 doi:10.20944/preprints202205.0158.v1

Review

Histone Deacetylases as Epigenetic Targets for Treating Parkinson's Disease

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Abstract: Parkinson's disease (PD) is a chronic progressive neurodegenerative disease that increasingly become a global threat for the elder people's health and life. Although there are some drugs in clinic for treating PD, these treatments only can alleviate the symptoms of PD patients but fail in curative therapies. Therefore, seeking other potential mechanisms to develop more effective treatments that can modify the course of PD is still highly desirable. In the last two decades, histone deacetylases as an important group of epigenetic targets in drug discovery have attracted much attention. This review is focused on the current knowledge about histone deacetylases involved in PD pathophysiology and their inhibitors used in PD study. Further perspectives related to small molecules that can inhibit or degrade histone deacetylases to treat PD are also discussed.

Keywords: Parkinson's disease; Epigenetic targets; Histone deacetylases; Inhibitors; PROTACs

1. Introduction

Parkinson's disease (PD) as the second most common neurodegenerative disease is characterized by motor (eg, bradykinesia, rigidity, and tremor) and non-motor (eg, constipation, hyposmia, depression, cognitive decline, and sleep alterations) signs and symptoms, which affects approximately 1% of the elders over the age of 60 years [1]. With the aging of the population, the incidence of PD rises. In some countries (primarily in North America and western Europe), the risk of Parkinson's disease has increased annually [2]. In China, according to the newly-released the seventh national census, the population aged 60 and over has reached 264.02 million, which may also cause a surge of the risk in developing neurodegenerative diseases such as Parkinson's disease (PD) [3]. Additionally, the incidence of PD is estimated to be doubled worldwide by 2040 [4-6]. In front of this global threat, the exact pathogenesis of PD remains unclear, but it likely involves both genetic and environmental factors. Since two classical hallmarks of a progressive loss of dopaminergic neurons from the substantia nigra pars compacta (SNpc) and the accumulation in Lewy bodies (LB) from the aggregates of α-synuclein have been established, the agents for "symptomatic" (alleviating the features of the condition) treatment of PD have been used in clinic or investigated in the clinical trials. The drugs approved by Food and Drug Administration (FDA) for treating Parkinson's disease can be roughly classified into dopaminergic system drugs, serotonergic system

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drugs, cholinergic system drugs, and others [7]. Dopaminergic system drugs included aromatic amino acid decarboxylase (AADC) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, monoamine oxidase B (MAO-B) inhibitors, dopamine transporter (DAT) inhibitors and dopamine receptor (DR) agonists; serotonergic system drugs are 5-hydroxytryptamine (5-HT) 2A and 2C receptor antagonists; cholinergic system drugs are mainly muscarinic acetylcholine receptor (mAChR) antagonists; adenosine receptor (A2A) inhibitors and glutamate receptor (NMDA) antagonists are considered as other drugs for treating PD [8-11]. These treatments only can alleviate the symptoms of PD patients in a short time, however, none of the treatments to date have yet translated into a clinically disease-modifying treatment [1, 12-14]. Therefore, there is still an urgent need by targeting other potential mechanisms to develop effective treatments that can modify the course of Parkinson's disease to improve PD patient's quality of life.

The term "epigenetics" is used to describe the regulatory mechanism involving modification of the expression levels of certain genes without altering their DNA sequence, generally, including DNA methylation, histone acetylation, and RNA modifications [15]. Because most diseases undergo epigenetic changes, epigenetic targets in drug discovery have attracted more and more attention in recent years. Among epigenetic targets, histone deacetylases (HDACs) have been intensively investigated due to their capability of removing acetyl group from the lysine residues of histone and nonhistone substrates and thus regulating chromatin remodeling or the expression of certain genes [16]. As shown in Table 1, HDACs have been divided into four classes, in which Class I (HDAC1, 2, 3 and 8), Class IIa (HDAC4, 5, 7 and 9), Class IIb (HDAC6 and 10) and Class IV (HDAC11) are zinc-dependent deacetylases, while Class III (SIRT 1-7) are nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylases (also called sirtuins) [17, 18]. Epigenetic modulation by HDAC inhibition has been proven to be beneficial for treating cancer [19]. Consequently, Food and Drug Administration (FDA) in USA has approved four HDAC inhibitors as monotherapy for treating cancer including Vorinostat (SAHA) [20], Romidepsin (FK228) [21] and Belinostat (PXD-101) [22] for treating cutaneous T-cell lymphoma (CTCL) or peripheral T cell lymphoma (PTCL) and Panbinostat (LBH-589) [23] for the treatment of multiple myeloma.

Table 1. Classification and cellular localization of histone deacetylases.

Mechanism of Action	Histone Deacetylase Class	Protein(s)	Cellular localization
Zn^{2+}-dependent	Class I	HDAC 1, 2, 8	Nucleus
		HDAC 3	Nucleus/cytoplasm
	Class IIa	HDAC 4, 5, 7	Nucleus/cytoplasm
		HDAC 9	Nucleus/cytoplasm
	Class IIb	HDAC 6, 10	Cytoplasm
	Class IV	HDAC 11	Nucleus
NAD^+-dependent	Class III	SIRT 1, 6,7	Nucleus
		SIRT 2	Cytoplasm
		SIRT 3, 4, 5	Mitochondria

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Additionally, Chidamide was approved by National Medical Products Administration (NMPA) in China for the treatment of PTCL [24]. Despite these successful applications of HDAC inhibitors in cancer treatment, recent studies have shown that the inhibition of histone deacetylases could be extended as a potential way for treating neurodegenerative diseases like Parkinson's disease [25-29].

In this review, we will focus on the current knowledge about the possible role of histone deacetylase in the pathophysiology of Parkinson's disease as well as examine the present state of pan- or selective inhibitors against histone deacetylase with the therapeutic potential for treating Parkinson's disease. Additionally, we discussed the future perspectives related to histone deacetylases as epigenetic targets for treating Parkinson's disease.

2. Histone deacetylases involved in Parkinson's disease pathophysiology

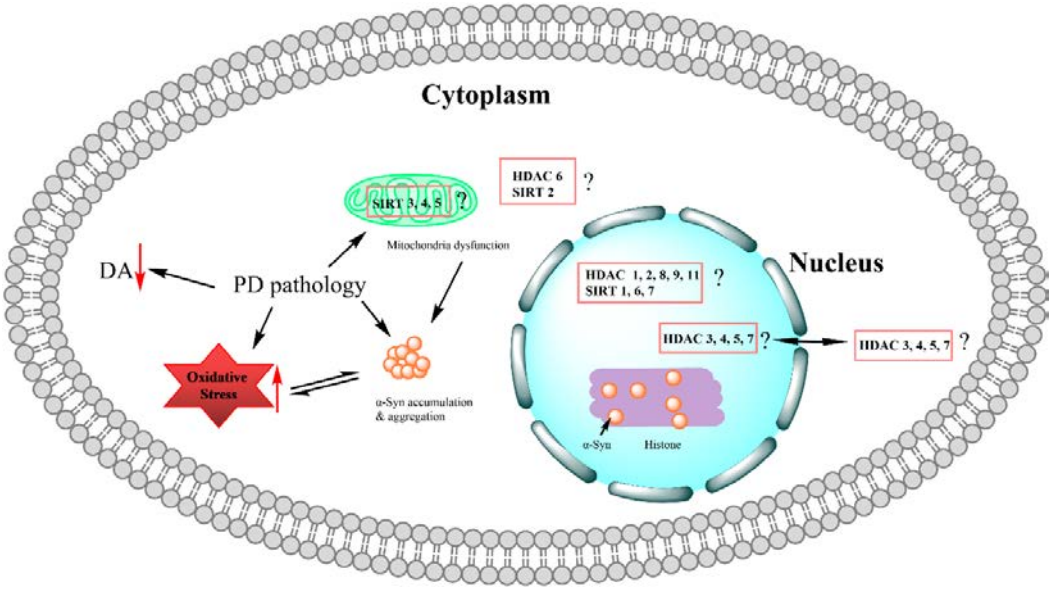

Figure 1. PD pathology and localizations of histone deacetylases.

