Epigenetics in Parkinson's Disease

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Maria Angeliki S. Pavlou and Tiago Fleming Outeiro

Abstract

Parkinson's disease (PD) is a highly complex neurodegenerative disorder with a multifactorial origin. Although several cellular mechanisms and genes have been implicated in the onset and progression of the disease, the precise molecular underpinnings of the disease remain unclear. In this context, epigenetic modulation of gene expression by environmental factors is emerging as an important mechanism in PD and in other neurodegenerative disorders. Thus, epigenetic mechanisms, such as DNA methylation, histone modifications and altered microRNA expression, have been under intense investigation due to their possible involvement in PD. Epigenetic modulation is responsible for inducing differential gene expression, a phenomenon which is essential throughout life in order to regulate multiple cellular responses such as development, cellular fate commitment and adaptation to the environment. Disturbances of a balanced gene expression can, therefore, have detrimental effects. Environmental factors can

M.A.S. Pavlou, B.Sc., M.Sc., Ph.D.
Department of NeuroDegeneration and Restorative Research, Center for Nanoscale Microscopy and Molecular Physiology of the Brain, University Medical Center Göttingen, Göttingen, Lower Saxony, Germany

Department of NeuroDegeneration and Restorative Research, University Medical Center Göttingen, Waldweg 33, 37073 Göttingen, Lower Saxony, Germany
e-mail: mpavlou@gwdg.de

T.F. Outeiro, B.Sc., M.Sc., Ph.D. (✉)
Department of NeuroDegeneration and Restorative Research, Center for Nanoscale Microscopy and Molecular Physiology of the Brain, University Medical Center Göttingen, Göttingen, Lower Saxony, Germany

Department of NeuroDegeneration and Restorative Research, University Medical Center Göttingen, Waldweg 33, 37073 Göttingen, Lower Saxony, Germany

Max Planck Institute for Experimental Medicine, Goettingen, Germany
e-mail: touteir@gwdg.de

R. Delgado-Morales (ed.), *Neuroepigenomics in Aging and Disease*, Advances in Experimental Medicine and Biology, DOI 10.1007/978-3-319-53889-1_19

challenge the establishment and maintenance of epigenetic modifications and could thereby fill the gap in our further understanding of origin and/or progression of neurodegenerative diseases. In this chapter, we focus on the role of epigenetics in PD.

Keywords
Parkinson's disease • Epigenetics • DNA methylation • Histone modifications • miRNA • Alpha-synuclein

Abbreviations

3′ UTR	3′ untranslated region
5-hmC	5-hydroxymethylcytosine
5-mC	5-methylcytosine is formed
Ago	Argonaute
aSyn	Alpha-synuclein protein
DLB	dementia with Lewy bodies
DNMT1	DNA methyltransferase 1
DNMT3a	DNA methyltransferase 3a
DNMT3b	DNA methyltransferase 3b
DNMTs	DNA methyltransferases
FGF20	Fibroblast growth factor 20
HAT	Histone acetyltransferase
HDACis	Histone deacetylase inhibitors
HDACs	Histone deacetylases
Hsp70	Heat sock protein 70
LB	Lewy bodies
LDID	Levodopa-induced dyskinesia
L-DOPA	Levodopa
LN	Lewy neurites
MBDs	methyl-CpG-binding domain proteins
mDNMT	Mitochondrial DNMT
miRNAs	microRNAs
MPP^+	1-methyl-4-phenylpyridinium
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NACP-Rep1	polymorphic microsatellite repeat region
Nurr1	Nuclear receptor-related 1 protein
PBMCs	Peripheral blood mononuclear cells
PD	Parkinson's disease
PKC δ	Protein kinase C δ
SAH	S-adenosylhomocysteine
SAM	S-adenosyl methionine

SN	*substantia nigra pars compacta*
SNCA	alpha-synuclein gene
SNPs	Single nucleotide polymorphisms
TSA	Trichostatin
VPA	Valproic acid
VSP35	vacuolar protein sorting 35

19.1 Introduction

The inability of the brain to replenish certain cell types, upon their death, is associated with the development of specific conditions, known as neurodegenerative disorders. In Parkinson's disease (PD), one of those conditions that usually manifests after 60 years of age, the demise of dopaminergic neurons from the substantia nigra, explains the typical motor symptoms of the disease. Due to the increase in life expectancy, the number of individuals affected by PD has also drastically increased, resulting in extensive socioeconomic challenges. In the USA alone, it has been estimated that the annual costs of PD rise up to $23 billion [1]. Several therapeutic options are presently available to treat some of the symptoms associated with PD. However, there is currently no cure or preventive strategy. The majority of PD cases is sporadic, with no known cause, and is thought to occur due to the interplay between susceptibility genes and the environment, in ways that are poorly understood.

The term epigenetics refers to alterations in gene expression, usually reversible, which can be inherited but are not engraved in the DNA sequence. These modifications can be implemented via methylation of the DNA, histone modifications or microRNAs (miRNAs). Chemical pollutants, nutrition, temperature changes and other environmental stresses can influence gene expression via changes in epigenetic modifications. Although no solid relationship has been yet identified, epigenetic deregulation is thought to play an important and poorly understood role in the aetiopathogenesis of various neurodegenerative disorders, including PD.

