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REVIEW

Epigenetic regulation in Parkinson's disease

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Abstract Recent efforts have shed new light on the epigenetic mechanisms driving gene expression alterations associated with Parkinson's disease (PD) pathogenesis. Changes in gene expression are a well-established cause of PD, and epigenetic mechanisms likely play a pivotal role in regulation. Studies in families with PD harboring duplications and triplications of the *SNCA* gene have demonstrated that gene dosage is associated with increased expression of both *SNCA* mRNA and protein, and correlates with a fulminant disease course. Furthermore, it is postulated that even subtle changes in *SNCA* expression caused by common variation is associated with disease risk. Of note, genome-wide association studies have identified over 30 loci associated with PD with most signals located in non-coding regions of the genome, thus likely influencing transcript expression levels. In health, epigenetic mechanisms tightly regulate gene expression, turning genes on and off to balance homeostasis and this, in part, explains why two cells with the same DNA sequence will have different RNA expression profiles. Understanding this phenomenon will be crucial to our interpretation of the selective vulnerability observed in neurodegeneration and specifically dopaminergic neurons in the PD brain. In this review, we discuss epigenetic mechanisms, such as DNA methylation and histone modifications, involved in regulating the expression of genes relevant to PD, RNA-based mechanisms, as well as the effect of toxins and potential epigenetic-based treatments for PD.

Keywords Parkinson's disease · Epigenetics · Methylation · Acetylation · Histones · RNA-based epigenetic mechanisms

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Introduction

As the second-most common neurodegenerative disorder after Alzheimer's disease, Parkinson's disease (PD) presents with motor symptoms, including tremor, bradykinesia, rigidity, postural instability, and non-motor symptoms, such as REM sleep behavior disorder, autonomic dysfunction, and cognitive impairment [45]. Cytoplasmic aggregates of the α-synuclein protein, termed Lewy bodies, form within neurons, which in combination with the loss of dopaminergic neurons in the substantia nigra pars compacta [20], represent the hallmarks of the disease.

PD heritability, from twin and familial studies, is estimated to be around 34–60 % [33, 120], yet the proportion of phenotypic variance based on known PD genetic loci is approximately 27 % [52] suggesting most of the causal variation is still unknown. The bulk of this missing heritability probably lies within the understudied variation, such as rare variants, structural variants, and variants located in regulatory non-coding regions (e.g., long non-coding RNAs and microRNAs). Furthermore, it is becoming clear that the link between DNA variation and phenotype is not necessarily direct: in general, all somatic cells of an organism have the same DNA, and yet, they can present with very diverse expression profiles, which suggests an additional level of control. An understanding of the precise PD gene expression patterns and regulatory mechanisms is essential

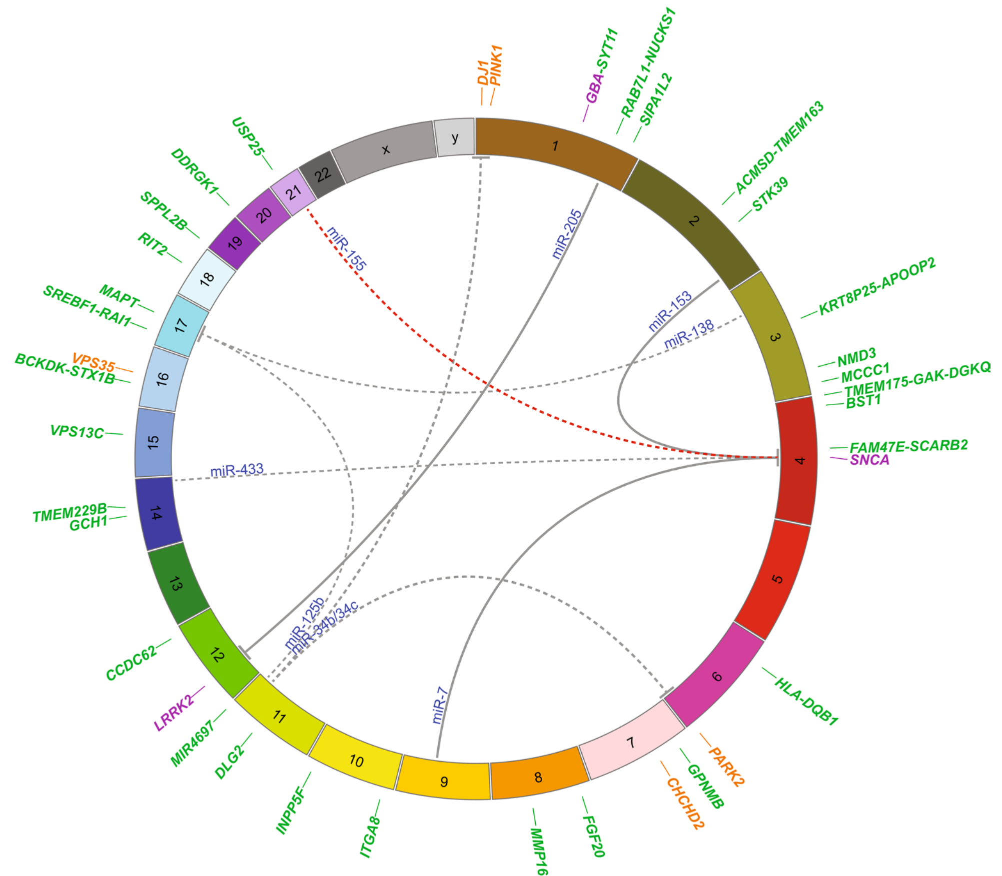

Fig. 1 Network of Parkinson's disease (PD) related genes, and microRNAs that regulate them. Human genome Circos plot [59] showing PD-related genes and regulatory microRNAs. PD-related genes are displayed in the outer part of the plot, and microRNAs are displayed in the inner part of the plot. *Green* PD genes that have been found using GWAS studies; *orange* PD genes that cause familial PD; *purple* PD genes that have been found in GWAS studies and that also cause familial forms of PD. *Solid grey lines* show direct repression of targeted genes by microRNAs; *dotted grey lines* represent indirect repression by acting on an intermediate mRNA that causes downstream PD gene repression; *dotted red lines* represent indirect increase of *SNCA*-related brain inflammatory response

to fully decipher the sequence of molecular events leading to PD.