Although we cannot fully understand the pathogenesis of PD, the loss of dopaminergic neurons [30-32], α-synuclein aggregation [33], metal ion accumulation [34] and oxidative stress [35] play crucial roles in PD pathogenesis (Figure 1) [36]. On the other hand, transcriptional dysregulation often occurs in the progression and development of many neurodegenerative central nervous system (CNS) diseases including Parkinson's disease [37]. In this regard, histone deacetylases as an important group of epigenetic targets associated with transcription regulators plays important roles in chromatin remodeling and gene expression by regulating the status of histone acetylation probably involving in PD pathogenesis (Figure 1). Among 18 mammalian histone deacetylases, there is a different role for each isoform of histone deacetylase displaying either neuroprotective or neurotoxic effect [38]. For example, HDAC1 has been proven to be a critical factor for protecting neurons from DNA damages in several neurodegenerative diseases. Furthermore, the activation of HDAC1 promoted neuroprotective activity in human neuronal models of neurodegeneration [39]. For Class III HDAC (Sirtuin), SIRT1 and

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SIRT5 are also known to be neuroprotective while SIRT2, SIRT3 and SIRT6 are known to be neurotoxic [40-42]. A study of the localization and expression of SIRT1, 2, 6 and plasticity-associated proteins in the recovery period after ischemic stroke in mice showed that during the recovery period there was an increase in the levels of SIRT1 and SIRT2. An increase in SIRT1 was associated with an increase in synaptic plasticity proteins, while an increase in SIRT2 was associated with α-tubulin acetylation, which may reduce neurite motility. Moreover, it was shown that SIRT1, SIRT2, and SIRT6 were not involved in ischemic stroke-induced penumbra cell apoptosis [43]. On the other hand, there are some evidences to show that most of Class II HDACs demonstrated neurotoxic effects [44]. Our inhibitory analysis using HPOB [45] and tubastatin A [46], a selective HDAC6 inhibitors, confirmed the involvement of this histone deacetylase in neurodegeneration. In terms of the expression levels of HDACs in PD brain samples, there are conflict results from two separate study. One study showed the decrease of protein levels of HDAC1, HDAC2, HDAC6 and SIRT1 in PD brain samples compared with that of controls [47]. In contrast, another study demonstrated there were no significant differences in the expression of Class I HDACs, Class II HDACs and Class III (SIRT1 and SIRT2) in PD SNpc, compared with age-matched controls [48]. However, a transcriptome study for clinical PD samples gave a 1.6-fold higher level of HDAC6 expression and a 1.65-fold higher level of histone acetyltransferase1 (HAT1) expression [49, 50], which is consistent with the increasing acetylation levels of H3 histone reported in the above studies [47, 48].

Recent study revealed that HDAC5 and HDAC9 are co-expressed with nigrostriatal dopaminergic markers not only in the human SN but also in dopaminergic neurons in the adult mouse substantia nigra (SN). Silencing the expression of HDAC5 or HDAC9 by siRNAs can promote neurite growth in SH-SY5Y cells. Pharmacological inhibition by their inhibitors MC1568 or LMK235 can protect rat dopaminergic neurons in presence of the neurotoxin, 1-methyl-4-phenylpyridinium ion (MPP^+) or α-synuclein [51, 52]. Further study showed that intraperitoneal (i.p.) administration of MC1568 in rats reduced HDAC5 levels in nucleus accumbens and thimerosal-induced apoptosis in rat prefrontal cortex. More importantly, MC1568 by i.p. treatment can exert neuroprotective effects in a 6-hydroxydopamine (6-OHDA)-induced rat model of PD [53, 54]. Besides, there is growing evidences that HDAC4 exerted neurotoxicity by its nuclear accumulation and involvement in both Lewy and Marinesco bodies in models of Parkinson's disease [55-57]. Class IIa HDACs exerted effects on neuronal survival and axonal growth by the nucleocytoplasmic shuttling [58, 59] and pharmacological inhibition by the Class IIa specific inhibitors protected dopaminergic neurons against neurotoxin- and α-synuclein-induced degeneration in cellular models of Parkinson's disease [52, 60]. Current results indicated that Class IIa HDACs had a detrimental effect on dopaminergic neurons and the inhibition or cytoplasmic shuttling of Class IIa HDACs (at least HDAC4 or HDAC5) might improve the neuroprotective effects in PD [51, 60].

Although dopaminergic neurons in brains have been shown to express both Class IIb HDACs (HDAC6 and HDAC10) [61], most studies have been focused on HDAC6

 doi:10.20944/preprints202205.0158.v1

and little is known about HDAC10 [44]. HDAC6 has been found to be highly expressed in Lewy bodies in PD patients' brain sections indicating that HDAC6 may play a key role in the clearance of those misfolded and aggregated proteins [62, 63]. In a α-synuclein-induced *Drosophila* model, HDAC6 was shown to directly interact with oligomeric α-synuclein and thus involve in the Lewy bodies formation [64]. In a lactacystin (a proteasome inhibitor)-induced mouse model, HDAC6 expression level was selectively increased in SN region of brains resulting in perinuclear inclusion bodies that were structurally like aggresomes. However, treatment with trichostatin A (TSA), a pan-HDAC inhibitor, increased α-synuclein oligomer levels in the SN and associated behavioral deficits while treatment with tubacin, a selective HDAC6 inhibitor, exacerbated lactacystin-induced cell death in primary neuron cells, suggesting that the deacetylase activity of HDAC6 is essential for its protective effects on dopaminergic neurons in this model [65]. Since R1441C and Y1669C mutations in leucine-rich repeat kinase 2 (LRRK2) are the pathogenic LRRK2 mutants in sporadic PD, a *Drosophila* model that expressed the LRRK2 mutants (R1441C and Y1669C) has been used in investigating the role of HDAC6 in PD [66-71]. In this *Drosophila* model, HDAC6 knockdown can effectively restore axonal transport and motor behavior. Moreover, treatment with TSA was also shown to restore axonal transport and improve the associated behavioral deficits [71]. Similar results were obtained by treatment with tubastatin A (a specific HDAC6 inhibitor) in an MPP+-induced Zebrafish PD model [72]. However, there were contrast results that treatment with tubastatin A did not rescue impairments in spontaneous movements or in sensorimotor reflexes in an MPP+-induced Zebrafish PD model while treatment with 4-phenylbutyrate, a pan-HDAC inhibitor, improved those PD symptoms [72]. Additional animal model was a 6-OHDA-induced mouse model of PD. In this PD model, HDAC6 deacetylation of peroxiredoxin1 (Prx1) and peroxiredoxin2 (Prx2) contributes to oxidative injury in PD [73]. Pharmacological inhibition of HDAC6 with tubastatin A increased acetylation of Prx1 and Prx2, reduced reactive oxygen species (ROS) production and alleviated dopaminergic neurotoxicity [73]. Overall, in several animal models of PD, HDAC6 seems to have a crucial role in PD pathogenesis and progression.

Among Class III HDACs (sirtuins), different subtypes may also have different roles in neuronal survival and neurodegeneration [74]. In general, SIRT1 and SIRT5 may have neuroprotective effects while SIRT2, SIRT3 and SIRT6 may have neurotoxic effects [75-77]. Especially, SIRT1 can bind with several transcription factors e.g., NF-κB, p65, retinoic acid receptor β (RARβ), forkhead box O (FOXO) and peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α) associated with PD, and the activation of SIRT1 can maintain mitochondrial number and function and further reduce α-synuclein aggregation [78-81]. On the contrary, although SIRT2 can directly bind with and deacetylate FOXO3a and subsequently induce cell apoptosis [82], significant overexpression of SIRT2 was found in Parkinson's patients compared to normal group [83]. Furthermore, the substrates of SIRT2 like α-tubulin and p53 may involve in neurotoxicity and neurodegeneration [84-86]. Most importantly, SIRT2 was found to regulate α-synuclein-mediated toxicity *in vitro* and *in vivo* models of PD although the exact mechanism remains uncertain [82, 87, 88].