19.2 Parkinson's Disease

19.2.1 Pathology and Clinical Features

PD, named after Dr. James Parkinson who first documented it in 1817, constitutes the second most prevalent neurodegenerative disorder today. With a prevalence of 1–2% over the age of 65 [2, 3] and of 4–5% over the age of 85 [4], it is estimated that this progressive disorder affects approximately 6.3 million individuals worldwide, with the number expected to increase to 8.3 million by 2030 [5].

The typical neuropathological hallmarks of PD are the loss of dopaminergic neurons from the *substantia nigra pars compacta* (SN) and the accumulation of

intracellular protein inclusions termed Lewy bodies (LBs), mainly composed of alpha-synuclein (aSyn) [6, 7]. Dopaminergic neurons extend their fibres from the SN towards the striatum, where they release dopamine, the neurotransmitter responsible for the learning and execution of motor functions [8, 9]. Due to decreased levels of dopamine, PD patients present characteristic motor dysfunctions such as bradykinesia, muscle rigidity, resting tremor and postural instability [10, 11]. Nonmotor symptoms, including anxiety, depression, dementia, sleep disturbances, constipation, hyposmia and anosmia, are also apparent and limit the quality of life of patients even further [8, 12]. Motor features remain the principal criteria for the clinical diagnosis of PD, although some nonmotor impairments are now valued as predictive markers for the disorder since they tend to appear prior to the onset of motor symptoms [13, 14]. Indeed, according to the Braak staging hypothesis, Lewy body pathology is quite dispersed not only throughout the brain but also in other tissues, such as the gut. According to this hypothesis, the progression of PD is classified into six stages. Stages 1–2 are linked with the presymptomatic phase where Lewy bodies appear in the enteric and peripheral autonomic nervous system and also spread from the olfactory bulb and vagus nerve to the lower brainstem. The symptomatic period starts on stage 3, when the midbrain, including the SN, starts to be affected. Finally, pathological changes involve the mesocortex in stage 4 and the neocortex in stages 5 and 6 [15]. Although this staging system has been confirmed by other groups and applies for the majority of the cases, deviations from this model can be observed, raising questions about the overall validity of the hypothesis [16, 17].

19.2.2 Genetic Forms of PD

Familial forms of PD account for only about 10–15% of all the cases [18]. However, it is possible that additional cases might be associated with yet unidentified genes, as additional genetic studies are conducted [19]. Thus, the list of genes implicated in the onset of PD (PARK genes) is expanding. The PARK gene family currently comprises 20 genes (Table 19.1) which are responsible for autosomal recessive, dominant or X-linked modes of inheritance. Moreover, PD-related genes can present point mutations, duplications or triplications and account for both early- or late-onset forms PD [20, 21]. Interestingly, over 500 DNA variants have been described in only five of the PD-associated genes [22].

A mutation in gene encoding for alpha-synuclein (*SNCA*) was the first to be associated with familial PD. Presently, six point mutations leading to amino acid substitutions have been linked with autosomal dominant forms of PD. In addition, duplications and triplications of the *SNCA* locus have also been associated with autosomal dominant forms of PD [23–25]. Although *SNCA* is an extensively studied gene, the precise function of alpha-synuclein (aSyn) and how it causes disease remain elusive. aSyn is typically described as a presynaptic protein participating in the regulation of the synaptic vesicle pool and in neurotransmitter release. However,

Table 19.1 Genes associated with familial forms of PD

Locus	Gene	Gene product	Inheritance/ PD onset	Chromosomal locus	References
PARK1/PARK4	*SNCA*	Alpha-synuclein (aSyn)	AD/EO	4q21.3-q22	[149]
PARK2	*PARKIN*	Parkin RBR E3 ubiquitin protein ligase	AR/EO	6q25.2-q27	[150, 151]
PARK3	Unknown	Unknown	AD	2p13	[152]
PARK5	*UCHL1*	Ubiquitin C-terminal hydrolase L1	AD	4p13	[153, 154]
PARK6	*PINK1*	PTEN induced putative kinase 1	AR/EO	1p36.12	[155]
PARK7	*DJ-1*	DJ-1	AR/EO	1p36.23	[156–158]
PARK8	*LRRK2*	Leucine-rich repeat kinase 2 (LRRK2)	AD/EO and LO cases	12q12	[159–161]
PARK9	*ATP13A2*	ATPase type 13A2 (ATP13A2)	AR/EO	1p36	[162–164]
PARK10	Unknown	AAOPD	Susceptibility	1p32	[165, 166]
PARK11	Unknown	GIGYF2 (GRB10 interacting GYF protein 2)	AR/EO	2q36-q37	[167–169]
PARK12	Unknown	Unknown	Susceptibility	Xq21-q25	[166, 168–170]
PARK13	*HTRA2*	HtrA serine peptidase 2	AD	2p13.1	[171, 172]
PARK14	*PLA2G6*	Phospholipase A2 group VI	AR/LO	22q13.1	[173–175]
PARK15	*FBXO7*	F-box protein 7 (FBXO7)	AR/EO	22q12.3	[176, 177]
PARK16	Unknown	Unknown	Susceptibility	1q32	[178, 179]
PARK17	*VPS35*	VPS35 retromer complex component	AD/LO	16q12	[32, 180]
PARK18	*EIF4G1*	Eukaryotic translation initiation factor 4 gamma 1	AD/LO	3q27.1	[181–183]
PARK19	*DNAJC6*	Auxilin	AR/EO	1p31.3	[184, 185]
PARK20	*SYNJ1*	Synaptojanin-1	AR/EO	21q22.11	[186, 187]

