a substantial constitutive source of free radicals especially under the conditions of an elevated mitochondrial NADPH/$NADP^+$ ratio [94]. Interestingly, previous studies showed that in the brain areas affected by AD disease and in the brain of late-stage PD cases there was an increased production of NADPH, a favorable condition for PDH-catalyzed production of free radicals [97]. PDH mediated ROS generation under physiological conditions, however, has yet to be defined. In addition, it has been reported that deficiency in E1 alpha subunit of PDH (PDHA1) is associated with O_2^- accumulation in the primary cultures of human skin fibroblasts [98]. The acetylation/deacetylation has been involved in the regulation of activity of PDH. Ozden et al. showed that PDHA1 can be acetylated in vitro and in vivo, and that there is a physical interaction between SIRT3 and PDH [99]. Using both mass spectrometry and in vitro deacetylation assays they further demonstrated that SIRT3 deacetylates PDHA1 lysine 321 that directs the activity of PDH activity [96]. Aconitase is another important enzyme in the TCA cycle. Mitochondrial aconitase catalyzes the conversion of citrate to isocitrate in the TCA cycle. Aconitase is susceptible to mitochondrial superoxide, which in turn facilitates the formation of hydroxyl radical via a Fenton-type mechanism, and thereby predisposing this enzyme as a source of hydroxyl radial [100,101]. Furthermore, the hyperacetylation of aconitase is observed in $SIRT3^{-/-}$ mice-derived embryonic fibroblasts [102]. However, the deacetylation of aconitase by SIRT3 exerts an inhibitory effect on its activity unlike in most cases where the SIRT3 mediated deacetylation results in the activation of its target proteins [103]. Although these data demonstrate that PDH and aconitase are under posttranslational modifications of SIRT3, all the results were generated in nonneural settings. The acetylation modification, and more importantly, the modulation of functions of these enzymes by SIRT3 has yet to be characterized in neurons or neural systems in order to implicate the SIRT3 mediated deacetylation into the mechanism of pathological progress of PD.

3.3. SIRT3 upregulates antioxidant defense

The role of SIRT3 in the regulation of antioxidative stress has been widely studied under various physical and pathological conditions. It is well characterized that SIRT3 regulates the activity of MnSOD through deacetylation on lysine 68 [104,105]. The genetic deletion of SIRT3 results in increased mitochondrial superoxide production which is associated with decreased MnSOD activity in the liver tissues of $SIRT3^{-/-}$ mice [106]. The deficiency in SIRT3 causes a reduction in the activity of MnSOD and induces increased oxidative damage to mitochondrial proteins in the heart of $SIRT3^{-/+}$ mice [72,107] On the contrary, the upregulation of SIRT3 deacetylates MnSOD and enhances its activity, and reduces mitochondrial oxidative stress [106,108]. These studies clearly demonstrate that MnSOD is a direct target of SIRT3, suggesting a critical role of SIRT3-dependent regulation of MnSOD in pathological conditions. Indeed, age-dependent decline of SIRT3 protection of mitochondrial oxidative stress has been implicated in dopaminergic neuron degeneration and PD [21]. It was found that SIRT3 deacetylates MnSOD on lysine 68 in dopaminergic neurons and regulates its activity, thereby modulating mitochondrial oxidative stress. More importantly, a significantly greater K68 acetylation of MnSOD was observed in the PD samples as compared with the controls [21]. These data strongly support the hypothesis that the loss of SIRT3 function increases the acetylation of MnSOD and induces mitochondrial oxidative stress contributing to the pathogenesis of PD.