3. Histone deacetylase inhibitors for Parkinson's disease

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Because imbalance of lysine acetylation of histones and nonhistone proteins, along with several isoforms of histone deacetylase, may contribute to the pathogenesis of PD and several isoforms of histone deacetylase may involve in the pathogenesis of PD, scientists have put many efforts to develop histone deacetylase inhibitors in PD studies (Figure 2) [16, 89-92]. Valproic acid as a pan-HDAC inhibitor was initially shown to protect dopaminergic neurons and attenuate lipopolysaccharide (LPS)-induced dopaminergic neurotoxicity in cells [93, 94]. The following studies have shown that valproic acid has the protective effects on the nigrostriatal dopamine system in several PD models including 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mice, lactacystin-induced mice, leucine-rich repeat kinase (LRRK2) R1441G transgenic mice and 6-OHDA-induced mice [95-98]. Sodium butyrate, another pan-HDAC inhibitor, structurally similar with valproic acid, was found to have beneficial effects in 6-OHDA-induced neurotoxicity and behavioral abnormalities [99, 100]. In a salsolinol-induced SH-SY5Y cells, sodium butyrate demonstrated neuroprotective effects [101]. In a rotenone-induced *Drosophila* model of PD, sodium butyrate could improve locomotor impairment and early mortality [102]. Additionally, a simple derivative of butyrate, phenylbutyrate, also exerted neuroprotective effects in MPTP-induced mice [103, 104]. TSA as one of potent pan-HDAC inhibitors attenuated manganese chloride-induced cell death and apoptosis in PC12 cells [105]. However, a single treatment with TSA resulted in enhanced cell death and increased apoptosis in a MPTP- or rotenone- induced dopaminergic neuronal cell lines [106]. In a MPP^+- or MPTP-induced cells and mice model, TSA could protect the integrity of mitochondria and neuron cell survival [107, 108]. Suberoylanilide hydroxamic acid (SAHA), one of the approved HDAC inhibitors for treating cancers, has been studied for its potential new indication for therapy of PD. SAHA was found to protect dopaminergic neurons from neurotoxin-induced damage in *in vitro* Parkinson's disease models [109]. These results suggested that pan-HDAC inhibitors may have a potentially neuroprotective role in PD [110]. On the other hand, selective inhibitors have been also investigated in the treatment of PD. RGFP109 as a selective inhibitor for HDAC 1 and 3, alleviated *L*-3,4-dihydroxyphenylalanine (*L*-DOPA)-induced dyskinesia in the MPTP-lesioned marmoset [111]. A HDAC1/2 dual inhibitor, K560, and its derivative, K-856, were shown to have protective effects in MPP^+- or MPTP-induced *in vitro* and *in vivo* PD models [112, 113]. By the comparison of MS-275 (a Class I HDAC inhibitor) and MC-1568 (a Class II HDAC inhibitor), it was found that inhibition of Class I HDAC attenuated polychlorinated biphenyls (PCBs)-induced neuronal cell death by preventing HDAC3 binding [114]. However, LMK235, a Class IIa HDAC inhibitor (especially for HDAC4/5), exerted neuroprotective effects in MPP^+-induced SH-SY5Y cells or cultured DA neurons. Furthermore, the similar results of LMK235 were obtained in protecting against axonal degeneration induced by overexpression of wild-type or A53T-mutant α-synuclein in both SH-SY5Y cells and cultured DA neurons [52].

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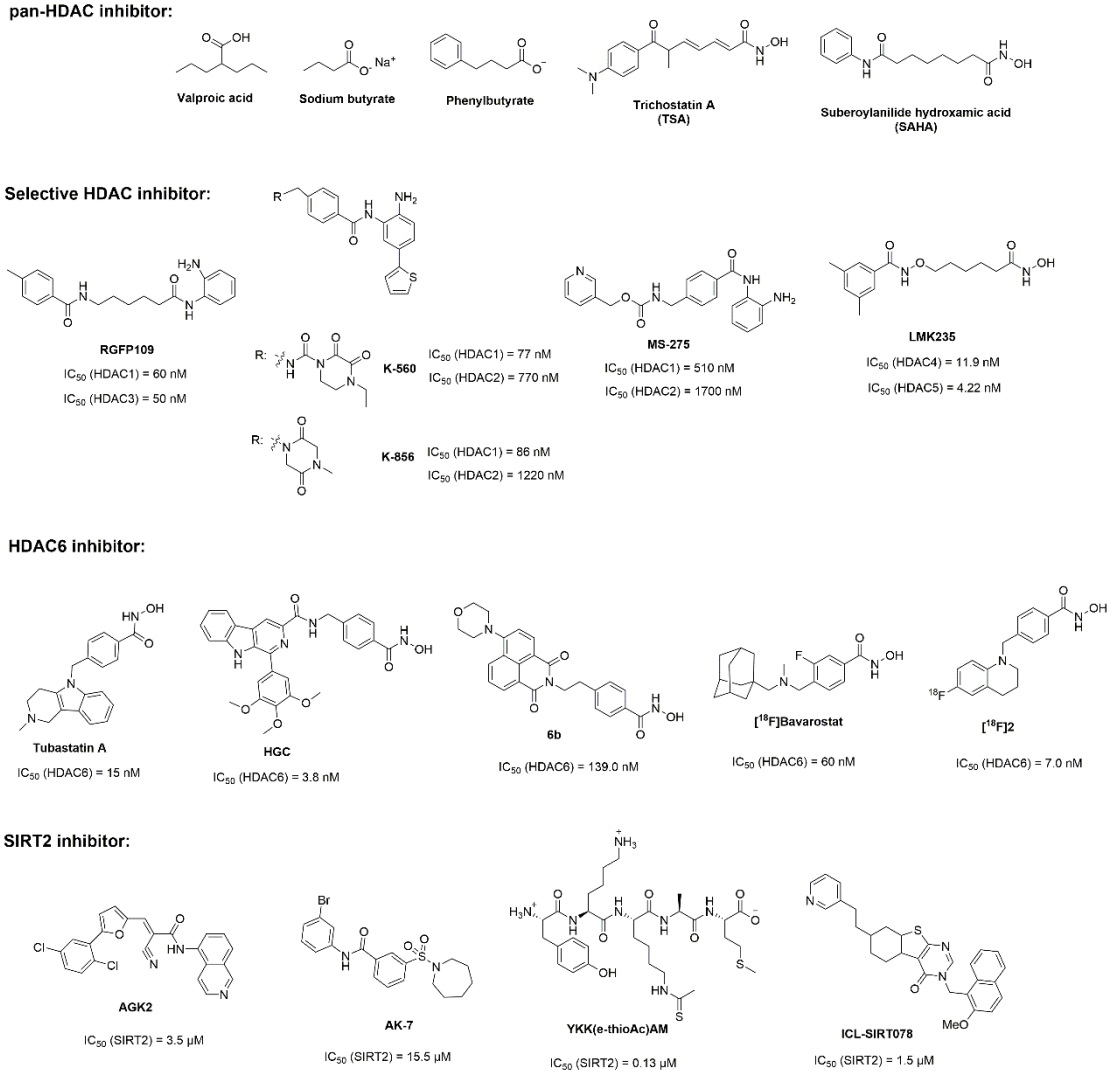

Figure 2. The structures of representative inhibitors of histone deacetylases used in PD study.

Among 18 different members of histone deacetylase in human, sharing a common deacetylation substrate of microtubule-associated tubulin, HDAC6 and SIRT2 are predominantly in cytoplasm and play significant roles in a variety of neurodegenerative disorders, which make these two isoforms become most attractive targets for treating neurodegenerative diseases including Parkinson's disease. Especially, HDAC6 is required for the centrosome recruitment and dispersion of parkin, which is linked to PD [115]. Tubastatin A as a HDAC6 inhibitor was shown to protect dopaminergic neurons in a rat model of PD through the reduction of α-synuclein level and neuroinflammation, promotion of the chaperone-mediated autophagy, and rescue of other PD-related pathological pathways [116, 117]. Notably, HGC is a newly developed HDAC6 inhibitor, which improves dopaminergic neuron viability and attenuates behavioral defects in PD modeled cells and animals by accumulation of K28 acetylation of NADH-ubiquinone-oxidoreductase flavoprotein 1 (NDUFV1) and thus maintaining mitochondrial integrity and functions [118]. Interestingly, venlafaxine, in clinically treating depression, was found to inhibit HDAC6 expression and then enhance α-synuclein clearance through the activation of the ubiquitin proteasome system (UPS) and autophagy in a rotenone-

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induced mice model of PD [119]. Additionally, several probes derived from HDAC6 selective inhibitors may provide powerful tools for investigating HDAC6 in various physiological and pathological conditions. By combination of Tubastatin A and 1,8-naphthalimide-based fluorophore, a fluorescent HDAC6 selective inhibitor **6b** has been developed, demonstrating the capability of labelling and visualizing HDAC6 in inclusion bodies and aggresomes [120]. From a brain penetrant HDAC6 inhibitor (Bavarostat), [^{18}F]Bavarostat, an ^{18}F labeled analogue was achieved and demonstrated the utility for mapping HDAC6 in the living brain [121]. Another ^{18}F-labeled tetrahydroquinoline derivative, [^{18}F]**2**, based on the HDAC6 selective inhibitor SW-100, was obtained and also shown the potential use for brain HDAC6 imaging by positron emission tomography (PET) [122]. AGK2 was the first SIRT2 inhibitor reported in PD study, which rescued α-synuclein toxicity and protected against dopaminergic cell death both *in vitro* and in a *Drosophila* model of PD [48, 88]. AGK2 was found to decrease H_2O_2-induced apoptosis of differentiated PC12 cells, suggesting that SIRT2 plays a significant role in oxidative stress-induced cell death [123]. Interestingly, SIRT2 inhibition by AGK2 also exerted the neuroprotective effects in ischemic stroke by the downregulation of AKT/FOXO3a and MAPK pathways [124]. AK-7 as another SIRT2 selective inhibitor was observed to ameliorate α-synuclein toxicity *in vitro* and significantly improve behavior abnormality and neurochemical deficits in a MPTP-induced mice model of PD [125-129]. ICL-SIRT078 as a substrate-competitive SIRT2 inhibitor demonstrated a significant neuroprotective effect in a lactacystin-induced mice model of PD [130]. By the similar strategy, recently developed peptide YKK(ε-thioAc)AM can structurally mimic SIRT2 substrate and thus competitively inhibit SIRT2 activity. YKK(ε-thioAc)AM further showed the neuroprotective effects in PC12 cells model of PD [131]. The scaffolds of 3-(N-arylsulfamoyl)benzamide and 5-((3-amidobenzyl)oxy)nicotinamides can provide other SIRT2 inhibitors to explore selective inhibition of SIRT2 as a potential therapy for Parkinson's disease [132, 133].