Mounting evidence supports the hypothesis that mechanisms which drive changes in gene expression and protein levels are associated with PD. One such phenomenon is epigenetic modification, which alters the functionality of a locus or chromosome without changing the underlying DNA sequence [32], and may account for some of the fundamental differences in expression patterns between PD patients and controls. Genomic DNA variation is now well-established to drive both familial and sporadic forms of PD. *SNCA*, which encodes the α-synuclein protein, was identified as the first PD risk gene in 1997 [88], and mutations in six additional genes (*PARK2*, *PINK1*, *PARK7*, *LRRK2*, *VPS35*, and *CHCHD2*) have been linked to familial forms of PD. In addition, genome-wide association studies (GWAS) have identified more than 30 loci associated with the modulation of PD risk at the population level (Fig. 1) [79]. Of note, most of the GWAS hits appear to be driven by non-coding variation and are thus likely associated with the regulation of gene expression [79].

Differences in gene expression and protein levels of the *SNCA* gene have been shown to play a critical role in PD susceptibility, as demonstrated in families with *SNCA* triplications and duplications. *SNCA* gene/protein levels correlate with the number of extra genomic copies found in PD patients carrying duplications or triplications [73, 78]. The carriers present with widespread cortical Lewy body pathology [56], and *SNCA* dosage correlates with earlier onset, faster progression, and more severe disease presentation [95]. In addition, even subtle changes in expression due to common *SNCA* variants can influence disease susceptibility. Indeed, the *SNCA* locus is a major GWAS peak of association with PD risk. Specific variation including a dinucleotide repeat sequence REP1 within the *SNCA* promoter, rs356168 in intron 4, and rs356210 in the 3′ UTR region have all been proposed to influence both *SNCA* expression and disease risk [28, 66, 103].

Gene expression and PD

Changes in gene expression and protein levels are the main consequence of epigenetic mechanisms. Fundamental differences in expression patterns between PD patients and controls have been highlighted by expression arrays and RNA-sequencing. It is also known that within PD patients, gene expression levels are different between different brain regions (i.e., substantia nigra vs less affected brain regions) [64]. One of the caveats of expression studies in PD is that

several different platforms and technologies have been used resulting in variability across studies; no specific expression pattern has consistently been replicated yet.

Gene expression can be modulated via a number of ways and can provide mechanistic insight into disease pathogenesis. Recently, the combination of RNA-sequencing, transcriptomics, and mass spectrometry proteomics data from prefrontal cortex allowed Dumitriu et al. to suggest that the main pathways involved in PD development are related to mitochondrial processes, protein folding mechanisms, and metallothioneins [22]. Moreover, the study identified ten genes overlapping with GWAS loci including *SNCA* which was strongly implicated in these pathways via proteomics. Hoss et al. proposed to differentiate PD brains from control brains by analyzing expression levels of a set of 125 microRNAs (miRNA) in prefrontal cortex [41]. The study used a subset of 29 miRNAs to differentiate PD brains from control brains at a genome-wide level of significance with 93.9 % specificity and 96.6 % sensitivity. The same study highlighted the differences between PD with dementia brains and PD without dementia brains using a subset of 36 miRNAs. These results strongly support a direct link between gene and protein expression and disease state.

In this review, we will present epigenetic regulatory mechanisms in the context of PD (“Appendix 1”), specifically events affecting the expression of *SNCA* and other PD genes. We will discuss: DNA methylation, histone modifications, and RNA-based mechanisms as well as the effects of neurotoxins and drugs on epigenetic mechanisms.

Epigenetics and the genome: DNA methylation

DNA methylation is the modification by which a methyl group is added to cytosine converting it to 5-methylcytosine. This process typically occurs on cytosines adjacent to guanines (the so-called CpG islands) and is crucial for the regulation of many cellular processes, such as gene expression, cellular differentiation, and development [89]. DNA methylation is analogous to an on/off switch: heavily methylated areas of the genome are usually less active at the transcriptional level (gene expression turned off), whereas areas with less methylation are more active (gene expression turned on). DNA methylation has been extensively studied in cancer research and new research focused on identifying differentially methylated genes and the process in which methylation is maintained or lost has recently become a major area of interest in neurodegenerative diseases research. In this section, we discuss the role of DNA methylation in PD, and we start with the methylation of the *SNCA* gene and its key regulatory enzyme DNA methyltransferase 1 (Dnmt1). We present the findings of large-scale methylation studies in PD, and we describe the issues with using RNA extracted from blood leukocytes. We then describe the use of S-adenosyl methionine (SAM)/S-adenosyl homocysteine (SAH) ratios as a biomarker and the epigenetic clock, a tool created by Horvath et al., to measure the age of tissues based on methylation markers. We end by discussing the methylation of mRNA and mitochondrial DNA.

Given the known influence of α-synuclein expression levels in disease, the initial PD methylation studies focused on the *SNCA* gene. In 2010, two groups studied the DNA methylation of *SNCA* using bisulfide treated cell models [49, 71]. Both groups observed the increased expression of *SNCA* when a CpG island in intron 1 was de-methylated. Lower methylation levels in several brain regions (substantia nigra, putamen, and cortex) in PD patients compared to controls were also observed. Interestingly, the methylation of the *SNCA* promoter polymorphism in PD patients was found to be correlated with the amount of L-dopa administered to the patient: patients receiving higher therapy dose have higher methylation levels and thus lower *SNCA* expression [99].

The Dnmt1 enzyme, one of the key regulators of DNA methylation in mammalian cells that preserves the methylation patterns established in development, has been recently examined in the context of PD. Desplats et al., of the University of California San Diego (UCSD), showed that α-synuclein interacts with Dmnt1, thereby keeping it in the cytoplasm and preventing its action on DNA. Dmnt1 levels are also lower in PD patients compared to controls, and Dmnt1 mislocalization directly alters the methylation of the *SNCA* gene [19]. Epigenetic regulatory mechanisms surrounding the *SNCA* gene and the α-synuclein protein are presented in Fig. 2.