Isocitrate dehydrogenase (IDH) is another enzyme regulated by SIRT3. The isoform IDH2 is a mitochondrial enzyme where it converts $NADP^+$ to NADPH and promotes regeneration of reduced glutathione (GSH) by supplying NADPH to glutathione reductase. Although IDH2 is not an antioxidant enzyme, being a major source of NADPH, it is closely involved in mitochondrial antioxidant defense through the regulation of H_2O_2 detoxification enzyme NADPH-dependent glutathione reductase [109]. Deacetylation regulation of IDH2 by SIRT3 has been demonstrated in a number of studies [109–112]. Moreover, the SIRT3-mediated deacetylation of IDH2 resulted in the elevation of NADPH levels and thus increased cellular GSH pool, and conferred cytoprotective effects against H_2O_2-induced oxidative damage to the cells [109,112]. Interestingly, although caloric restriction increased the GSH to GSSH ratio in the wildtype mouse brain, liver, and inner ear, this effect was not observed in SIRT3 deficient tissues [112]. These studies provide evidence in favor of indirect actions of SIRT3 in regulating the glutathione system through IDH as a source of NADPH.

However, to date, there have been very few studies on the acetylation status of IDH2 and its role in the scenario of neurodegenerative conditions. It is worth noting that the deletion of SIRT3 deteriorates the oxidative stress of $DJ\text{-}1^{-/-}$ knockout mice, leading to age-dependent dopaminergic neuron degeneration [21]. Although MnSOD is perhaps one of the major downstream players in this increased oxidative stress setting, the contribution of hyperacetylation of IDH2 caused by loss of SIRT3 to the increased oxidative stress remains to be investigated. More importantly, dopaminergic neurons located in the substantia nigra pars compacta seem to be more vulnerable to oxidative stress. Additionally, the substantia nigra contains lower levels of glutathione than other areas in the brain [113,114]. Therefore, it will be of great significance to study the neuronal protective effect of SIRT3 from the perspective of the SIRT3-IDH-GHS pathway.

4. Transcriptional regulation of antioxidants by SIRT3

In addition to direct activation of the activities of antioxidant target proteins, SIRT3 also regulates the expression of antioxidant enzymes through the transcription factor forkhead box O3 (FOXO3a) and the transcriptional coactivator peroxisome proliferator activated receptor-gamma coactivator-1alpha (PGC-1α). Jocobs et al. first demonstrated that SIRT3 interacted with FOXO3a to form a complex and regulate the activity of the FOXO3a, thus enhancing DNA-binding of FOXO3a at two

promoters resulting in an increase in gene expression along with an alteration in the intracellular oxidative environment [115]. The activation of FOXO3a by SIRT3 elevated mRNA transcripts of a series of antioxidant genes, among which the levels of MnSOD and catalase were dramatically increased, which was confirmed by notably higher protein levels [116]. Further studies revealed the deacetylation regulation of FOXO3a through which SIRT3 regulates FOXO3a dependent antioxidant gene expression to protect mitochondria against oxidative stress, which is implicated in the intervention of aging-related pathogenesis [117].

In addition, SIRT3 also upregulates the expression of MnSOD through SIRT3-dependent upregulation of the transcriptional regulator PGC-1α. PGC-1α regulates the expression of a number of mitochondrial antioxidant genes, including MnSOD and catalase, and thus prevents oxidative injury [118]. The transcriptional activation of PGC-1α is regulated mainly by CREB in different tissues [119], while SIRT3 promotes CREB phosphorylation, which in turn triggers transcriptional activation of PGC-1α [120]. Furthermore, it has been shown that the activation of SIRT3 causes increased mRNA levels of PGC-1α, leading to reduced oxidative stress and improved mitochondrial function in a mouse model of pressure overload hypertrophy [83]. On the other hand, however, research also showed that PGC-1a deficiency resulted in a reduction of SIRT3 gene expression in muscle cells and hepatocytes, which was mediated by an estrogen-related receptor (ERR) binding element (ERRE) [121]. These results suggest a bidirectional regulation between SIRT3 and PGC-1a which is involved in the mitochondrial antioxidant defense (Fig. 3). However, whether there exists a mutual regulatory interplay between SIRT3 and PGC-1α in the neural settings remains to be defined. In our recent study we demonstrated that downregulation of SIRT3 decreased the expression of PGC-1α in PC12 cell line, while sensitizing the cells to rotenone induced cytotoxicity; however, the genetic knockdown of PGC-1α did not affect the expression of SIRT3 [22]. These data did not suggest a mutual interaction between PGC-1α and SIRT3 in the cell model of rotenone neurotoxicity. Nonetheless, it does not rule out the possibility of an interplay between these two proteins in the scenario of either neurotoxicity or neurodegeneration. There are factors such as cell types and different experimental models that may influence the interaction between SIRT3 and PGC-1α, which has yet to be further studied.