4. Further perspectives

Parkinson's disease (PD) increasingly become global threat and burden. The risk of Parkinson's disease has increased worldwide, especially for those elders over the age of 60 years. Current treatments only can alleviate the PD symptoms, but none of the treatments are disease-modifying treatment [1, 12-14]. Whether targeting other potential mechanism to develop effective treatments has an opportunity for modifying Parkinson's disease? To our knowledge, this is still a key question awaiting scientists to address and needs further research. Epigenetic therapy is a relatively new concept and epigenetic targets have attracted much attention in drug discovery for dealing with many human diseases [15]. In this context, our attention was focused on an important group of epigenetic targets, histone deacetylases including HDACs and sirtuins, for the treatment of Parkinson's disease (PD) (Figure 3). There are 18 histone deacetylases in human that may play different role in PD. From the current knowledge, Class I HDACs seem to be neuroprotective while Class II appear to be neurotoxic [38-42]. Especially, the activation of HDAC1, one of Class I HDACs, was beneficial for treating

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neurodegenerative diseases including PD. Similarly, the activation of SIRT1, one of Class III HDACs, was helpful for reducing α-synuclein aggregation in PD. On the contrary, Class IIa HDACs like HDAC4 and HDAC5 were shown to have detrimental effects on dopaminergic neurons in cellular models of PD. HDAC6, one of Class IIb HDACs, is the most intensively studied member of histone deacetylases in PD study. HDAC6 was found to directly interact with α-synuclein and involve in the Lewy bodies formation, implying that HDAC6 may relate to PD pathogenesis and progression. SIRT2, one of Class III HDACs, was found to be significant overexpression in PD and its regulatory substrates also involved in neurotoxicity and neurodegeneration.

Although these studies have disclosed that some isotypes of histone deacetylases may be suitable epigenetic targets for treating PD, the amount of information about the roles of histone deacetylase in PD is relatively limited, and more deep investigations are necessary to validate their roles and regulatory mechanism in PD by using their inhibitors. Actually, there are both HDAC inhibitors and sirtuin inhibitors reported to be neuroprotective effects on midbrain dopamine neurons (Figure 3). And they have been investigated in cell and animal models of PD. Initially, many studies have reported neuroprotective effects of some pan-HDAC inhibitors, such as valproic acid, sodium butyrate, phenylbutyrate, TSA, SAHA and others, in different animal models of PD [93-

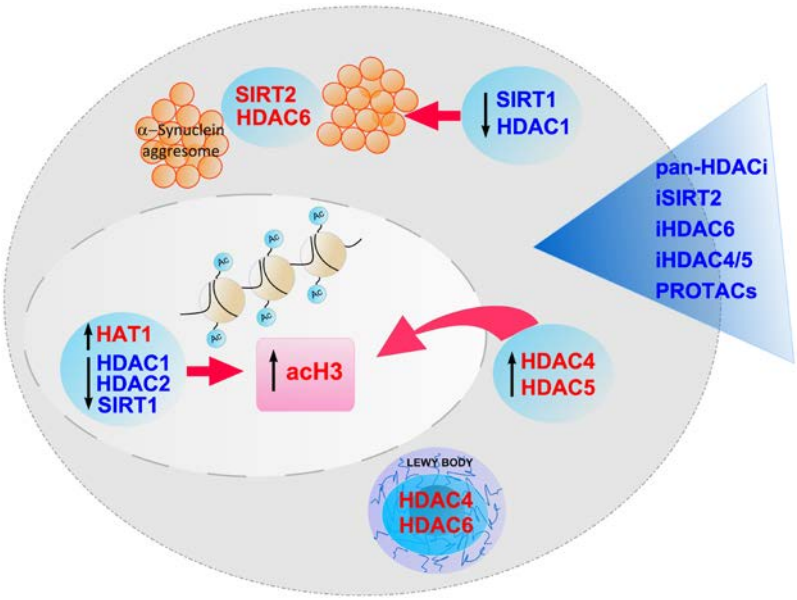

Figure 3. Histone deacetylases and their inhibitors in PD pathology.

110]. However, most of these pan-HDAC inhibitors have less inhibitory potency and poor selectivity, which raises concerns about the efficacy and toxicity of PD treatment. There is evidence for the neuroprotective potential of isotype-selective inhibitors of human histone deacetylases in *in vivo* models of PD although the neuroprotective effects of class II inhibitors are still under question. At least, SIRT2 inhibitor showed neuroprotective effects not only in an α-synuclein-induced *Drosophila* model of PD, but also in a MPTP-induced mice model of PD [48, 88, 123-133]. Besides, HDAC6 inhibitors also showed neuroprotective potentials in several mice models of PD [115-122].

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Some isotypes of human histone deacetylases may have neuroprotective roles in PD and nicotinamide, as a Class III HDAC inhibitor against all SIRT1-7, exacerbated the neurotoxic effects in a lactacystin-induced rats model of PD [134]. There is an urgent need for more comprehensive investigation to explore the exact role of each isotype of histone deacetylases in PD by the corresponding isotype-specific inhibitors. It will be critical to ascertain the role and regulatory mechanism of each isotype of histone deacetylases in PD to have isotype-selective inhibitors with higher therapeutic efficacy and lower toxicity in the clinical treatment of PD in the future. Future studies on development of isotype-selective inhibitors especially against HDAC6 and SIRT2 with more inhibitory potency, high selectivity, and the ability to cross the blood-brain barrier will facilitate further exploration of their therapeutic potentials in PD.

Recently, the emerging proteolysis targeting chimera (PROTAC) technology has been considered for artificial, selective degradation of aberrant target proteins including epigenetic proteins, which have potentially clinical applications for treating many human diseases including neurodegenerative diseases [135, 136]. Compared to those traditional inhibitors, PROTACs may have several advantages for treating PD. For example, PROTACs have higher specificity and bypass the potential toxic effects induced by traditional inhibitors. Besides, PROTACs can exert chemically-induced degradation of a target protein and thus interfere with the enzymatic and non-enzymatic function of a target protein. Moreover, PROTACs can be reused for many cycles until the target proteins are eliminated. Therefore, PROTACs only need very low concentrations in the administration, which is sufficient to degrade a target protein. These advantages make PROTACs become a highly effective way to target and destroy those proteins involved in the pathophysiology of many neurodegenerative disorders including PD. Very recently, some PROTACs with high selectivity and lower cytotoxicity have been developed for degrading HDAC6 or SIRT2 [137-146]. However, none of them have been tested in therapeutic potential for treating PD yet. Future investigations of these PROTACs-targeting epigenetic proteins to treat PD would be exciting to explore.

Author Contributions: Conceptualization, S.D. and B.H.; writing—original draft preparation, Y.L.; writing—review and editing, L.C., V.D., M.E., B.H. and S.D.; visualization, Z.G. and S.L.; supervision, S.D. and B.H.; project administration, S.D. and B.H.; funding acquisition, Y.L., B.H. and S.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Guizhou Science and Technology Department of China (no. ZK[2022]035, [2020]1Y395 and [2020]4Y206) and the National Natural Science Foundation of China (no. 81960628 and 82160655); and A part of this article, devoted to the study of sirtuins and HDAC inhibitors, in addition to the Figure 3, was funded by the Russian Science Foundation, grant #21-15-00188.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Vijiaratnam, N.; Simuni, T.; Bandmann, O.; et al. Progress towards therapies for disease modification in Parkinson's disease. *Lancet Neurol.* **2021**, *20(7)*, 497-584.
2. Rocca. W.A. The burden of Parkinson's disease: a worldwide perspective. *Lancet Neurol*. **2018** *17(11)*, 928-929.
3. http://www.stats.gov.cn/tjsj/zxfb/202105/t20210510_1817176.html
4. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **2019**, *18(5)*, 459-480.
5. Dorsey, E.R.; Sherer, T.; Okun, M.S.; et al. The emerging evidence of the Parkinson pandemic. *J. Parkinsons Dis*. **2018**, *8(s1)*, S3-S8.