In 2013, a genome-wide epigenome study (EWAS) in frontal cortex and in blood of five PD patients and six controls was reported [70]. Less than 1 % of probes on the microarray presented significant differences in methylation levels in the cases vs controls, but more than 80 % of differentially methylated sites identified were hypomethylated in PD cases. Similar patterns were observed in brains and blood. Among the top hits of PD, hypermethylated genes was *MAPT*, which encodes protein tau, and is also one of the top PD GWAS hits [79]. Coupland et al. studied *MAPT* methylation in bisulfite-treated leukocytes (358 PD patients and 1084 controls) and brain tissues (3 brain regions from 28 PD patients and 12 controls) [15]. In tissue from healthy controls, they observed higher methylation in women compared to men and 1.5-fold higher levels of methylation in *MAPT* H1/H1 diplotype vs H2/H2; higher methylation correlated with lower expression levels of *MAPT*. In PD samples, lower methylation was detected in the putamen of PD patients compared to controls. Being female, having a later age at onset and carrying the *MAPT* H1 haplotype were all

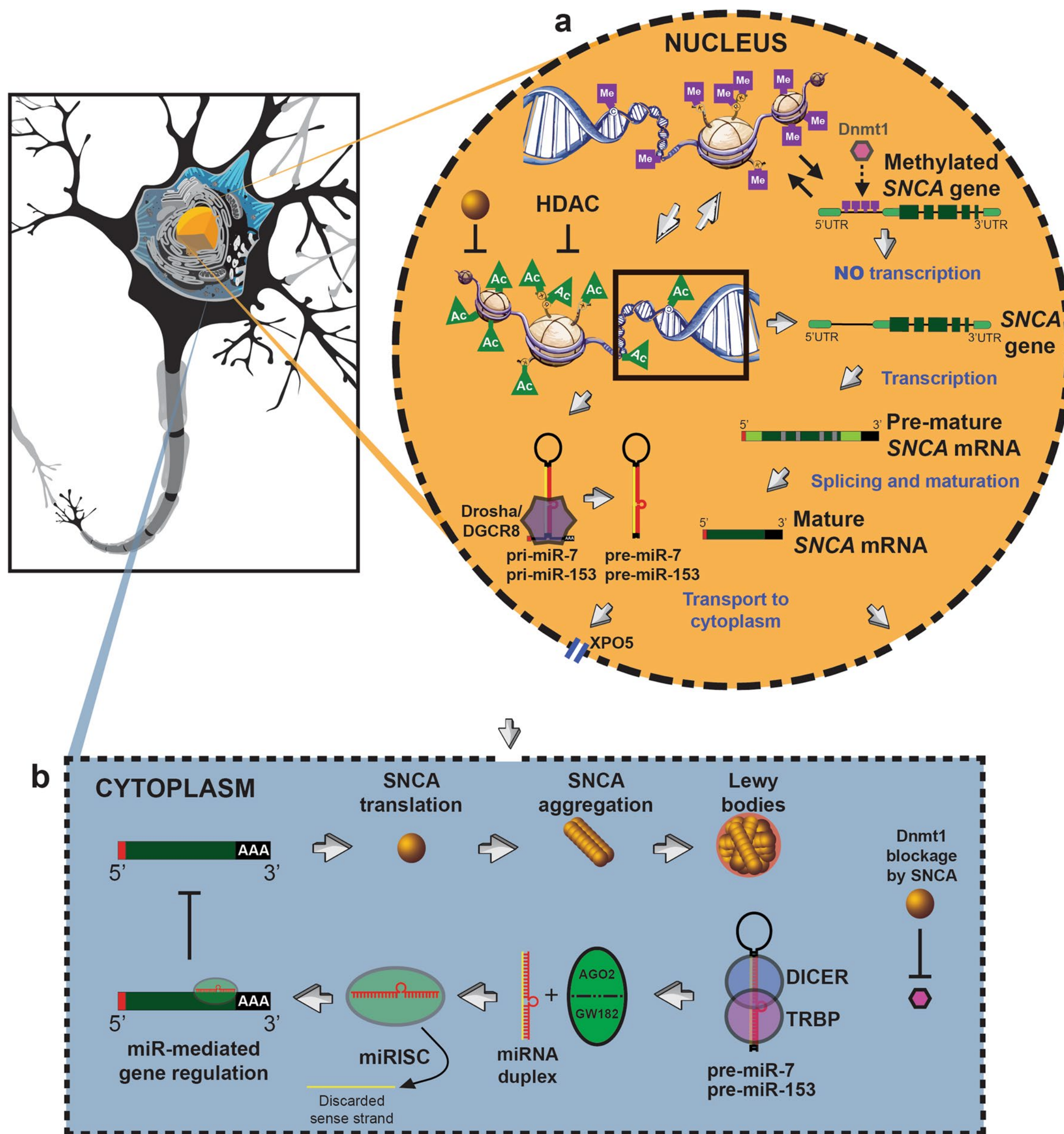

Fig. 2 Epigenetic mechanisms involved in α-synuclein pathology. **a** Nucleus. Methylation of histones promotes histone compression and the formation of condensed heterochromatin. Conversely, acetylation of histones decreases their affinity for DNA allowing nucleosome spacing and heterochromatin to transform into its relaxed form, euchromatin, which is conducive to the transcription of genes such as *SNCA*. Histone deacetylases (HDAC) remove acetyl group from histone and, as a result, repress gene expression. When DNA methylation occurs at the CpG island in the first intron of *SNCA*, transcription is also repressed. The enzyme Dnmt1 is involved in maintaining methylation patterns. When intron 1 is de-methylated, transcription of *SNCA* can proceed. *SNCA* demethylation can be due to Dnmt1 being sequestered in the cytosplasm by α-synuclein. Histone methylation–acetylation status dynamically changes by complex mechanisms that promote or repress gene transcription depending on cellular conditions and stress. Primary miRNAs are processed by the microprocessor complex, which consists of Drosha and DGCR8. Resulting precursor miRNAs (pre-miR) are transported to the cytoplasm by XPO5. **b** Cytoplasm. *SNCA* mRNA is translated in the cytoplasm into α-synuclein. In their pathological form α-synuclein monomers are assembled in oligomers and fibrils rich in β-sheets; such fibrils form the basis of the mature Lewy bodies. Pre-miRs are processed by the DICER/TRBP complex into 22 bp-miRNA duplexes. The functional strand of a miRNA duplex is incorporated to the AGO2/GW182 complex to generate mature miRISC. MiRISCs containing either miR-7 or miR-153 can bind to the 3′UTR of *SNCA* mRNA, destabilize the mRNA and induce translational repression. *AAA* poly(A) tail; *Ac* acetylated residue; *AGO2* argonaute-2; *DICER* endoribonuclease Dicer or helicase with RNase motif; *Dnmt1* DNA (Cytosine-5-)-Methyltransferase 1; *HDAC* histone deacetylases; *GW182* trinucleotide repeat-containing gene 6A (*TNRC6A*); *Me* methylated residue; *miR* microRNA; *miRISC* miRNA-mediated silencing complex; *mRNA* messenger RNA; *pre-miR* precursor microRNA; *pri-miR* primary microRNA; *SNCA* Synuclein, Alpha; *TRBP* transactivation-responsive binding protein; *UTR* untranslated region; *XPO5* exportin 5

associated with higher methylation levels. It is not clear why the *MAPT* H1 risk haplotype is more methylated than the protective H2 haplotype, since previous studies have shown that H1 leads to increased *MAPT* expression [2, 61], but it is possible that other epigenetic mechanisms regulate *MAPT* gene expression.