5. Genetic manipulation of SIRT3 alters pathological progression in PD

Increasing evidence demonstrates that alteration of SIRT3 activity is strongly involved in mitochondrial oxidative stress and mitochondrial functions, and that the upregulation of SIRT3 exerts neuroprotective effects in various in vivo and in vitro models of PD [21,122–124]. It has been shown that the overexpression of SIRT3 ameliorates the neuronal degeneration induced by classical complex I inhibitors MPTP and rotenone in the substantia nigra pars via increasing mitochondrial antioxidant activities [91,125]. Studies in virally-expressing mutant α-synuclein rat model of PD demonstrate that overexpression of myc-tagged SIRT3 reverses cellular dysfunctions to normal conditions such as reduction of oxidative stress, and prevents the loss of nigro-striatal neurons and slows down the pathological progression of PD [123].

Similarly, it has been demonstrated that genetic deletion of SIRT3 dramatically exacerbated the degeneration of nigrostriatal dopaminergic neurons in MPTP-induced PD mice, and decreased mitochondrial antioxidant capacity, although SIRT3 deficiency per se does not cause motor and non-motor deficits when compared with wild-type controls [126]. Additionally, SIRT3 was identified as a target of miR-494-3p, and up-regulation of miR-494-3p suppressed SIRT3 expression and enhanced motor impairment in MPTP-induced PD mouse model [127]. These findings strongly suggest that SIRT3 plays a protective role in MPTP-induced neurodegeneration via preserving the free radical scavenging capacity of mitochondria. Recent studies demonstrated that overexpressing α-syn resulted in a decrease in the protein level of SIRT3 in mitochondria of nigral tissue in rodents [128]. Importantly, a decrease in the SIRT3 level was also observed in human post mortem brain with a confirmed neuropathological diagnosis of Lewy body disease [128]. Moreover, overexpression of SIRT3 in the rodent model of α-syn overexpression rescues α-syn-induced cell loss in the substantia nigra pars compacta [129]. These results suggest that SIRT3 might be a critical player in the α-syn-mediated pathogenesis involved in the development of PD. Taken all together, SIRT3 serves as a pro-survival factor in neurons under stress and various insults where it improves mitochondrial function, and protects dopamine neurons, which may confer a potential therapeutic target for the intervention of neurodegenerative diseases.

The neuroprotective effect of SIRT3 has also been demonstrated in a variety of cell models. In SH-SY5Y cells, it was found that miR-494-3p negatively regulates SIRT3, while the upregulation of SIRT3 by inhibition of miR-494-3p remarkably reduces 1-methyl-4-phenylpyridinium (MPP+)-induced cell injury [127]. Nicotinamide N-methyltransferase is neuroprotective against toxins that impact various aspects of mitochondrial function [130]. Studies have found that the cytoprotective