6. Dorsey, E.R.; Bloem. B.R. The Parkinson Pandemic-A Call to Action. *JAMA. Neurol*. **2018**, *75(1)*, 9-10.
7. Zhang, K.; Zhu, S.; Li, J. et al. Targeting autophagy using small-molecule compounds to improve potential therapy of Parkinson's disease. *Acta. Pharm. Sin. B*. **2021**, *11(10)*, 3015-3034.
8. Beaulieu, J.M.; Gainetdinov, R.R. The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol. Rev*. **2011**, *63(1)*, 182-217.
9. Doty, R.L. Olfactory dysfunction in Parkinson disease. *Nat. Rev. Neurol*. **2012**, *8(6)*, 329-339.
10. Santangelo, R.M.; Acker, T.M.; Zimmerman, S.S.; et al. Novel NMDA receptor modulators: an update. *Expert Opin. Ther. Pat.* **2012**, *22(11)*, 1337-1352.
11. Shook, B.C.; Jackson, P.F. Adenosine A(2A) Receptor Antagonists and Parkinson's Disease. *ACS. Chem. Neurosci*. **2011**, *2(10)*, 555-567.
12. Valera, E.; Masliah, E. Therapeutic approaches in Parkinson's disease and related disorders. *J. Neurochem*. **2016**, *139 Suppl 1(Suppl 1)*, 346-352.
13. McFarthing, K.; Buff, S.; Rafaloff, G.; et al. Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2020. *J. Parkinsons Dis*. **2020**, *10(3)*, 757-774.
14. McFarthing, K.; Rafaloff, G.; Baptista, M.A.S.; et al. Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2021 Update. *J. Parkinsons Dis*. **2021**, *11(3)*, 891-903.
15. Berger, S.L.; Kouzarides, T.; Shiekhattar, R.; et al. An operational definition of epigenetics. *Genes Dev*. **2009**, *23(7)*, 781-783.
16. Gupta, R.; Ambasta, R.K.; Kumar. P. Pharmacological intervention of histone deacetylase enzymes in the neurodegenerative disorders. *Life Sci*. **2020**, *243*, 117278.
17. Gregoretti, I.V.; Lee, Y.M.; Goodson, H.V. Molecular evolution of the histone deacetylase family: functional implications of phylogenetic analysis. *J. Mol. Biol*. **2004**, *338(1)*, 17-31.
18. Haigis, M.C.; Guarente, L.P. Mammalian sirtuins-Emerging roles in physiology, aging, and calorie restriction. *Genes Dev*. **2006**, *20(21)*, 2913-2921.
19. Li, Y; Wang, F.; Chen, X; et al. Zinc-dependent Deacetylase (HDAC) Inhibitors with Different Zinc Binding Groups. *Curr. Top. Med. Chem*. **2019**, *19(3)*, 223-241.
20. Duvic, M.; Talpur, R.; Ni, X.; et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). *Blood*. **2007**, *109(1)*, 31-39.
21. Piekarz, R.L.; Frye, R.; Turner, M.; et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. *J. Clin. Oncol*. **2009**, *27(32)*, 5410-5417.
22. Poole, R.M. Belinostat: first global approval. *Drugs*. **2014**, *74(13)*, 1543-1554.
23. Garnock-Jones, K.P. Panobinostat: first global approval. *Drugs*. **2015**, *75(6)*, 695-704.
24. Li, Y.; Chen, K.; Zhou, Y.; et al. A New Strategy to Target Acute Myeloid Leukemia Stem and Progenitor Cells Using Chidamide, a Histone Deacetylase Inhibitor. *Curr. Cancer Drug Targets*. **2015**, *15(6)*, 493-503.
25. Rodrigue, D.A.; Pinheiro, P.S.M.; Sagrillo, F.S.; et al. Histone deacetylases as targets for the treatment of neurodegenerative disorders: Challenges and future opportunities. *Med. Res. Rev*. **2020**, *40(6)*, 2177-2211.
26. Yang, S.S.; Zhang, R.; Wang, G.; et al. The development prospection of HDAC inhibitors as a potential therapeutic direction in Alzheimer's disease. *Transl. Neurodegener*.**2017**, *6*, 19.
27. Gray, S.G. Targeting Huntington's disease through histone deacetylases. *Clin. Epigenetics*. **2011**, *2(2)*, 257-277.
28. Sharma, S.; Taliyan, R. Targeting histone deacetylases: a novel approach in Parkinson's disease. *Parkinsons Dis*. **2015**, *2015*, 303294.
29. Faraco, G.; Cavone, L.; Chiarugi, A. The therapeutic potential of HDAC inhibitors in the treatment of multiple sclerosis. *Mol. Med*. **2011**, *17(5-6)*, 442-447.
30. Raza, C.; Anjum, R.; Shakeel, N.U.A. Parkinson's disease: Mechanisms, translational models and management strategies. *Life Sci*. **2019**, *226*, 77-90.
31. Kordower, J.H.; Olanow, C.W.; Dodiya, H.B.; et al. Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. *Brain*. **2013**, *136(Pt 8)*, 2419-2431.
32. Kalia, L.V.; Lang, P.E. Parkinson's disease. *Lancet*. **2015**, *386(9996)*, 896-912.
33. Peng, C.; Trojanowski, J.Q.; Lee, V.M. Protein transmission in neurodegenerative disease. *Nat. Rev. Neurol*. **2020**, *16(4)*, 199-212.
34. Mezzaroba, L.; Alfieri, D.F.; Colado Simão, A.N.; et al. The role of zinc, copper, manganese and iron in neurodegenerative diseases. *Neurotoxicology*. **2019**, *74*, 230-241.
35. Puspita, L.; Chung, S.Y.; Shim, J.W. Oxidative stress and cellular pathologies in Parkinson's disease. *Mol. Brain*. **2017**, *10(1)*, 53.
36. Przedborski, S. The two-century journey of Parkinson disease research. *Nat. Rev. Neurosci*. **2017**, *18(4)*, 251-259.
37. Abeliovich, A.; Gitler, A.D. Defects in trafficking bridge Parkinson's disease pathology and genetics. *Nature*. **2016**, *539(7628)*, 207-216.
38. Thomas, E.A.; D'Mello, S.R. Complex neuroprotective and neurotoxic effects of histone deacetylases. *J. Neuro. chem*. **2018**, *145(2)*, 96-110.
39. Patnaik, D.; Pao, P.C.; Zhao, W.N.; et al. Exifone Is a Potent HDAC1 Activator with Neuroprotective Activity in Human Neuronal Models of Neurodegeneration. *ACS. Chem. Neurosci*. **2021**, *12(2)*, 271-284.
40. Harrison, I.F.; Powell, N.M.; Dexter, D.T. The histone deacetylase inhibitor nicotinamide exacerbates neurodegeneration in the lactacystin rat model of Parkinson's disease. *J. Neuro. chem*. **2019**, *148(1)*, 136-156.
41. Dobbin, M.M.; Madabhushi, R.; Pan, L.; et al. SIRT1 collaborates with ATM and HDAC1 to maintain genomic stability in neurons. *Nat. Neurosci*. **2013**, *16(8)*, 1008-1015.
42. Donmez, G.; Outeiro, T.F. SIRT1 and SIRT2: emerging targets in neurodegeneration. *EMBO. Mol. Med*. **2013**, *5(3)*, 344-352.
43. Demyanenko, S.; Gantsgorn, E.; Rodkin, S.; et al. Localization and Expression of Sirtuins 1, 2, 6 and Plasticity-Related Proteins in the Recovery Period after a Photothrombotic Stroke in Mice. *J. Stroke. Cerebrovasc. Dis*. **2021**, *29(10)*, 105152.
44. Mazzocchi, M.; Collins, L.M.; Sullivan, A.M.; et al. The class II histone deacetylases as therapeutic targets for Parkinson's disease. *Neuronal Signal*. **2020**, *4(2)*, NS20200001.
45. Demyanenko, S.V.; Dzreyan, V.A.; Uzdensky, A.B. Overexpression of HDAC6, but not HDAC3 and HDAC4 in the penumbra after photothrombotic stroke in the rat cerebral cortex and the neuroprotective effects of α-phenyl tropolone, HPOB, and sodium valproate. *Brain Res. Bull*. **2020**, *162*, 151-165.
46. Demyanenko, S.; Berezhnaya, E.; Neginskaya, M.; et al. Class II histone deacetylases in the post-stroke recovery period-expression, cellular, and subcellular localization-promising targets for neuroprotection. *J. Cell Biochem*. **2019**, *120(12)*, 19590-19609.