Nalls et al. examined CpG methylation related to GWAS hits in cortex and cerebellar tissue samples from neurologically normal individuals [79], and identified 30 significant associations between GWAS variants and CpG methylation or mRNA expression across six loci. Interestingly, while no differential methylation pattern was observed in *MAPT* itself, four of the associations observed implicated genes at the chromosome 17q *MAPT* locus: long non-coding RNA *MGC57346* and genes *PLEKHM1*, *ARL17A*, and *KANSL1*. These findings suggest that tag SNPs from GWAS hits can be related to non-coding functional variants located in regulatory regions and influencing gene expression. In addition, these findings suggest that functional studies are necessary complement of GWAS studies to adequately nominate causal genes within GWAS loci.

In the last few years, EWAS have become more and more popular to study methylation profiles in PD. Since the first reported study by Masliah et al. [70], sample size has increased exponentially. Moore and colleagues [77] were particularly interested in methylation patterns specific to anxiety in PD patients. Blood samples from 45 individuals (15 PD, 15 PD with anxiety, and 15 controls) were analyzed and led to the identification of more than 12,000 genes with differential methylation patterns between PD with and without anxiety. These genes are involved in brain-centric pathways, such as neuroactive ligand-receptor interaction and the neurotrophin signaling, among others. More than 9900 differentially methylated genes in PD vs controls were identified. A subset of the top hits was followed up in 219 PD subjects and 223 controls, and two genes, *FANCC* and *TNKS2*, which are, respectively, involved in neuronal apoptosis and post-translational signaling, showed significant differential methylation.

To determine whether methylation patterns in leukocytes reflect methylation patterns in the brain, the use of blood leukocytes as a proxy has been popular (because the tissues are more readily accessible) but controversial. Some studies have not been able to observe significant hypomethylation at the well-characterized *SNCA* intron 1 CpG island in blood leukocytes DNA from PD patients [93, 105], while others have [87, 107]. These differences might be attributable in part to sample size, but Fernandez-Santiago et al. have shown differential methylation profiles in different cell types from PD patients [25]. They derived dopaminergic neurons from induced pluripotent stem cells (iPSCs) of PD patients and healthy controls. They showed that dopaminergic neurons presented with differential methylation patterns in PD and controls, but these changes were not seen in fibroblasts or the parental iPSC. This suggests studies that aim to decipher how epigenetic regulation affects neurons should be performed in carefully chosen neuronal models or brain tissue.

Methylation has been proposed as a biomarker for cognitive impairment in PD by Obeil et al. [81]. Given S-adenosyl methionine (SAM) is a co-substrate involved in methyl group transfer and S-adenosyl homocysteine (SAH) is a product of the methylation reaction involving SAM, a higher SAM/SAH ratio is a sign of higher methylation potential. Obeid et al. discovered an association between plasma SAM/SAH ratio and cognitive function scores [81]. PD patients with no cognitive impairment had a significantly higher plasma SAM/SAH ratio than patients presenting with mild or severe cognitive dysfunction. Better cognitive functions were also related to higher levels of vitamin B6, a vitamin known to improve methylation status and protect against the production of amyloid-β [29, 34].

Horvath [39] created an epigenetic clock which predicts age based on the methylation status at 353 CpG sites in the human genome. The clock was developed using publicly available methylation array data from 7844 non-cancer samples from several different studies. Horvath named age acceleration the difference between chronological age and epigenetic age predicted by the epigenetic clock. By analyzing blood samples for PD patient and controls, Horvath et al. were able to show that there was an increased age acceleration in PD patients compared to controls [40]. They suggest that this accelerated aging of blood cells precede the onset of motor and non-motor symptoms, and could be used as a biomarker.

Methylation mechanisms affect not only DNA, but also mRNA [72, 117]. N6-methyladenosine (m^6A) and 5-methylcytosine (m^5C) are two mRNA methylation post-transcriptional modifications. Adenosine methylation occurs mainly in brain tissue, and it has been suggested that m^6A methylation could play a role in the intracellular response to neuronal signaling by downregulating the expression of neuronal mRNAs [97]. One of the m^6A demethylases is encoded by the *FTO* (fat mass and obesity-associated) gene. Mutations in *FTO* are involved in neurodegenerative disorders, such as AD [51, 92] and in impaired brain function [92]. In addition, the inactivation of *FTO* in a mouse model affects dopamine receptor type 2 (D2R) and dopamine receptor type 3 (D3R)-dependent control of dopaminergic neuron activity [37]. This dysfunction was caused by increased m^6A levels of a specific subset of mRNAs (*KCNJ6*, *GRIN1*, and *DRD3*) directly involved in the dopaminergic signaling pathway, resulting in low protein expression [37].

In addition, a recent study showed that PD patients ($n = 10$) have a loss of m^5C levels in the displacement

loop (D-loop) of the substantia nigra mitochondrial DNA when compared with controls ($n = 10$) [4]. This could be attributable to dopaminergic neuronal loss in the substantia nigra, but methylation levels of mitochondrial NADH dehydrogenase 6 (*ND6*) in this region were similar between PD patients and controls, suggesting that the m^5C methylation changes in the mitochondrial D-loop are not due to neuronal loss [4]. Interestingly, nuclear DNA is not the only type showing differential methylation patterns. Blanch et al. reported loss of mitochondrial DNA 5-methylation levels in the substantia nigra of PD patients [4]. These findings could support the hypothesis that mitochondrial dysfunction is a common molecular mechanism in PD pathogenesis.

DNA methylation is the most intensely studied epigenetic mechanism, based on the number of papers available in Pubmed, yet the role it plays in PD pathogenesis is just starting to be explored. Methylation correlates with aging of tissues and cognitive impairment and directly influences the expression of *SNCA* and other PD genes. Furthermore, the influence of methylation on the regulation of gene expression can only be understood by taking into account the other epigenetic mechanisms at play.