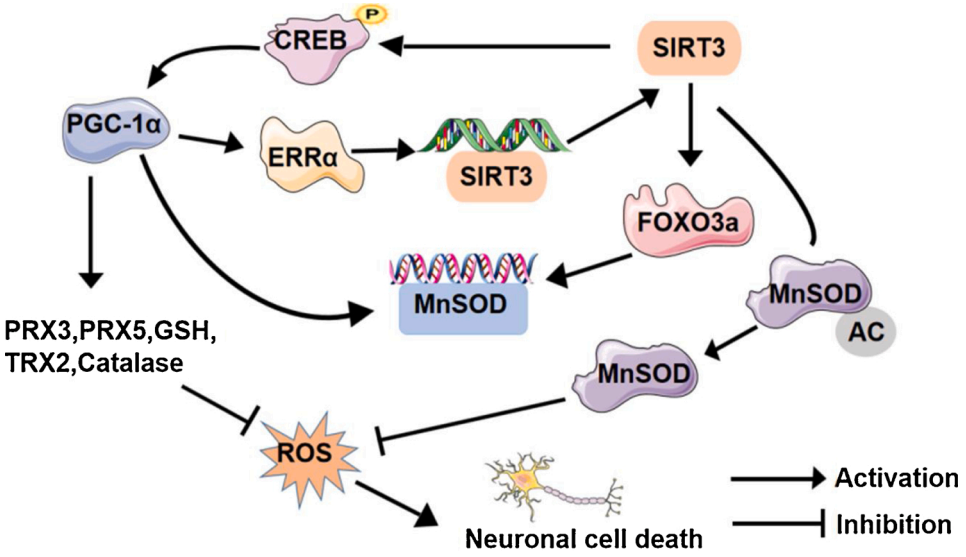

Fig. 3. Mutual interplay between SIRT3 and PGC-1α in the regulation of antioxidant system. In addition to its deacetylation activity, SIRT3 upregulates the expression of PGC-1α through increased phosphorylation of CREB, and subsequently stimulates the expression of the downstream antioxidant genes of PGC-1α. PGC-1α may also enhance transcription of SIRT3 through activating ERRα. The resultant increase in antioxidant activities mitigate cellular oxidative stress and protects neuronal cell death. CREB, cAMP-response element binding protein. ERRα, estrogen-related receptor alpha.

effect of NNMT is achieved through SIRT3-regulated protection on mitochondrial complex I activity and ATP production, while silencing of SIRT3 expression abolishes the NNMT-mediated cytoprotective effect in SH-SY5Y cells [52].

In an in vitro PD model of rotenone-induced SH-SY5Y cells, Zhang et al. demonstrated that the SIRT3 knockdown worsened the rotenone-induced loss of cell viability, while SIRT3 overexpression significantly increased cell viability and reduced cellular ROS generation, along with a decrease in the accumulation of α-syn, a hallmark of all synucleinopathies including PD [91]. It is now generally believed that the misfolding and subsequent aggregation of α-syn is a primary cause of dopaminergic degradation in PD [45]. The α-syn-induced mitochondrial impairment has been proposed to be a key event in the pathogenesis, and the inter-relationship between α-syn and mitochondrial dysfunction has thus been a hot research area. A recent study by Park et al. revealed that α-syn induced mitochondrial respiratory deficit was mediated through downregulation of SIRT3, which was accompanied by decreased phosphorylation of AMPK and cAMP-response element binding protein (CREB), whereas the α-syn -induced mitochondrial dysfunction was counteracted by upregulation of SIRT3 [128]. Undoubtedly, these data highlight that the regulation of SIRT3 may be crucial in the PD associated pathways. It is worth emphasizing that aging is an important factor implicated in the pathogenesis of PD, and the protein level of SIRT3 significantly decreases as one ages [91]. Given the fact that SIRT3 regulates oxidative stress and mitochondrial functions decline with age [131], it is likely that a compromised function of SIRT3 may be one of the key culprits entangled in the net of aging-mediated pathogenesis of PD, which remains to be further investigated. In summary, these data support a protective role for SIRT3 in PD-associated pathways and contribute significant mechanistic insight into the interplay of SIRT3 and α-syn.