47. Park, G.; Tan, J.; Garcia, G.; et al. Regulation of Histone Acetylation by Autophagy in Parkinson Disease. *J. Biol. Chem.* **2016**, *291(7)*, 3531-3540.
48. Harrison, I.F.; Smith, A.D.; Dexter, D.T. Pathological histone acetylation in Parkinson's disease: Neuroprotection and inhibition of microglial activation through SIRT 2 inhibition. *Neurosci. Lett.* **2018**, *666*, 48-57.
49. Gebremedhin, K.G.; Rademacher, D. J. Histone H3 acetylation in the postmortem Parkinson's disease primary motor cortex. *Neurosci. Lett.* **2016**, *627*, 121-125.
50. Dijkstra, A.A.; Ingrassia, A.; de Menezes, R.X. et al. Evidence for Immune Response, Axonal Dysfunction and Reduced Endocytosis in the Substantia Nigra in Early Stage Parkinson's Disease. *PLoS. One.* **2015**, *10(6)*, e0128651.
51. Mazzocchi, M.; Wyatt, S.L.; Mercatelli, D.; et al. Gene Co-expression Analysis Identifies Histone Deacetylase 5 and 9 Expression in Midbrain Dopamine Neurons and as Regulators of Neurite Growth via Bone Morphogenetic Protein Signaling. *Front. Cell Dev. Biol.* **2019**, *7*, 191.
52. Mazzocchi, M.; Goulding, S.R.; Wyatt, S.L.; et al. LMK235, a small molecule inhibitor of HDAC4/5, protects dopaminergic neurons against neurotoxin and α-synuclein-induced degeneration in cellular models of Parkinson's disease. *Mol. Cell Neurosci.* **2021**, *115*, 103642.
53. Taniguchi, M.; Carreira, M.B.; Cooper, Y.A.; et al. HDAC5 and Its Target Gene, Npas4, Function in the Nucleus Accumbens to Regulate Cocaine-Conditioned Behaviors. *Neuron.* **2017**, *96(1)*, 130-144.
54. Mazzocchi, M.; Goulding, S.R.; Morales-Prieto, N.; et al. Peripheral administration of the Class-IIa HDAC inhibitor MC1568 partially protects against nigrostriatal neurodegeneration in the striatal 6-OHDA rat model of Parkinson's disease. *Brain Behav. Immun.* **2022**, *102*, 151-160.
55. Takahashi-Fujigasaki, J.; Fujigasaki, H. Histone deacetylase (HDAC) 4 involvement in both Lewy and Marinesco bodies. *Neuropathol Appl. Neurobiol.* **2006**, *32(5)*, 562-566.
56. Wu, Q.; Yang, X.; Zhang, L.; et al. Nuclear Accumulation of Histone Deacetylase 4 (HDAC4) Exerts Neurotoxicity in Models of Parkinson's Disease. *Mol. Neurobiol.* **2017**, *54(9)*, 6970-6983.
57. Lang, C.; Campbell, K.P.; Ryan, B.J.; et al. Single-Cell Sequencing of iPSC-Dopamine Neurons Reconstructs Disease Progression and Identifies HDAC4 as a Regulator of Parkinson Cell Phenotypes. *Cell Stem. Cell.* **2019**, *24(1)*, 93-106.
58. Cho, Y.; Cavalli, V. HDAC5 is a novel injury-regulated tubulin deacetylase controlling axon regeneration. *EMBO. J.* **2012**, *31(14)*, 3063-3078.
59. Cho, Y.; Sloutsky, R.; Naegle, K.M.; et al. Injury-induced HDAC5 nuclear export is essential for axon regeneration [published correction appears in Cell. *Cell.* **2013**, *155(4)*, 894-908.
60. Collins, L.M.; Adriaanse, L.J.; Theratile, S.D.; et al. Class-IIa Histone Deacetylase Inhibition Promotes the Growth of Neural Processes and Protects Them Against Neurotoxic Insult. *Mol. Neurobiol.* **2015**, *51(3)*, 1432-1442.
61. Akase, K.; Oda, S.; Kuroda, M.; et al. Monoaminergic and neuropeptidergic neurons have distinct expression profiles of histone deacetylases. *PLoS. One.* **2013**, *8(3)*, e58473.
62. Kawaguchi, Y.; Kovacs, J.J.; McLaurin, A.; et al. The deacetylase HDAC6 regulates aggresome formation and cell viability in response to misfolded protein stress. *Cell.* **2003**, *115(6)*, 727-738.
63. Richter-Landsberg, C.; Leyk, J. Inclusion body formation, macroautophagy, and the role of HDAC6 in neurodegeneration. *Acta. Neuropathol.* **2013**, *126(6)*, 793-807.
64. Du, G.; Liu, X.; Chen, X.; et al. Drosophila histone deacetylase 6 protects dopaminergic neurons against {alpha}-synuclein toxicity by promoting inclusion formation. *Mol. Biol. Cell.* **2010**, *21(13)*, 2128-2137.
65. Du, Y.; Wang, F.; Zou, J.; et al. Histone deacetylase 6 regulates cytotoxic α-synuclein accumulation through induction of the heat shock response. *Neurobiol. Aging.* **2014**, *35(10)*, 2316-2328.
66. Paisán-Ruíz, C.; Jain, S.; Evans, E.W.; et al. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. *Neuron.* **2004**, *44(4)*, 595-600.
67. Zimprich, A.; Biskup, S.; Leitner, P.; et al. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron.* **2004**, *44(4)*, 601-607.
68. Gilks, W.P.; Abou-Sleima, P.M.; Gandhi, S.; et al. A common LRRK2 mutation in idiopathic Parkinson's disease. *Lancet.* **2005**, *365(9457)*, 415-416.
69. Satake, W.; Nakabayashi, Y.; Mizuta, I.; et al. Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. *Nat. Genet.* **2009**, *41(12)*, 1303-1307.
70. Simón-Sánchez, J.; Schulte, C.; Bras, J.M.; et al. Genome-wide association study reveals genetic risk underlying Parkinson's disease. *Nat. Genet.* **2009**, *41(12)*, 1308-1312.
71. Godena, V.K.; Brookes-Hocking, N.; Moller, A.; et al. Increasing microtubule acetylation rescues axonal transport and locomotor deficits caused by LRRK2 Roc-COR domain mutations. *Nat. Commun.* **2014**, *5*, 5245.
72. Pinho, B.R.; Reis, S.D.; Guedes-Dias, P. et al. Pharmacological modulation of HDAC1 and HDAC6 in vivo in a zebrafish model: Therapeutic implications for Parkinson's disease. *Pharmacol. Res.* **2016**, *103*, 328-339.
73. Jian, W.; Wei, X.; Che, L.; et al. Inhibition of HDAC6 increases acetylation of peroxiredoxin1/2 and ameliorates 6-OHDA induced dopaminergic injury. *Neurosci. Lett.* **2017**, *658*, 114-120.
74. Harrison, I.F.; Powell, N.M.; Dexter, D.T. The histone deacetylase inhibitor nicotinamide exacerbates neurodegeneration in the lactacystin rat model of Parkinson's disease. *J. Neurochem.* **2019**, *148(1)*, 136-156.
75. Pfister, J.A.; Ma, C.; Morrison, B.E.; et al. Opposing effects of sirtuins on neuronal survival: SIRT1-mediated neuroprotection is independent of its deacetylase activity. *PLoS. One.* **2008**, *3(12)*, e4090.
76. Donmez, G. The neurobiology of sirtuins and their role in neurodegeneration. *Trends Pharmacol. Sci.* **2012**, *33(9)*, 494-501.
77. Dobbin, M.M.; Madabhushi, R.; Pan, L.; et al. SIRT1 collaborates with ATM and HDAC1 to maintain genomic stability in neurons. *Nat. Neurosci.* **2013**, *16(8)*, 1008-1015.
78. Zheng, B.; Liao, Z.; Locascio, J.J.; et al. PGC-1α, a potential therapeutic target for early intervention in Parkinson's disease. *Sci. Transl. Med.* **2010**, *2(52)*, 52ra73.
79. Austin, S.; St-Pierre, J. PGC1α and mitochondrial metabolism--emerging concepts and relevance in ageing and neurodegenerative disorders. *J. Cell Sci.* **2012**, *125(Pt 21)*, 4963-4971.
80. Donmez, G.; Outeiro, T.F. SIRT1 and SIRT2: emerging targets in neurodegeneration. *EMBO. Mol. Med.* **2013**, *5(3)*, 344-352.