Chromatin remodeling

Chromatin remodeling, orchestrated by histone modifications, is a dynamic process by which important physiological functions, such as gene expression, are regulated. Post-translational modifications of histone proteins, such as methylation and acetylation, can modify chromatin structure and regulate accessibility of DNA for transcription. Histone acetylation is associated with transcriptionally active genes. In general, there are higher levels of histone acetylation in the midbrain of dopaminergic neurons from PD patients compared to controls [84]. Specific PD genes and molecules are regulated by histone modifications. The case of α-synuclein is interesting, because it is regulated by histone acetylation and it can also regulate histone acetylation, possibly due to a feedback loop. It was shown that α-synuclein interacts with histones in the nucleus and this accelerates α-synuclein fibrillation and toxicity [31]. Kontopoulos et al. confirmed these findings and further demonstrated that α-synuclein binds directly to histones and inhibits the acetylation of histone H3 through interaction with SIRT2, a deacetylase [57]. Furthermore, they showed that the α-synuclein disease-related mutants p.A30P and p.A53T present an increased nuclear localization compared with wild-type α-synuclein. Voutsinas et al. looked at *SNCA* gene expression in a PD patient heterozygous for the p.A53T mutation. They observed that the p.A53T allele was silenced and it could be reactivated through the use of inhibitors of histone deacetylases (HDACs), demonstrating that the silencing of the mutant *SNCA* allele is due to histone deacetylation [114]. Supporting these findings, a histone 3 lysine 27 acetylation (H3K27ac)-enriched enhancer sequence has been identified at the *SNCA* locus [113]. Interestingly, HDACs inhibitors have also been shown to be neuroprotective against α-synuclein -mediated toxicity [57, 76, 83].

Other PD-associated genes also seem to be regulated by histones modifications. *MAPT* haplotype H1 is preferentially associated with H3K4me3 histone modification, which normally indicates gene activation, whereas the H2 haplotype is associated with the repressive H3K27me3 histone modification [90]. The PINK1 protein can bind to HDAC3, a transcriptional repressor recruited to specific promoters, and upregulate its histone deacetylase activity through phosphorylation in neuronal cell lines [13]. This event leads to increased binding of phosphorylated HDAC3 to p53, which decreases p53 acetylation and stability, thus inhibiting p53-mediated neuronal apoptosis. The knockdown of HDAC3 abolishes the effect of PINK1 on p53 [13]. Known PD-associated variants in *PINK1* do not promote phosphorylation of HDAC3 suggesting *PINK1* mutations lead to a deregulation of HDAC3 activity and increased susceptibility to p53-dependent neuronal apoptosis and neurodegeneration [13].

RNA-based mechanisms of gene regulation

A number of RNA-based regulatory pathways based on non-coding RNAs and miRNAs influence gene expression. In this section, we will discuss specific examples of long non-coding RNAs (lncRNA) and microRNAs (miRs) which regulate the expression of PD genes. LncRNA are long (more than 200 nucleotides) non-protein coding transcripts, which are involved in gene expression regulation [118]. LncRNA *RP11-115D19*.1 binds to *SNCA* 3′-flanking region and can be stimulated prominently by YY1, a ubiquitous transcription factor involved in several biological pathways. This stimulation does not significantly modify *SNCA* expression levels in an SH-SY5Y cell model [75]; however, the knockdown of *RP11-115D19*.1 in the same cell model results in a significant increase of α-synuclein expression. This suggests that this lncRNA has a repressive effect on *SNCA* expression [75]. Another study using four different neuroblastoma cell lines revealed a lncRNA complementary to *PINK*1 3′-mRNA sequence, which was able to stabilize and increase *PINK1* expression levels, which may prove beneficial [98].

MicroRNAs (miRs) are small non-coding nucleotide RNA molecules (21-25 nucleotides) that bind to imperfect complementary sequences within the 3′UTR region of their target messenger RNAs (mRNAs) [6, 43]. This

binding inhibits the expression of proteins encoded by these mRNAs [111]. Several studies show that miRs are crucial in the regulation of PD-related gene expression (Fig. 1) and that they affect specific neuronal functions. MiR-133b is highly expressed in midbrain dopaminergic neurons of healthy subjects, but has lower levels in brains from patients with PD [55]. MiR-133b is normally expressed in mice midbrain and levels have been shown to be reduced in two different PD mice models: an adult Aphakia mouse model, which has a reduced expression of transcription factor Pitx3, and the classical 6-OHDA mouse model. Pitx3 promotes midbrain dopaminergic neuron gene expression [69, 102] and induces miR-133b transcription, while miR-133b overexpression reduces Pitx3 protein levels. These results suggest a negative-feedback loop in which Pitx3 induces miR-133b transcription and miR-133b overexpression downregulates Pitx3 activity [55].

It has been shown that miR-7 and miR-153, which bind specifically to *SNCA*, downregulate its expression and that their effect is additive (Fig. 2) [21]. The brain expression patterns of miR-7 and miR-153 mimic that of *SNCA* in adult brains as well as neuronal development, suggesting a tight balance in the regulatory mechanisms. Overexpression of either or both miRs reduces endogenous *SNCA* levels, whereas their inhibition promotes the translation of a chimeric luciferase mRNA bearing *SNCA* 3′UTR region in primary neurons [21]. MiR-7 is highly conserved across species, and it has been suggested to confer stability and robustness to certain regulatory networks against environmental fluctuation during development [38, 65], and to protect neurons against oxidative stress [50]. Moreover, a recent study suggests that miR-7 and miR-153 may protect neurons against neurotoxin 1-Methyl-4-Phenyl-Pyridinium (MPP+)-induced cell death by upregulating mTOR and SAPK/JNK signaling pathways [27]. Both pathways have been involved in apoptotic cell death mechanisms in PD [94]. In addition, miR-7 protects neurons against (MPP+) cell damage by targeting RelA [12], a structural component of inflammatory transcription factor NF-κB. These studies support miR-7 and miR-153 as potential therapeutic targets for PD and several other α-synucleinopathies.

A recent study showed that miR-155 was upregulated early in an in vivo PD model overexpressing α-synuclein [108]. A miR-155 knockout mouse model revealed that the absence of miR-155 reduced neuronal proinflammatory responses to α-synuclein and blocked α-synuclein-related neurodegeneration. The underlying mechanisms of this blockage involved the microglia's response to α-synuclein aggregation. Primary microglia from miR-155 knockout mice presented with reduced inflammatory response to α-synuclein fibrils, including a diminished major histocompatibility complex class II and nitric oxide synthase expression. The treatment of this microglia with a synthetic miR-155 replicated their inflammatory response to α-synuclein fibrils [108]. These results suggest that miR-155 plays a key role in brain inflammatory response and in α-synuclein-dependent neurodegeneration and implies that miR-155 could be used as therapeutic target to modulate brain inflammatory responses to α-synuclein in patients with PD. In addition, it has been suggested that variant rs12720208 located in the miR-433 binding site of fibroblast growth factor 20 gene (*FGF20*), located in a GWAS locus, increases PD risk by upregulating the expression of α-synuclein [115], but this mechanism remains controversial [17, 119].