AD autosomal dominant, *AR* autosomal recessive, *EO* early onset, *LO* late onset

other studies reported aSyn binds mitochondria and is present in the interconnection of mitochondrial membranes and ER or in the nucleus [26–29].

LRRK2 mutations are the most common cause of autosomal dominant PD [30]. Some *LRRK2* mutations are more prevalent in certain ethnic groups [22]. The majority of patients carrying *LRRK2* mutations present the classical pathological features of PD, including the presence of LBs, but the age of onset of the symptoms can vary appearing either earlier or later than idiopathic forms of the disease [30].

The *VPS35* gene codes for the vacuolar protein sorting 35 (VPS35). VPS35 is one of the central components of the retromer cargo-recognition complex which is involved in the trafficking and recycling of synaptic vesicles and proteins [30]. The p.D620N mutation was recognised as a novel cause of autosomal dominant, late-onset PD [31, 32], displaying a dominant negative protein sorting phenotype [33, 34].

The lysosomal enzyme β-glucocerebrosidase, encoded by *GBA*, plays an important role in glycolipid metabolism [35]. Mutations in this gene are known to cause Gaucher disease, one of a growing list of lysosomal storage disorders. However, *GBA* mutations have been described to increase the risk of developing PD and are quite common in PD patients [36–39].

On the other hand, mutations in *PARK2*, *PINK1* and *PARK7* can cause autosomal recessive forms of early-onset PD. All three genes share identical clinical phenotypes, but LB pathology appears to be more variable [35]. *PARK3*, *PARK10* and *PARK12* loci have been implicated in PD, but the genes have not yet been identified. Thus, further analyses will be necessary in order to elucidate the role these loci play in PD pathogenesis [40].

19.2.3 Sporadic Forms of PD

Most PD cases have no known cause, suggesting environmental and lifestyle factors play important and poorly understood roles in the disease. Although these factors are indeed valid and important, it is now estimated that genetics may explain up to 60% of PD cases, underscoring the complexity of the disorder [12]. Toxins, such as methyl-phenyl-tetrahydropyridine (MPTP) [41], 6-hydroxydopamine [42], the herbicide paraquat [43] and the pesticide rotenone [44], have been shown to cause loss of dopaminergic cells in the substantia nigra. In addition, exposure to heavy metals or electromagnetic radiation, head trauma and viral infections are also known risk factors in PD [12, 45]. On the contrary, caffeine [46], uric acid levels [47], nicotine [48] and antagonists of the A_{2A} receptor [49] have been suggested to act as neuroprotectors.

19.3 Epigenetics in PD

PD, as other neurodegenerative diseases, is a complex disorder occurring from the interplay between genetic, environmental, nutritional and other factors, together with ageing. As epigenetics may be altered in response to, at least, some of these factors, it is becoming increasingly accepted; it may also play an important role in the aetiology and pathogenesis of PD.

19.3.1 The Role of DNA Methylation

DNA methylation involves the covalent addition of a methyl group from S-adenosyl methionine (SAM) to the 5′ position of cytosines. In this way, 5-methylcytosine is formed (5-mC), with the concomitant conversion of SAM to S-adenosylhomocysteine (SAH) [50–52]. Methylation is a dynamic process that is apparent in multiple genomic sites, although it is mainly described to occur in repeats of CG dinucleotides [53]. In the human genome, these dinucleotides cluster in areas known as CpG islands which are associated with promoter regions, at least for about 60% of human genes [54]. Functionally, DNA methylation is associated with transcriptional inhibition. This can be executed either directly, by hindering the association of the DNA machinery with chromatin, or indirectly, with the recruitment of methyl-CpG-binding domain proteins (MBDs) [55, 56]. MBDs, in turn, attract histone-modifying and chromatin-remodelling complexes to the methylated sites. DNA methyltransferases (DNMTs) are the enzymes responsible for mediating DNA methylation. In mammals, DNMT1 is able to maintain DNA methylation following replication, while DNMT3a and DNMT3b exert de novo methylation [50].

Genome-wide DNA methylation analysis in blood and brain samples of healthy individuals and PD patients revealed a significant dysregulation of CpG island methylation in the group of patients. Many genes were found to be either hypo- or hypermethylated, including PD risk genes [57]. Another study identified 20 genes that were differentially methylated in blood samples obtained from PD patients in comparison to controls [58].