81. Donmez, G.; Arun, A.; Chung, C.Y.; et al. SIRT1 Protects against α-Synuclein Aggregation by Activating Molecular Chaperones. *J. Neurosci*. **2016**, *36(14)*, 4138.
82. Liu, L.; Arun, A.; Ellis, L.; et al. Sirtuin 2 (SIRT2) enhances 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced nigrostriatal damage via deacetylating forkhead box O3a (Foxo3a) and activating Bim protein. *J. Biol. Chem*. **2013**, *288(33)*, 24163.
83. Singh, A.P.; Ramana, G.; Bajaj, T.; et al. Elevated Serum SIRT 2 May Differentiate Parkinson's Disease From Atypical Parkinsonian Syndromes. *Front. Mol. Neurosci*. **2019**, *12*, 129.
84. Kazantsev, A.G.; Kolchinsky, A.M. Central role of alpha-synuclein oligomers in neurodegeneration in Parkinson disease. *Arch. Neurol*. **2008**, *65(12)*, 1577-1581.
85. Portran, D.; Schaedel, L.; Xu, Z.; et al. Tubulin acetylation protects long-lived microtubules against mechanical ageing. *Nat. Cell Biol*. **2017**, *19(4)*, 391-398.
86. Garske, A.L.; Smith, B.C.; Denu, J.M. Linking SIRT2 to Parkinson's disease. *ACS. Chem. Biol*. **2007**, *2(8)*, 529-532.
87. Singh, A.P.; Nigam, L.; Yadav, Y.; et al. Design and in vitro analysis of SIRT2 inhibitor targeting Parkinson's disease. *Mol. Divers*. **2021**, *25(4)*, 2261-2270.
88. Outeiro, T.F.; Kontopoulos, E.; Altman, S.M. et al. Sirtuin 2 inhibitors rescue alpha-synuclein-mediated toxicity in models of Parkinson's disease. *Science*. **2007**, *317(5837)*, 516-519.
89. Mohd Murshid, N.; Aminullah Lubis, F.; Makpol, S. Epigenetic Changes and Its Intervention in Age-Related Neurodegenerative Diseases. *Cell Mol. Neurobiol*. **2022**, *42(3)*, 577-595.
90. Wang, R.; Sun, H.; Wang, G.; et al. Imbalance of Lysine Acetylation Contributes to the Pathogenesis of Parkinson's Disease. *Int. J. Mol. Sci*. **2020**, *21(19)*, 7182.
91. Teijido, O.; Cacabelos, R. Pharmacoepigenomic Interventions as Novel Potential Treatments for Alzheimer's and Parkinson's Diseases. *Int. J. Mol. Sci*. **2018**, *19(10)*, 3199.
92. Harrison, I.F.; Dexter, D.T. Epigenetic targeting of histone deacetylase: therapeutic potential in Parkinson's disease?. *Pharmacol. Ther*. **2013**, *140(1)*, 34-52.
93. Wu, X.; Chen, P.S.; Dallas, S.; et al. Histone deacetylase inhibitors up-regulate astrocyte GDNF and BDNF gene transcription and protect dopaminergic neurons. *Int. J. Neuropsychopharmacol*. **2008**, *11(8)*, 1123-1134.
94. Chen, P.S.; Wang, C.C.; Bortner, C.D.; et al. Valproic acid and other histone deacetylase inhibitors induce microglial apoptosis and attenuate lipopolysaccharide-induced dopaminergic neurotoxicity. *Neuroscience*. **2007**, *149(1)*, 203-212.
95. Kidd, S.K.; Schneider, J.S. Protective effects of valproic acid on the nigrostriatal dopamine system in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. *Neuroscience*. **2011**, *194*, 189-194.
96. Harrison, I.F.; Crum, W.R.; Vernon, A.C.; et al. Neurorestoration induced by the HDAC inhibitor sodium valproate in the lactacystin model of Parkinson's is associated with histone acetylation and up-regulation of neurotrophic factors. *Br. J. Pharmacol*. **2015**, *172(16)*, 4200-4215.
97. Kim, T.; Song, S.; Park, Y.; et al. HDAC Inhibition by Valproic Acid Induces Neuroprotection and Improvement of PD-like Behaviors in LRRK2 R1441G Transgenic Mice. *Exp. Neurobiol*. **2019**, *28(4)*, 504-515.
98. Hsu, S.W.; Hsu, P.C.; Chang, W.S.; et al. Protective effects of valproic acid on 6-hydroxydopamine-induced neuroinjury. *Environ. Toxicol*. **2020**, *35(8)*, 840-848.
99. Rane, P.; Shields, J.; Heffernan, M.; et al. The histone deacetylase inhibitor, sodium butyrate, alleviates cognitive deficits in pre-motor stage PD. *Neuropharmacology*. **2012**, *62(7)*, 2409-2412.
100. Sharma, S.; Taliyan, R.; Singh, S. Beneficial effects of sodium butyrate in 6-OHDA induced neurotoxicity and behavioral abnormalities: Modulation of histone deacetylase activity. *Behav. Brain. Res*. **2015**, *291*, 306-314.
101. Getachew, B.; Csoka, A.B.; Bhatti, A.; et al. Butyrate Protects Against Salsolinol-Induced Toxicity in SH-SY5Y Cells: Implication for Parkinson's Disease. *Neurotox. Res*. **2020**, *38(3)*, 596-602.
102. St Laurent, R.; O'Brien, L.M.; Ahmad, S.T. Sodium butyrate improves locomotor impairment and early mortality in a rotenone-induced Drosophila model of Parkinson's disease. *Neuroscience*. **2013**, *246*, 382-390.
103. Gardian, G.; Yang, L.; Cleren, C.; et al. Neuroprotective effects of phenylbutyrate against MPTP neurotoxicity. *Neuromolecular Med*. **2004**, *5(3)*, 235-241.
104. Zhou, W.; Bercury, K.; Cummiskey, J.; et al. Phenylbutyrate up-regulates the DJ-1 protein and protects neurons in cell culture and in animal models of Parkinson disease. *J. Biol. Chem*. **2011**, *286(17)*, 14941-14951.
105. Guo, Z.; Zhang, Z.; Wang, Q.; et al. Manganese chloride induces histone acetylation changes in neuronal cells: Its role in manganese-induced damage. *Neurotoxicology*. **2018**, *65*, 255-263.
106. Wang, Y.; Wang, X.; Liu, L.; et al. HDAC inhibitor trichostatin A-inhibited survival of dopaminergic neuronal cells. *Neurosci. Lett*. **2009**, *467(3)*, 212-216.
107. Zhu, M.; Li, W.W.; Lu, C.Z. Histone decacetylase inhibitors prevent mitochondrial fragmentation and elicit early neuroprotection against MPP+. *CNS. Neurosci. Ther*. **2014**, *20(4)*, 308-316.
108. Suo, H.; Wang, P.; Tong, J.; et al. NRSF is an essential mediator for the neuroprotection of trichostatin A in the MPTP mouse model of Parkinson's disease. *Neuropharmacology*. **2015**, *99*, 67-78.
109. Chen, S.H.; Wu, H.M.; Ossola, B.; et al. Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, protects dopaminergic neurons from neurotoxin-induced damage. *Br. J. Pharmacol*. **2012**, *165(2)*, 494-505.
110. Kidd, S.K.; Schneider, J.S.; Protection of dopaminergic cells from MPP+-mediated toxicity by histone deacetylase inhibition. *Brain Res*. **2010**, *1354*, 172-178.
111. Johnston, T.H.; Huot, P.; Damude, S.; et al. RGFP109, a histone deacetylase inhibitor attenuates L-DOPA-induced dyskinesia in the MPTP-lesioned marmoset: a proof-of-concept study. *Parkinsonism Relat. Disord*. **2013**, *19(2)*, 260-264.
112. Choong, C.J.; Sasaki, T.; Hayakawa, H.; et al. A novel histone deacetylase 1 and 2 isoform-specific inhibitor alleviates experimental Parkinson's disease. *Neurobiol Aging*. **2016**, *37*, 103-116.
113. Hirata, Y.; Sasaki, T.; Kanki, H.; et al. New 5-Aryl-Substituted 2-Aminobenzamide-Type HDAC Inhibitors with a Diketopiperazine Group and Their Ameliorating Effects on Ischemia-Induced Neuronal Cell Death. *Sci. Rep*. **2018**, *8(1)*, 1400.
114. Formisano, L.; Guida, N.; Laudati, G.; et al. MS-275 inhibits aroclor 1254-induced SH-SY5Y neuronal cell toxicity by preventing the formation of the HDAC3/REST complex on the synapsin-1 promoter. *J. Pharmacol. Exp. Ther*. **2015**, *352(2)*, 236-243.
115. Jiang, Q.; Ren, Y.; Feng, J. Direct binding with histone deacetylase 6 mediates the reversible recruitment of parkin to the centrosome. *J. Neurosci*. **2008**, *28(48)*, 12993-13002.