MiR-205 regulates the expression of *LRRK2*, a familial PD gene, and GWAS hit, where the most frequent causal mutation in sporadic and familial PD is located (LRRK2 p.G2019S). A study found that expression of the LRRK2 protein was increased in frontal cortex of sporadic PD patients when compared to controls, while mRNA levels were not significantly different between both groups, suggesting post-transcriptional modifications of LRRK2 protein expression [11]. The same study showed that miR-205, which is conserved across different vertebrate species, binds specifically to the 3′UTR *LRRK2* mRNA region and that this binding suppressed LRRK2 protein expression. MiR-205 was also underexpressed in sporadic PD subjects with an increased LRRK2 protein expression compared to controls. These results were supported by experiments which showed that overexpression of miR-205 in cultured mouse hippocampal neurons expressing PD-causing LRRK2 p.R1441G mutation prevented neurite outgrowth defects suggesting miR-205 has a protective effect against neurodegeneration [11].

Proteins encoded by *PARK2* (Parkin RBR E3 Ubiquitin Protein Ligase) and *PARK7* (DJ1) genes are implicated in the disruption of the mitochondrial pathway in PD patients [1]. Their expression is tightly regulated by miR-34b and miR-34c. The expression of miR-34b and miR-34c is decreased in several brain areas (amygdala, frontal cortex, substantia nigra, and cerebellum) in PD patients with Braak stages 4 and 5 but also in PD patients in pre-motor stages (Braak stages 1–3) compared to controls, suggesting that this is an early event in PD pathogenesis. The decreased expression of miR-34b and miR-34c correlates with a reduced DJ1 and Parkin expression in human PD brains. However, overexpression of these miRs does not lead to any change in DJ1 or Parkin expression levels [74], suggesting that they are not direct targets of miR-34b and miR-34c, but that the miRs are involved in an intermediate regulatory step. Additional experiments in differentiated SH-SY5Y dopaminergic neuronal cells showed that a depletion of miR-34b or miR-34c resulted in a reduction in DJ1 and Parkin expression levels and cell viability along with mitochondrial dysfunction altered oxidative stress and a decrease of total cellular adenosine triphosphate [74].

Interestingly, miR-34b and miR-34c share a common non-coding precursor and they both play a key role in apoptosis pathways, as they are direct targets of the tumor suppressor gene P53 [36].

There is evidence that miRs can modulate tau expression. In primary hippocampal neurons extracted from an Alzheimer's disease (AD) rat model, overexpression of miR-125b increased tau hyperphosphorylation and upregulated p35, cdk5, and p44/42-MAPK signaling [3]. Overexpression of miR-125b downregulated its direct targets, DUSP6 and PPP1CA phosphatases, and the anti-apoptotic factor Bcl-W. When overexpressed, PPP1CA and Ccl-W prevented miR-125-induced tau phosphorylation, suggesting that they intervene in the action of miR-125b on tau. Likewise, miR-125b suppression in neurons reduced tau phosphorylation and its kinase activity [3]. In addition, miR-125b hippocampal injection in mice leads to tau phosphorylation and produces learning impairment [3]. Similarly, miR-138 induces tau phosphorylation by targeting the retinoic acid receptor alpha (RARA)/glycogen synthase kinase-3β (GSK-3β) pathway [116]. A study by Wang et al. showed that miR-138 was increased in AD cell models [116]. MiR-138 overexpression activates GSK-3β and increases tau phosphorylation in HEK293/tau cells. It was also shown that 3′-UTR of RARA mRNA is a direct target of miR-138 and that overexpression of RARA attenuates GSK-3β activity and reduces tau phosphorylation induced by miR-138 [116].

Finally, a recent study analyzing variants in miRs or miR-binding sites on their target genes based on the largest PD GWAS [79], showed a significant association of two miR variants (rs897984 [chr16:30886643T>C] in miR-4519 and rs11651671 [chr17:40646803A>G] in miR-548at-5p) with PD [30]. In both cases, the variant's alternative allele modified the secondary structure of the miR and decreased their expression level. However, only miR-4519 expression was detectable in brain tissue. An analysis of genetic variants in all putative miR-4519 target genes revealed a significant association of four genes with PD: *NSF*, *TMEM163*, *CCNT2*, and *SH3GL2* [30]. Interestingly, the *NSF* gene lies in the PD-associated *MAPT* locus. In addition, 13 miR-binding sites located in ten known PD genes (*RAB29* formerly known as *RAB7L1*, *DGKQ*, *TMEM175*, *SNCA*, *STX1B*, *PLEKHM1*, *ARHGAP27*, *CRHR1*, *MAPT*, and *SPPL2B*) and three other genes (*CSTB*, *IGSF9B*, and *HSD3B7*) showed a significant association with PD [30].

RNA editing

RNA-based epigenetics mechanisms can be disrupted by RNA editing, a process that is catalyzed by ADAR (adenosine deaminase acting on RNA) enzymes. These proteins convert adenosines (A) located in intronic regions, 5′ and 3′ UTR regions of mRNAs into an inosine (I) [101]. The cell machinery recognizes I as guanosine (G), because they have the same pairing properties. This process is similar to silent mutations at the mRNA level. While not affecting the nature of the mRNA, these changes can disrupt the binding of the miRs to the mRNA. Although the process is common and necessary for normal life and development [44, 112], in certain circumstances, it can disrupt the normal epigenetic regulation performed by non-coding RNA machinery. It has been described in several neurodegenerative diseases, such as amyotrophic lateral sclerosis [60], but so far, not in PD.

Taken together, these studies exemplify how small or long non-coding RNAs can be crucial to finely regulate gene and protein expression in both healthy and PD affected subjects. Moreover, these mechanisms hint to a new era in therapeutic tools development, where the focus is on managing protein aggregation and PD-causing dysfunctional pathways.

Neurotoxins and drugs interfere with epigenetic mechanisms in PD

It is widely accepted that certain environmental factors, such as pesticides, can induce parkinsonian symptoms. In fact, certain neurotoxins have been used to generate animal models that mimic parkinsonian symptoms of PD patients. The first animal models developed using 6-OHDA [110], methamphetamine [109], or rotenone [35] have certain features similar to the loss of dopaminergic neurons observed in PD patients, but they do not replicate all the pathogenic mechanisms present in PD. For that reason, the discovery of the selective nigral toxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) driven by its MPP+ metabolite was a breakthrough. The MPTP model [5] mimics several PD clinical and pathogenic mechanisms: oxidative stress, reactive oxygen species, energy failure, and inflammation. However, only a few studies using the MPTP model have been able to replicate the definitive pathological PD hallmark: the development of Lewy bodies [26, 58].