6. Therapeutic potential of targeting SIRT3 in PD

There is no cure for Parkinson's disease. Current treatments available improve the symptoms of PD, but do not stop the progression of this devastating disorder. SIRT3 has been increasingly implicated in the pathogenesis of neurodegeneration, and emerges as a potential therapeutic target of PD. One of the promising strategies is to enhance mitochondrial NAD^+ that activates SIRT3 activities. Interest in the studies of NAD^+ biology has resurfaced over the past few years, which has led to the implication of NAD^+-deficiency in a variety of human diseases. In particular, NAD^+ intermediates, such as nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR), have been extensively tested for their ability to increase NAD^+ levels and beneficial effects in biosynthesis as a potential target for prevention and treatment of aging and aging-associated diseases [132]. Nicotinamide riboside is a trace nutrient in foods functioning as a precursor to nicotinamide adenine dinucleotide [133]. As a NAD^+ booster, NR has been mostly studied for its pharmacological effects in aging-related pathologies and disorders in not only animals but humans as well. It has been shown that NR promotes longevity and increases health span in multiple animal models [134–136]. In addition, NR confers neuroprotective effects and reduces neurodegeneration in animal models. Studies demonstrated that NR improves behavioral functions and mitochondrial functions, and protects against neuronal cell death in both AD and PD animal models [137,138].

NMN is an intermediate of nicotinamide adenine dinucleotide biosynthesis, which is rich in various types of foods such as broccoli, cabbage and some fruits [139]. Similar to NR, NMN has been demonstrated to be protective over aging and aging-associated disorders in various animal models. In mice aging model, long-term administration of NMN suppresses age-associated body weight gain and protects against age-associated functional decline along with an increase in mitochondrial respiratory rate [140]. In AD animal models, studies have shown that treatment of NMN restored mitochondrial function and cognition in AD animal models [141,142]. The neuroprotective effects of NMN have also been demonstrated in the in vitro PD model revealing that NMN treatment attenuates apoptosis and improves energy metabolism in rotenone-treated PC12 cells [143]. Importantly, the oral administration of NMN and NR has been demonstrated to be safe and effectively metabolized in human subjects, and to elevate NAD^+ levels in tissues without causing any significant deleterious effects, indicating a potential therapeutic strategy of enhancing NAD^+ levels in fighting against aging and aging-related disorders in humans [144,145]. Despite the confirmed neurological benefits in animal studies, however, to date, there has largely been a shortage of solid data supporting the beneficial effects of NR and NMN supplementation in humans, although NR and NMN have been demonstrated to enhance NAD^+ bioavailability and increase tissue NAD^+ levels [146]. Additionally, the renewed interest in the longevity and neuroprotection effects of NAD^+ precursors has raised concerns over the safety of long-term use. Although part of the coenzyme nicotinamide adenine dinucleotide is essential to a variety of biological functions, nicotinamide at high doses causes cytotoxicity and adverse effects that have been documented in cultured cells as well as in animal studies [147]. With respect to the neurotoxicity of nicotinamide, Mori et al. reported that the exposure of mouse brain striatum neuronal cells to neurotoxicant manganese caused a dose-dependent increase in the NNMT activity and thereby increased the level of *N*-methyl nicotinamide (MNA), the metabolite of nicotinamide catalyzed by NNMT, which brings about neuronal death [148]. Importantly, it has been reported that the levels of both NNMT and MNA are elevated in the brain of PD patients [149,150]. Nonetheless, there has been no proof that MNA can be attributed as one of the causes of PD. Although the mechanism of nicotinamide-linked neurotoxicity remains perplexing, one thing appears to be clear — that nicotinamide manifests as a double-edged sword, acting as a neuroprotectant or as a protoxin at high dosages or in susceptible individuals [151]. Considering the species differences in the metabolism of nicotinamide, as well as individual variations in pharmacogenetics of nicotinamide, further studies of the nicotinamide-NAD^+ metabolism would be needed regarding long-term application of nicotinamide supplementation as a strategy for the treatment of PD.