116. Francelle, L.; Outeiro, T.F.; Rappold, G.A. Inhibition of HDAC6 activity protects dopaminergic neurons from alpha-synuclein toxicity. *Sci. Rep*. **2020**, *10(1)*, 6064.
117. Yan, S.; Wei, X.; Jian, W.; et al. Pharmacological Inhibition of HDAC6 Attenuates NLRP3 Inflammatory Response and Protects Dopaminergic Neurons in Experimental Models of Parkinson's Disease. *Front. Aging Neurosci*. **2020**, *12*, 78.
118. Li, B.; Yang, Y.; Wang, Y.; et al. Acetylation of NDUFV1 induced by a newly synthesized HDAC6 inhibitor HGC rescues dopaminergic neuron loss in Parkinson models. *iScience*. **2021**, *24(4)*, 102302.
119. El-Saiy, K.A.; Sayed, R.H.; El-Sahar, A.E.; et al. Modulation of histone deacetylase, the ubiquitin proteasome system, and autophagy underlies the neuroprotective effects of venlafaxine in a rotenone-induced Parkinson's disease model in rats. *Chem. Biol. Interact*. **2022**, *354*, 109841.
120. Zhang, Y.; Yan, J.; Yao, T.P. Discovery of a fluorescent probe with HDAC6 selective inhibition. *Eur. J. Med. Chem*. **2017**, *141*, 596-602.
121. Strebl, M.G.; Campbell, A.J.; Zhao, W.N. et al. HDAC6 Brain Mapping with [^{18}F]Bavarostat Enabled by a Ru-Mediated Deoxyfluorination. *ACS. Cent. Sci*. **2017**, *3(9)*, 1006-1014.
122. Tago, T.; Toyohara, J.; Ishi, K. Preclinical Evaluation of an ^{18}F-Labeled SW-100 Derivative for PET Imaging of Histone Deacetylase 6 in the Brain. *ACS. Chem. Neurosci*. **2021**, *12(4)*, 746-755.
123. Nie, H.; Hong, Y.; Lu, X.; et al. SIRT2 mediates oxidative stress-induced apoptosis of differentiated PC12 cells. *Neuroreport*. **2014**, *25(11)*, 838-842.
124. She, D.T.; Wong, L.J.; Baik, S.H. et al. SIRT2 Inhibition Confers Neuroprotection by Downregulation of FOXO3a and MAPK Signaling Pathways in Ischemic Stroke. *Mol. Neurobiol*. **2018**, *55(12)*, 9188-9203.
125. Chopra, V.; Quinti, L.; Kim, J.; et al. The sirtuin 2 inhibitor AK-7 is neuroprotective in Huntington's disease mouse models. *Cell Rep*. **2012**, *2(6)*, 1492-1497.
126. Szegő, É.M.; Gerhardt, E.; Outeiro, T.E. Sirtuin 2 enhances dopaminergic differentiation via the AKT/GSK-3β/β-catenin pathway. *Neurobiol. Aging*. **2017**, *56*, 7-16.
127. Wang, X.; Wang, M.; Yang, L.; et al. Inhibition of Sirtuin 2 exerts neuroprotection in aging rats with increased neonatal iron intake. *Neural Regen. Res*. **2014**, *9(21)*, 1917-1922.
128. Guan, Q.; Wang, M.; Chen, H.; et al. Aging-related 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurochemial and behavioral deficits and redox dysfunction: improvement by AK-7. *Exp. Gerontol*. **2016**. *82*. 19-29.
129. Chen, X.; Wales, P.; Quinti, L.; et al. The sirtuin-2 inhibitor AK7 is neuroprotective in models of Parkinson's disease but not amyotrophic lateral sclerosis and cerebral ischemia. *PLoS. One*. **2015**, *10(1)*, e0116919.
130. Di Fruscia, P.; Zacharioudakis, E.; Liu, C.; et al. The discovery of a highly selective 5,6,7,8-tetrahydrobenzo[4,5] thieno [2,3-d]pyrimidin-4(3H)-one SIRT2 inhibitor that is neuroprotective in an in vitro Parkinson's disease model. *Chem. Med. Chem*. **2015**, *10(1)*, 69-82.
131. Singh, A.P.; Nigam, L.; Yadav, Y.; et al. Design and in vitro analysis of SIRT2 inhibitor targeting Parkinson's disease. *Mol. Divers*. **2021**, *25(4)*, 2261-2270.
132. Ai, T.; Wilson, D.J.; More, S.S.; et al. 5-((3-Amidobenzyl) oxy) nicotinamides as Sirtuin 2 Inhibitors. *J. Med. Chem*. **2016**, *59(7)*, 2928-2941.
133. Choi, S.H.; Quinti, L.; Kazantsev, A.G.; et al. 3-(N-arylsulfamoyl) benzamides, inhibitors of human sirtuin type 2 (SIRT2). *Bioorg. Med. Chem. Lett*. **2012,** *22(8)*, 2789-2793.
134. Harrison, I.F.; Powell, N.M.; Dexter, D.T. The histone deacetylase inhibitor nicotinamide exacerbates neurodegeneration in the lactacystin rat model of Parkinson's disease. *J. Neurochem*. **2019**, *148(1)*, 136-156.
135. Wang, C.; Zheng, C.; Wang, H.; et al. The state of the art of PROTAC technologies for drug discovery. *Eur. J. Med. Chem*. **2022**, *235*, 114290.
136. Kumar, D.; Hassan, M.I. Targeted protein degraders march towards the clinic for neurodegenerative diseases. *Ageing Res. Rev*. **2022**, *78*, 101616.
137. Cao, Z.; Gu, Z.; Lin, S.X.; et al. Attenuation of NLRP3 Inflammasome Activation by Indirubin-Derived PROTAC Targeting HDAC6. *ACS. Chem. Biol*. 2021, *16(12)*, 2746-2751.
138. Yang, K.; Zhao, Y.; Nie, X.; et al. A Cell-Based Target Engagement Assay for the Identification of Cereblon E3 Ubiquitin Ligase Ligands and Their Application in HDAC6 Degraders. *Cell Chem. Biol*. **2020**, *27(7)*, 866-876, e8.
139. Yang, K.; Wu, H.; Zhang, Z.; et al. Development of Selective Histone Deacetylase 6 (HDAC6) Degraders Recruiting Von Hippel-Lindau (VHL) E3 Ubiquitin Ligase. *ACS. Med. Chem. Lett*. **2020**, *11(4)*, 575-581.
140. Yang, H.; Lv, W.; He, M.; et al. Plasticity in designing PROTACs for selective and potent degradation of HDAC6. *Chem. Commun. (Camb)*. **2019**, *55(98)*, 14848-14851.
141. An, Z.; Lv, W.; Su, S.; et al. Developing potent PROTACs tools for selective degradation of HDAC6 protein. *Protein Cell*. **2019**, *10(8)*, 606-609.
142. Wu, H.; Yang, K.; Zhang, Z.; et al. Development of Multifunctional Histone Deacetylase 6 Degraders with Potent Antimyeloma Activity. *J. Med. Chem*. **2019**, *62(15)*, 7042-7057.
143. Yang, K.; Song, Y.; Xie, H.; et al. Development of the first small molecule histone deacetylase 6 (HDAC6) degraders. *Bioorg. Med. Chem. Lett*. **2018**, *28(14)*, 2493-2497.
144. Hong, J.Y.; Jing, H.; Price, I.R.; et al. Simultaneous Inhibition of SIRT2 Deacetylase and Defatty-Acylase Activities via a PROTAC Strategy. *ACS. Med. Chem. Lett*. **2020**, *11(11)*, 2305-2311.
145. Schiedel, M.; Lehotzky, A.; Szunyogh, S.; et al. HaloTag-Targeted Sirtuin-Rearranging Ligand (SirReal) for the Development of Proteolysis-Targeting Chimeras (PROTACs) against the Lysine Deacetylase Sirtuin 2 (Sirt2)*. *Chembiochem*. **2020**, *21(23)*, 3371-3376.
146. Schiedel, M.; Herp, D.; Hammelmann, S.; et al. Chemically Induced Degradation of Sirtuin 2 (Sirt2) by a Proteolysis Targeting Chimera (PROTAC) Based on Sirtuin Rearranging Ligands (SirReals). *J. Med. Chem*. **2018**, *61(2)*, 482-491.