Several neurotoxins not only produce a PD phenotype, but also affect different epigenetic mechanisms, such as methylation, demethylation, hyperacetylation, and deacetylation of certain genomic regions (Table 1). In addition, some histone acetyltransferase inhibitors and histone deacetylases inhibitors may counteract the effects of toxin- or disease-related epigenetic changes and are potential therapeutic avenues to explore (Table 1).

Table 1 Drugs and toxins and their epigenetic effects

	Epigenetic modification	Pathogenic/rescue mechanism	Refs.
Toxins			
MPTP	H3 hyperacetylation and dephosphorylation, H4 deacetylation	Dopaminergic neurons death by accumulation of MPP + metabolite	[80]
Methamphetamine	Decreases mRNA expression of HDACs	Promotes α-tubulin (*TUBA1A*) deacetylation Increases *SNCA* expression by decreasing cytosine methylation in the *SNCA* promoter region	[24, 47, 82]
Paraquat	H3 hyperacetylation	Induces apoptotic mechanisms	[7, 104]
Rotenone	HDAC inhibitor protect toxicity	Targets *SIRT1* and blocks its deacetylasing histone protective role	[23, 106]
Dieldrin	H3, H4 hyperacetylation	Induces proteasomal dysfunction and thus promotes apoptosis in dopaminergic neurons	[104]
6-OHDA	Hyperacetylation	Produces selective toxicity in monoaminergic neurons by increasing oxidative stress and decreasing the activity of tubulin deacetylase SIRT2	[16, 85]
Chronic drug use			
Levodopa	*SNCA* methylation H4 deacetylation	Induces a dose dependent *SNCA* methylation at CpG2-23 of, reducing *SNCA* expression Long-term levodopa treatment induces dyskinesia that associates with marked H4 deacetylation	[80, 99]
Histone acetyltransferase inhibitor			
Anacardic acid	Deacetylation	Attenuates the apoptotic effects of dieldrin in dopaminergic neurons	[104]
Curcumin	Represses histone acetylation	Improves motor impairment in a DJ1 knockout PD rat model acting as anti-apoptotic and neurotrophic factor	[10]
HDAC (histone deacetylases) inhibitors			
Vorinostat (SAHA)	Hyperacetylation/promoter activation/di, trimethylation	Reduces α-synuclein mediated toxicity in PD Drosophila model overexpressing α-synuclein Prevents MPTP mediated apoptosis in human derived SK-N_SH and rat derived MES 23.5 cells Upregulates levels of the neuroprotective heat shock protein 70 (HSP70) in rat astrocytes	[53, 57, 67]
Valproic acid (VPA)	H3 Hyperacetylation/promoter activation/di, trimethylation	Upregulates neurotrophic factors expression, including glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), in astrocytes, which may play a major role in mediating VPA-induced neurotrophic effects on dopaminergic neurons Counteracts α-synuclein nuclear translocation and toxicity in rotenone-induced PD rat model Prevents striatal dopamine depletion and protects against substantia nigra dopaminergic cell loss in MPTP PD mouse model Induces microglial apoptosis accompanied by disruption of mitochondrial membrane potential and decreases in lipopolysaccharide-induced proinflammatory responses and protects dopaminergic neurons from damage in mesencephalic neuron–glia cultures Potent neuroprotective agent against lipopolysaccharide (LPS)-induced neurotoxicity in neuron-glia cultures from rat midbrain Has a neuroprotective role by inducing HSP70 in cortical neurons via the activation of phosphatidylinositol 3-kinase/Akt pathway and Sp1 acetylation in cultured neurons Prevents MPTP mediated apoptosis in human derived SK-N_SH and rat derived MES 23.5 cells	[8, 9, 53, 54, 62, 67, 68, 76, 86, 121]
Trichostatin A	Hyperacetylation/promoter activation/di, trimethylation	Upregulates GDNF and BDNF neurotrophic factors protecting dopaminergic neurons Upregulates levels of the neuroprotective heat shock protein 70 (HSP70) in rat astrocytes	[67, 121]

Table 1 continued

	Epigenetic modification	Pathogenic/rescue mechanism	Refs.
Sodium butyrate	Hyperacetylation/promoter activation	Upregulates GDNF and BDNF neurotrophic factors protecting dopaminergic neurons Reduces the oxidative stress and neuroinflammatory response in 6-OHDA PD rat model Improves pre-motor cognitive deficits in 6-OHDA PD rat model Upregulates DJ-1 expression and reduces neurotoxicity in MPTP PD mouse model Improves locomotor function in rotenone-induced PD fly model Reduces α-synuclein mediated toxicity in PD Drosophila model overexpressing α-synuclein Prevents MPTP mediated apoptosis in human derived SK-N_SH and rat derived MES 23.5 cells Upregulates levels of the neuroprotective heat shock protein 70 (HSP70) in rat astrocytes	[53, 57, 67, 91, 100, 106, 121, 122]
AGK2	Hyperacetylation	Reduces α-synuclein mediated toxicity in PD Drosophila model overexpressing α-synuclein	[83]
Entinostat (MS-275)	Promoter activation/di, trimethylation	Upregulates levels of the neuroprotective heat shock protein 70 (HSP70) in rat astrocytes	[67, 68]
Apicidin	Promoter activation/di, trimethylation	Upregulates levels of the neuroprotective heat shock protein 70 (HSP70) in rat astrocytes	[67, 68]
Sodium phenylbutyrate (NaPB)	Promoter activation	Increases DJ-1 expression in mice and protects dopaminergic neurons against MPTP toxicity Suppresses nigral activation of glial cells promoting protection of dopaminergic neurons, normalizes striatal neurotransmitters and improves motor functions in MPTP-intoxicated mice	[96, 122]
Urocortin	H3 hyperacetylation	Increases survival of dopaminergic neurons in mesencephalic neuron cultures by increasing intracellular cAMP levels and phosphorylating glycogen synthase kinase-3β (GSK-3β) on Ser9	[42]
RGFP109	Hyperacetylation	Improves levodopa induced dyskinesia in a MPTP marmoset PD model	[48]
K560	Hyperacetylation	Diminishes cell death induced by MPP + in differentiated SH-SY5Y cells by the expression of an anti-apoptotic protein, X-linked inhibitor of apoptosis (XIAP)	[14]

MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, *AGK2* SIRT2 inhibitor, *SAHA* suberoyl anilide hydroxamic acid

Harnessing epigenetics mechanism for therapeutics

Epigenetic-based therapies are attractive strategies to treat neurodegenerative disorders. The key to their usefulness is specificity. Ideally, a desired outcome would be downregulation of a specific pathogenic gene-like *SNCA* or upregulation of gatekeeper genes or both. As mentioned previously, several molecules can affect DNA methylation, but their effects are highly unspecific which probably would lead to considerable adverse effects. Interestingly, L-dopa appears to increase *SNCA* methylation in vitro and in vivo [99]. However, its long-term use induces dyskinesia, which appears to be correlated with increased H4 deacetylation [80]. Similar to molecules involved in methylation, the effects of HDACs inhibitors are wide ranging. We highlight some of the outcomes and rescue mechanisms related to HDACs inhibitors, such as Vorinostat (SAHA) and sodium butyrate (Table 1). All the proposed HDACs related compounds are still in experimental stages in terms of their effect on PD.