In addition, a number of natural products have been demonstrated to activate SIRT3 activities, thereby displaying neuroprotective properties. One of the most studied agents is resveratrol. Resveratrol is a stilbenoid polyphenol produced by several plants [152]. As a phytoalexin, resveratrol has been found to perform many pharmacological activities, including its role in neurodegeneration. One of the mode of actions relating to the neuroprotection of resveratrol may rely on its strong antioxidant and free radical scavenging ability. Previous studies have shown that resveratrol attenuates H_2O_2-induced cell injury and MPTP-induced rat injury, and improves mitochondrial functions [153,154]. In vivo studies have also demonstrated that resveratrol exerts a protective effect on 6-OHDA induced neurotoxicity and behavioral abnormalities in rats [155]. Further studies have found that resveratrol confers dopaminergic neuroprotection by upregulating SIRT3 activity, thereby activating SOD2 activity and decreasing oxidative attack in mitochondrial complex I-deficient PD models [156].

Honokiol is another poly-phenolic compound that is able to modulate SIRT3 activity and exert neuroprotective properties. It has been demonstrated that honokiol-mediated upregulation of SIRT3 attenuates mitochondrial dysfunction and suppresses ROS production in amyloid-β oligomer-treated hippocampal neuronal cells and in the AD mice model [157]. In a PD model, Chen et al. demonstrated that honokiol ameliorates motor impairment and progressive dopaminergic damage in 6-OHDA-lesioned mice [158]. Although the mechanism underlying honokiol mediated neuroprotection in these studies remains to be further defined, the activation of SIRT3 signaling may be one of the critical events involved in the pathogenesis, which is worthy of some exploratory efforts. Indeed, honokiol is one of the positive SIRT3 activators, which has been studied most and is frequently implicated in the

protective modes of actions in a variety of diseases [159].

Icariin is a flavonoid glucoside extracted from Epimedium that displays various pharmacological functions. Previous studies have demonstrated that icariin is protective in PD models and ameliorates neurotoxicity induced by a wide variety of neurotoxicants such as 6-OHDA, LPS and MPTP [160–162]. Our group recently demonstrated that icariin could up-regulate SIRT3, enhance cellular antioxidant defense capacity, and protect rotenone-induced neuronal cell death in PD model [22]. In this study we further showed that treatment of cells with 3-TYP, a SIRT3 inhibitor, abolished the protective effects of ICA in PC12 cells treated with rotenone. Mechanistically, the SIRT3-mediated neuroprotection may relate to the regulation of PGC-1α, however, the interplay between SIRT3 and PGC-1α has yet to be further studied in terms of the role that SIRT3 plays in the pathogenesis of PD, as discussed earlier in Section 4.

Kaempferol is another positive modulator of SIRT3 that exerts neuroprotective effects in PD models. Kaempferol is a flavonoid found in a variety of plants and plant-derived foods including kale, beans, tea, spinach and broccoli [163]. In a mouse PD model induced by MPTP, Li and Pu showed that kaempferol was able to prevent dopaminergic neuron loss and increase superoxide dismutase and glutathione peroxidase activities [164]. The neuroprotection of kaempferol has also been demonstrated in other in vivo and in vitro PD models induced by rotenone [165,166]. Although kaempferol-mediated neuronal cell protection may be involved in multiple modes of action in these PD models, reduction of oxidative stress is a common phenomenon reported in these studies, which has been proposed to play a central role in the protective mechanisms of flavonoids in PD [167]. Interestingly, it has been demonstrated that kaempherol upregulates deacetylation activity of SIRT3, and thus gives rise to a decrease in the acetylation of the SDHA subunit, leading to increased complex II activity [168]. This suggests another possibility that kaempferol may regulate mitochondrial functions and cellular oxidative status through modulation of SIRT3, which implicates its possible involvement in the neuroprotection mechanism of kaempferol.