The observation that the *SNCA* promoter is hypermethylated in patients with alcoholism [59] or anorexia [60] suggested that epigenetics, perhaps through metabolic alterations, may also play a role in PD. Indeed, it was described that *SNCA* expression was upregulated upon methylation-mediated inhibition of *SNCA* intron 1 and that the SN, putamen and cortex of PD patients exhibited a significant hypomethylation pattern compared to healthy controls (Fig. 19.1) [61]. Another study was not able to detect methylation differences in the anterior cingulate or putamen of PD patients when examined a CpG region of the promoter of *SNCA*. However, substantial methylation reduction was apparent in the SN of these patients [62]. A reduction in the nuclear levels of DNMT1 was reported in postmortem brain tissue from dementia with Lewy bodies (DLB) or PD patients, as well as in brains from transgenic mice overexpressing *SNCA*. This alteration in the subcellular localisation of DNMT1 resulted in a global hypomethylation, including CpG islands upstream of *SNCA* and other genes, while aSyn was identified as the sequester of DNMT1 from the nucleus to the cytoplasm (Fig. 19.1) [63]. On the other hand, when the promoter and a CpG-rich region of *SNCA* intron 1 were analysed in patients with PD versus healthy individuals, hypermethylation at various positions in different brain regions was detected [64].

The methylation status of *SNCA* intron 1 was further investigated in blood samples [65], peripheral blood mononuclear cells (PBMCs) [66] or leukocytes of PD patients [67]. In agreement with results in brain tissue, these studies reported a significant decrease in methylation of the *SNCA* promoter. Nevertheless, a correlation between *SNCA* mRNA levels and the methylation pattern of its promoter could not

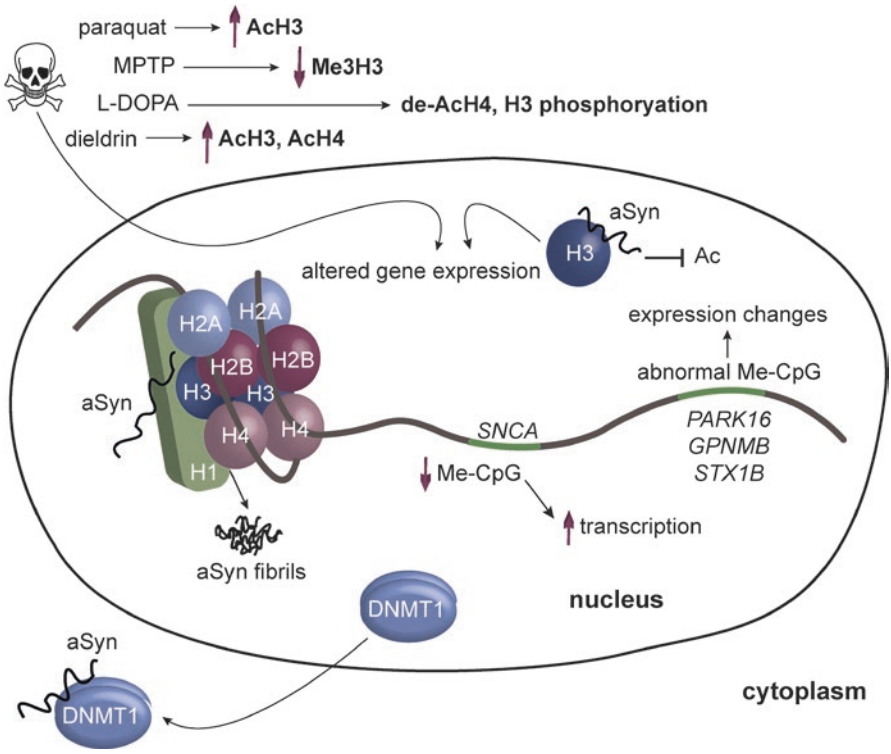

Fig. 19.1 Epigenetic modifications in dopaminergic neurons. Certain toxins enter the neuronal cells and cause histone modifications, thereby influencing the expression of several genes. In the nucleus, aSyn interacts with H1 forming a tight complex and also with H3 inhibiting its acetylation. In turn, histones trigger the aggregation of aSyn. Several PD-associated genes, such as *PARK16*, *GPNMB* and *STX1B*, show altered expression as a result of aberrant DNA methylation. The promoter of *SNCA* is usually found hypomethylated in PD, leading to increased levels of aSyn. aSyn is able to sequester DNMT1 from the cytoplasm in the nucleus resulting in a general reduction of the methylation pattern. *Ac* acetylation, *de-Ac* deacetylation, ↑ increase, ↓ decrease, ┤ inhibition

be firmly established [65, 66]. Another study in leukocytes from PD patients and healthy individuals revealed no alterations in the levels of methylation in any of the investigated regions [68].

Additional genes, namely, *PARK16*, *GPNMB* and *STX1B*, have been found to present aberrant methylation in postmortem PD brain samples (Fig. 19.1) [69]. The methylation status of the *TNF* promoter was significantly diminished in the SN compared to the cortex of both PD patients and healthy individuals, suggesting that a possible overexpression of TNF may trigger inflammatory reactions compromising the vulnerability of the dopaminergic neurons [70]. Postmortem samples obtained from the cortex and putamen showed decreased CpG methylation and

increased mRNA levels of the *CYP2E1* gene in PD patients [71]. Interestingly, a single nucleotide polymorphism (SNP) in this gene has been associated with PD [72], and its protein product, cytochrome P450 2E1, is implicated in the production of toxic metabolites that influence degeneration of dopaminergic neurons [50]. Although mutations in *PARK2* have been associated with autosomal recessive juvenile parkinsonism, abnormal methylation levels of *PARK2* promoter have been described in acute lymphoblastic and in chronic myeloid leukaemia [73], but not in PD cases [74]. In a similar manner, increased methylation of the *UCHL1* promoter was reported in diverse types of cancer [75, 76], while no significant alterations in CpG methylation was observed in the hippocampus and frontal cortex from PD brains [77]. Similar results were obtained for *ATP13A2* gene. DNA methylation of the promoter revealed an association with the progression of Kufor-Rakeb syndrome, although no such link has been made for PD so far [78].

DNA methylation in mitochondria might also be a relevant phenomenon in the context of PD. Recently, the mammalian mitochondrial DNMT (mtDNMT) was discovered [79]. Despite some controversy regarding CpG methylation in the genome of human mitochondria [80], some studies claim this can occur [81, 82]. Moreover, alterations in mitochondrial DNA methylation have been associated with cancer [83] and liver disease [84]. Finally, it was suggested that age-related changes in the DNA methylation of mitochondria may influence gene expression, alter mitochondrial metabolism and increase ROS production [85]. On the other hand, both *PARK2* and *PINK1* genes are essential for physiological mitochondrial function, and, when either of them is mutated, they can lead to mitochondrial impairment [12]. Considering the involvement of mitochondria in PD, further investigation will unravel possible implication of mitochondrial DNA methylation in PD pathogenesis.

19.3.2 Hydroxymethylation

Recently, the enzyme ten-eleven translocation1 (Tet1) was found to catalyse the oxidation of 5-mC to 5-hydroxymethylcytosine (5-hmC) [86]. Following studies have associated 5-hmC with euchromatin, indicating its relation with promoter regions and increased transcriptional levels [87, 88]. This intriguing, novel epigenetic modification is essentially unexplored in the context of neurodegeneration.

A detailed study revealed that 5-hmC levels increase in the mouse cerebellum in an age-dependent manner. In addition, an intragenic and proximal (to transcription start or termination sites regions) enrichment of 5-hmC was identified and associated with elevated gene expression. Gene ontology pathway analysis of the differentially expressed genes pointed towards pathways which are associated with neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and PD [89], but additional studies are necessary in order to establish whether this type of DNA alteration is relevant in neurodegeneration.

19.3.3 Histone Modifications

The N-terminal tails of the histones are around 25–40 amino acid residues long and constitute a suitable region where chromatin-modifying enzymes can execute their function [90]. Histone modifications include methylation of lysine or arginine residues, acetylation, phosphorylation, ubiquitination, SUMOylation, ADP-ribosylation, crotonylation, hydroxylation and proline isomerisation [52, 81]. Histone modifications have been described to play pivotal roles in the development, differentiation and maintenance of dopaminergic neurons [91]. However, little is known concerning alterations in the physiological pattern histone modifications and their implications in PD pathogenesis.

In a recent study, the use of isolated dopaminergic neurons from brain tissue from PD patients revealed increased acetylation levels of histone H2A, H3 and H4 compared to age-matched control individuals. Furthermore, the levels of various histone deacetylases (HDACs) are reduced in 1-methyl-4-phenylpyridinium (MPP^+)-treated cells and in MPTP-treated mouse brains and also in midbrain samples from PD patients [92]. These findings highlighted the presence of histone modifications suggesting that chromatin remodelling may be highly implicated in the pathogenesis of PD. Exposure to additional toxins also induces alterations into histones. For instance, when the pesticide dieldrin was administered in mice, elevated acetylation of histones H3 and H4 occurred in mesencephalic dopaminergic neurons due to proteasomal dysfunction (Fig. 19.1). Subsequently, the cAMP response element-binding protein, a histone acetyltransferase (HAT), was found to accumulate in the cells [93]. Another neurotoxic agent, paraquat, induces acetylation of histone H3 in dopaminergic cells in vitro (Fig. 19.1) [94].

In murine and primate models of levodopa-induced dyskinesia (LDID), dopamine depletion via MPTP administration was associated with a reduction in histone H3 trimethylation at Lys4 (Fig. 19.1). Chronic levodopa (or L-DOPA) therapy of these models was accompanied by deacetylation of striatal histone H4 at Lys5, 8, 12 and 16 (Fig. 19.1). The presence of histone modifications is evident, suggesting they may contribute to the development and maintenance of LDID in PD [95]. LDID has been associated with abnormal dopamine D1 receptor transmission. Histone H3 phosphoacetylation is blocked by D1 receptor inactivation, suggesting that inhibition of histone H3 acetylation and/or phosphorylation may be used for the prevention or reversion of dyskinesia [96]. In a mouse model of PD, it was shown that administration of L-DOPA induced phosphorylation of histone H3 on Ser28 in regions marked by trimethylation of the adjacent Lys27 (Fig. 19.1). This phenomenon was specifically observed in neurons expressing the D1 receptor and correlated with aberrant expression of genes that may be accountable for motor complications or dyskinesia [97].