Salidroside is also a positive modulator of SIRT3. Salidroside is a phenylpropanoid glycoside isolated from Rhodiola rosea L., which has been shown to upregulate the expression of SIRT3 [169]. Studies in recent years have found that salidroside exerts pharmacological effects on neurodegeneration, and protects dopaminergic neurons by preserving complex I activity [170]. Whether the modulation of SIRT3 by salidroside is involved in the mechanism of salidroside-mediated neuroprotection, however, remains unknown. Several other compounds such as oroxylin A, viniferin, and 7-hydroxy-3-(4′-methoxyphenyl) coumarin have also been shown to display activity in activating SIRT3 [171]. These additional compounds are not discussed here, however, since to date there is limited data indicating regulation of SIRT3 by these compounds in the setting of neurodegeneration.

7. Conclusion and perspectives

Parkinson's disease is a devastating and progressive neurodegenerative disorder. There are currently no effective treatments for PD. The dysregulation of SIRT3 has been found in mitochondria implicated in a wide variety of pathogenic progressions including neurodegeneration. With increasing evidence supporting the protective role of upregulation of SIRT3 in neuroprotection, SIRT3 is emerging as a target for pharmacological intervention for the treatment of PD.

Despite decades of research, the etiology of PD still remains elusive. However, mitochondrial dysfunction and oxidative stress have been recognized to play central roles in the loss of progressive dopaminergic neuron, one of the key features in the pathology of PD. A growing body of research has demonstrated that SIRT3 not only regulates mitochondrial antioxidant defense capacity through deacetylation activation of MnSOD and IDH2, and transcriptional activation of FOXO3a and PGC-1α, but is also directly involved in the regulation of mitochondrial function, particularly, in the regulation of all five complexes in the MRC under neurodegenerative settings, which strongly suggests a potential for pharmacological targeting of SIRT3 as a therapeutic intervention for PD. Identification of natural compounds as SIRT3 activators, or positive modulators, combined with the research data available showing effectiveness and efficacy in various animal models, makes targeting SIRT3 an attractive and promising strategy. From a clinical standpoint, further characterization of the mechanism of SIRT3 activators mediated neurological benefits is essential. In the case of resveratrol, multiple mechanisms of action may contribute to its neuroprotection. With regards to resveratrol's antioxidant activity, deemed to be a major function associated with its beneficial effects, the molecular mechanism behind SIRT3 mediated regulation of cellular oxidative status and improvement in the oxidative damage may be distinctly dependent on physiological and pathological conditions. The SIRT3 mediated reduction in the cellular oxidative stress may be due to its upregulation of antioxidant capacity, or the reduction in the source of ROS generation because of an improved mitochondrial electron transport system, or a combination at any given condition. As a polyphenol, resveratrol has been well shown to function as a potent antioxidant and free radical scavenger involved in cytoprotective actions. On the other hand, deficits in the MRC may cause increased oxidative stress which in turn exerts a deleterious force on the components of the MRC, and may further exacerbate cellular oxidative stress. SIRT3 thus may regulate cellular oxidative stress either through upregulating antioxidant defense or improving mitochondrial respiratory function, or possibly both. Dissection of the underlying mechanism is critical in order to pinpoint the events linking the beneficial effects, and to prospectively identify any possible adverse effects in potential therapeutic applications for PD.

Despite the beneficial and promising neuroprotective effects of the natural products discussed in this review, a more potent and specific activator(s) of SIRT3 has yet to be discovered for an effective treatment or intervention of PD. On the other hand, low levels of NAD^+ may be at least one of the central phenomena causing age-related problems. NAD^+ supplements nicotinamide riboside and nicotinamide mononucleotide are receiving attention for their purported effectiveness at increasing NAD^+ levels. Yet, it remains a question that although these supplements increase the concentration of NAD^+ in blood or other tissues, there has not been any solid data demonstrating that having more NAD^+ will increase life span or improve neurodegenerative disorders in humans. Nonetheless, accumulating data available on the beneficial effects on neuroprotection, combined with continued efforts on the characterization of the detailed mechanisms of action, makes targeting of SIRT3 a promising strategy for the treatment of the devastating disorder of PD.

Declaration of Competing Interest

The authors declare no conflict of interest.

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