Dopaminergic neurons of paraquat-treated mice displayed accumulation of aSyn in the nucleus, where it co-localises with acetylated histone H3. Further investigation revealed that aSyn binds directly to histone H1 and forms a tight 2:1 complex (Fig. 19.1). On the other hand, histone H1, together with the core histones, was able to boost the formation of aSyn fibrils (Fig. 19.1) [98]. Another study reported both

in vitro and in *Drosophila* that nuclear aSyn associated with histone H3 reduces its acetylation (Fig. 19.1) [99]. Similar results were also described in PC12 cells expressing monoamine oxidase B. aSyn co-localised with histone H3 and once more was able to decrease its acetylation [27]. Finally, overexpression of dHDAC6 in a *Drosophila* model of PD ectopically expressing *SNCA* promoted aSyn inclusion formation and reduced aSyn oligomerisation. On the other hand, depletion of dHDAC6 enhanced the detrimental effects of aSyn overexpression, including the loss of dopaminergic neurons and locomotor dysfunction [100].

In *C. elegans* overexpressing human wt or A53T *SNCA*, nine histone genes coding for linker H1 and two core histones, H2B and H4, were downregulated [101].

19.3.4 miRNAs in PD

miRNAs bind to the 3′ untranslated region (UTR) of mRNA targets and modulate protein translation [102]. Thus, given their pleiotropic effects in cell biology, miRNAs are also emerging as relevant contributors to neurodegeneration in PD. Recently, an overall downregulation of miRNAs was found in tissue samples isolated from the SN of PD patients when compared to samples from healthy individuals [103].

Transgenic mice lacking Dicer in their dopaminergic neurons display neuronal cell death in the SN [104], suggesting overall miRNA processing is detrimental for dopaminergic cell function. Interestingly, studies in PD patients revealed that miR-133b, which is specifically expressed in midbrain dopaminergic neurons, is deficient in midbrain tissue. miR-133b is involved in a negative feedback circuit that contains the paired-like homeodomain transcription factor Pitx3, having a regulatory role in the maturation and function of midbrain dopaminergic neurons [104]. miR-132 has also been linked to midbrain dopaminergic neuronal differentiation. In a rat model of PD, miR-132 was significantly increased, and, in turn, the levels of its target protein, nuclear receptor-related 1 protein (Nurr1), were reduced [105, 106].

In a study using the MPTP-induced mouse model of PD, miR-124 was found to be downregulated in the SN of the mice, along with an increase in the levels of calpain/CDK5 proteins [107]. Interestingly, activation of calpains has been associated with dopaminergic cell death in the MPTP-induced mouse model and in postmortem nigral tissue from PD brains [108]. Another study reported a functional role of elevated miR-126 in SN dopaminergic neurons of PD patients through the inhibition of IGF-1/PI3K signalling pathway, contributing to neurotoxicity [109].

The levels of miR-1, miR-22* and miR-29 are reduced in blood samples of PD patients. Interestingly, the levels of miR-16-2*, miR-26a2* and miR30a enabled the distinction between treated from non-treated PD patients [110]. On the other hand, miR-1826/miR-450b-3p, miR-505 and miR-626 are upregulated in the plasma of PD patients and may be useful as PD biomarkers [111].

LRRK2 was found to influence the miRNA pathway, possibly by associating with Argonaute (Ago), in both human and *Drosophila* samples. Furthermore, in a *Drosophila* model of PD, it was observed that mutant LRRK2 suppresses the function

of let-7 and miR-184* which normally regulate the translation of E2F1/DP complex, involved in cell cycle and survival control (Fig. 19.2) [112]. Furthermore, frontal cortex samples from PD patients contain high levels of LRRK2 and reduced levels of miR-205. It was then found that miR-205 is able to bind to the 3′ UTR of *LRRK2* mRNA and suppress its expression. Further in vitro studies included the introduction of miR-205 in neurons carrying the R1441G LRRK2 mutation, which prevented outgrowth defects [113]. These findings suggested the regulatory role of miR-205 on *LRRK2* expression and, therefore, a possible role in PD pathogenesis (Fig. 19.2).

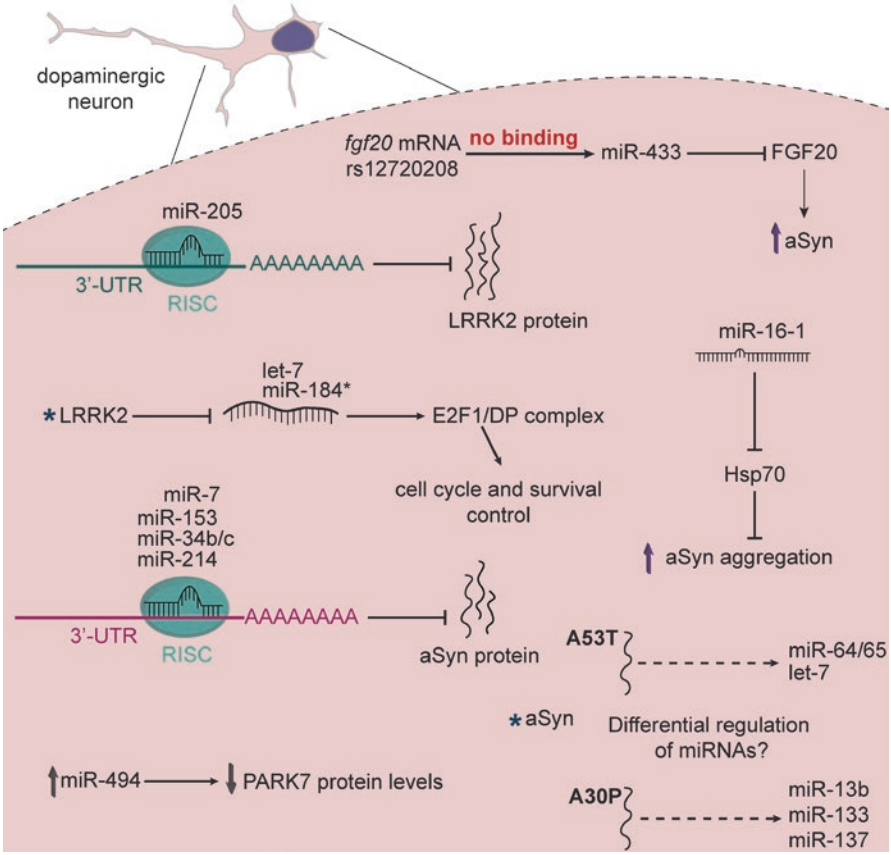

Fig. 19.2 The impact of miRNAs on TH$^+$ neurons. miR-205 is able to suppress the expression of LRRK2 protein by binding to its 3′ UTR mRNA region. On the contrary, mutant LRRK2 inhibits let-7 and miR-184* which participate in cell survival. Overexpression of miR-494 reduces the levels of PARK7. Furthermore, several miRNAs bind to *snca* mRNA sequence and prevent its translation. On the other hand, the levels and aggregation of aSyn are indirectly increased due to increased FGF20 or decreased Hsp70 protein levels. Finally, mutant aSyn is thought to affect the production of certain miRNAs. **LRRK2* mutant LRRK2, **aSyn* mutant aSyn, ↑ increase, ↓ decrease, ┤ inhibition

DJ-1, the product of *PARK7*, is thought to be an oxidative sensor that protects cells from oxidative stress. Decreased levels of DJ-1 have been detected in the SN of sporadic PD patients suggesting a connection with PD. miR-494 was found to bind to the 3′ UTR of *PARK7* mRNA and, when overexpressed, was able to significantly reduce DJ-1 protein levels in vitro and in an MPTP mouse model, while concomitantly rendering the cells more susceptible to oxidative stress and leading to dopaminergic cell death (Fig. 19.2) [114].

A global miRNA expression profiling in *C. elegans* showed that three members of the let-7 family (cel-miR-241, 230 and 48) were deregulated in animals mutated for *PARK2*. Similarly, 12 differentially regulated miRNAs from the miR-64/miR-65 and let-7 families were identified in animals overexpressing human A53T *SNCA* (Fig. 19.2) [115].

The levels of miR-34b and c were found significantly reduced in the amygdala, frontal cortex, cerebellum and SN of PD patients, accompanied by a decrease in the expression of *PARK2* and *PARK7*. In addition, depletion of miR34-b and c in in vitro differentiated dopaminergic neurons caused an alteration of mitochondrial function and oxidative stress [116, 117]. In addition, both miRNAs appear to repress *SNCA* expression. Overexpression of miR-34b and c in SH-SY5Y cells resulted in a substantial reduction of aSyn protein levels via targeting the 3′ UTR of *SNCA* mRNA (Fig. 19.2), while inhibition, using anti-miRs, increased both the levels and the aggregation of the protein. Finally, a polymorphic variation in the 3′ UTR of human *SNCA* mRNA was associated with resistance to miR-34b binding and therefore to increased aSyn [118].

Two other abundant brain miRNAs, miR-7 and miR-153, bind to the 3′ UTR of *SNCA* mRNA and inhibit its translation (Fig. 19.2). More precisely, miR-7, a neuron-specific miRNA, was found to downregulate the expression of *SNCA* in HEK293T cells, protecting against oxidative stress. On the other hand, a specific miR-7 inhibitor caused a significant increase of aSyn protein levels in SH-SY5Y cells. Results obtained from MPTP-treated mice were in agreement with those obtained in the in vitro models, showing a substantial reduction of miR-7 levels and suggesting that elevated *SNCA* expression may be attributed to this downregulation [119]. Furthermore, treatment of primary cortical neurons with MPP^+ followed by miR-7 overexpression resulted in neuronal protection from MPP^+-induced toxicity and restored neuronal viability [120]. This protection from cell death was achieved via preservation of active mTOR signalling, possibly promoting aSyn clearance [120, 121].

miR-153 is another brain predominant miRNA that binds to the 3′ UTR of *SNCA* mRNA resulting in a significant decrease of its mRNA and protein levels [122]. The miR-153 binding site is predicted to be located within nucleotides 459–465. A variation identified in one male PD patient (464 C > A) was never encountered in healthy individuals or in patients with familial PD that were involved in the study and was suggested to be a rare cause of PD [123]. Interestingly, it seems that miR-7 and miR-153 have a synergistic effect on reducing aSyn levels [122].

In contrast, it was reported that SH-SY5Y cells treated with miR-106a* significantly increased their aSyn protein levels [124]. Moreover, other miRNAs such as miR-301b, miR-26b, miR-373* and miR-21 which regulate the levels of chaperone-mediated autophagy proteins were significantly increased in the SN of human PD brain tissues [124].

Administration of MPP^+ or MPTP to cell or mouse models, respectively, resulted in a decline of miR-214 levels and in an increase in aSyn levels. In particular, a miR-214 inhibitor caused a reduction in the amount of TH^+ cells when administered in vivo. Thus, as a result, miR-214 may contribute to the upregulation of *SNCA* and, therefore, to the toxic effects of aSyn in dopaminergic neurons (Fig. 19.2) [125].

Alterations in synaptosomal proteins were investigated in early symptomatic A30P *SNCA* transgenic mice, indicating that several proteins related to mitochondrial function were differentially expressed. Moreover, miRNA expression profiling revealed that the levels of miR-10a, 10b, 212, 132 and 495 were altered in brainstem samples when compared those from wild-type control animals [126]. In a *Drosophila* A30P *SNCA* model, high-throughput sequencing of small RNAs revealed that five miRNAs were upregulated. Among them, miR-13b, miR-133 and miR-137 are enriched in the brain and highly conserved from *Drosophila* to humans. miR-137 was shown to target the 3′ UTR mRNA of the dopamine D2 receptor. Therefore, it was suggested that mutant aSyn may be responsible for the dysregulation of miRNAs which are implicated in neuroactive-ligand receptor pathways (Fig. 19.2) [127].

Heat sock protein 70 (Hsp70) is capable of inhibiting cellular toxicity caused by aSyn via reduction of aSyn misfolding and aggregation [128–132]. Chemical blockade of Hsp70 in a cellular model (SH-SY5Y cells) overexpressing *SNCA* promotes aSyn aggregation. Interestingly, administration of miR-16-1 mimics those results given that miR-16-1 targets *HSP70* mRNA and downregulates both its mRNA and protein levels (Fig. 19.2) [133]. Therefore, aSyn toxicity and the protective effects of Hsp70 are corroborated via this novel mechanism, opening new perspectives for intervention in PD.

A polymorphism (rs1989754) in the *FGF20* gene was reported to be associated with increased risk of developing PD [134]. Another *FGF20* polymorphism that was identified a few years later (rs12720208) was suggested to obstruct the binding of miR-433 to the *FGF20* mRNA both in vitro and in vivo and, therefore, lead to increased FGF20 protein levels. Interestingly, elevated FGF20 protein levels have been linked to the subsequent increase of aSyn levels, observed both in SH-SY5Y cells and in human brain samples. In this way, elevated FGF20 levels may account for susceptibility towards developing PD through the increase of aSyn (Fig. 19.2) [135].

19.4 Epigenetic-Based Therapeutic Approaches for PD

HDAC inhibitors (HDACis) are commonly used as anticancer molecules. However, they have also emerged in the field of neurodegenerative disorders, in models of PD and AD, due to their effects on different members of the histone deacetylase family

of proteins [136–139]. Valproic acid (VPA) has been shown to protect against rotenone [140], aSyn [140] and MPTP toxicity [141]. The responses triggered by VPA were mediated by decreasing the levels of pro-inflammatory factors and inducing microglia apoptosis [142, 143]. Finally, trichostatin A (TSA) has been described to increase the expression of *HSP70,* thereby having neuroprotective and anti-inflammatory properties [144], and to induce microglia apoptosis accompanied by increased histone H3 acetylation [143]. Nevertheless, the positive effects of these compounds conceal certain drawbacks. For example, in one study, it was shown that hyperacetylation of histone H4 via the administration of sodium butyrate, an HDACi, induces the expression of the protein kinase C δ (PKCδ) in the striatum and SN of mice. This upregulation was responsible for increasing the sensitivity of the cells to oxidative stress, rendering the dopaminergic neurons more prone to cell death and potentially contributing to PD [145]. TSA was also found to induce neuronal cell death and activate pro-apoptotic genes, likely contributing to PD pathogenesis [146, 147]. In addition, it was described that TSA potentiated pro-inflammatory responses in microglial cells, a process that is associated with several degenerative conditions [148]. The balance between HAT and HDAC activities is vital for normal cellular function, and, although many studies are evaluating the therapeutic potential of HDACis in PD, it should also be noted that they may cause undesired side effects and responses not only in neurons but also in other cell types, due to putative effects in nonhistone protein targets. Thus, despite current hopes and potential, additional work is still necessary in order to improve the applicability of these approaches.

Acknowledgements TFO is supported by the DFG Center for Nanoscale Microscopy and Molecular Physiology of the Brain and from BMBF Grant DecipherPD (01KU1503B).

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