The power to specifically downregulate or knockdown genes of interest makes RNA molecules particularly interesting therapeutic strategies. Small interfering RNAs (siRNA) are short (20–25 bp) double-stranded RNA molecules complementary to a specific mRNA region. Unstable in their native form, siRNA are often coupled to a vector for transfection into cells. Nonviral vectors specific for neuronal cells can cross the blood–brain barrier rapidly and deliver *SNCA*-specific siRNAs to neurons knocking down α-synuclein protein expression, thereby preventing PD-like symptoms in in vitro and in vivo experimental models [46, 63]. Pre-treatment of M17 cells with a vector/siRNA complex in in vitro models resulted in a greater survival rate when exposed to MPP+ toxin, than untreated M17 cells [46]. In addition, in MPTP mouse models, the release of these vector/siRNAs complexes improved the motor symptoms generated by the MPP+ toxin via downregulation of *SNCA* [46]. The inhibition *SIRT2*, a deacetylase, can also rescue α-synuclein toxicity in a cellular model of PD [83]. In fact, when transfecting human neuroglioma cells (H4) with *SNCA* and synthetic siRNA against *SIRT2* or *SIRT3*,

only those transfected with *SIRT2* siRNA were rescued from α-synuclein toxicity [83].

Mirtrons are a specific class of miRNAs that are encoded in the introns of genes. They have been shown to silence certain genes in both in vitro and in vivo PD models [18]. Deng et al. created artificial mirtrons based on miR-1224 to target *LRRK2* and *SNCA*. They achieved an 85 % *LRRK2* gene expression reduction in HEK293 cells cotransfected with artificial mirtrons and exogenous *LRRK2*, but the reduction of endogenous *LRRK2* was only 36 % in SH-SY5Y cells. A similar assay targeting *SNCA* could only achieve a 26 % reduction in its expression [18], suggesting that artificial mirtrons may have therapeutic uses but optimization is needed.

The off-target effects of a miR could seriously damage normal cell machinery. For RNA-based epigenetic treatments to be successful, specific neurons, as opposed to every cell in a tissue have to be targeted. For this purpose, the chosen delivery system is of utmost importance. MiRs have to: (1) cross the blood–brain barrier, (2) enter the targeted neurons, and (3) remain in the brain long enough to perform their actions.

Another aspect to be considered is the potential effects of therapeutic miRs on different isoforms that could lead to undesirable results. Additional experiments need to be carried out to identify which gene isoforms need to be downregulated to improve PD symptoms and delay pathological effects and which ones should be upregulated in neurons, so that they perform their expected role to maintain normal neuronal function. Mutations in miRs target regions of PD genes could impair binding of miRs to their target mRNA, thus pre-treatment sequencing of the targeted region in patients should be performed to avoid potential therapeutic failures.

While inherently more specific than HDAC inhibitors, RNA-based epigenetic mechanisms have several caveats that need to be considered before they can be harnessed into safe and generic treatments for PD patients. Epigenetic-based cancer treatments aim to kill cells that are proliferating without control. The situation is somewhat different for neurodegenerative diseases in that the goal is to prevent cell death. The ideal treatment for PD would be to overcome the selective vulnerability of dopaminergic neurons by administering treatment early in pre-clinical phases of disease.

Future perspectives

In genetic terminology, PD is a complex disease: one caused by the interplay of several genetic and environmental factors. As such, more often than not, predicting phenotype from DNA variation alone is difficult and this assessment might have led to the previous perception that PD is not a genetic disease. In truth, a diverse array of regulatory mechanisms is acting as mediator between genotype and phenotype and contributes to differential gene expression; some of these mechanisms are epigenetic-based. We have highlighted a number of these different levels of regulatory mechanisms involved in PD-related gene expression: methylation of promoter regions, histone modifications, and RNA-based mechanisms. Some of the factors involved in these regulatory processes are potential therapeutic targets or potential biomarkers for improved and earlier diagnosis. PD-related therapy using epigenetic processes is in its infancy but will most likely continue to develop and perhaps someday become part of routine treatment. It is becoming clear that epigenetic mechanisms play key roles in neurodegenerative diseases. Additional research efforts aimed at determining the complete epigenetic map of the human brain, both healthy and diseased, is needed to fully understand the etiology of PD and other complex diseases.

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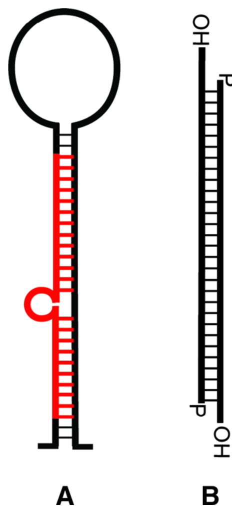
Appendix 1

- *Epigenetics* Study of the molecular changes that modify the final outcome of a locus or chromosome without changing the underlying DNA sequence.
- *Heritability* Proportion of individual phenotypic differences in a population that is due to genetic variation within this population.
- *Methylation* Process by which methyl groups are added to DNA, this occurs most often in promotor regions. Methylation generally represses gene expression.
- *Demethylation* Process that removes a methyl group from DNA to make genes in these regions accessible for expression.
- *Acetylation* Inclusion of an acetyl functional group which carries a negative charge into a free lysine of the N-terminal tail of the histone leading to transcriptional activation.

- *Deacetylation* Removal of an acetyl group from the N-terminal tail of the histone repressing gene expression.
- *Long non-coding RNA* (*lncRNA*) Non-protein coding transcripts longer than 200 nucleotides that can be involved in the regulation of gene expression.
- *Small RNA* Non-protein coding transcript smaller than 200 nucleotides which are often involved in RNA silencing. This group includes MicroRNAs, Short interfering RNAs and Mirtrons.
- *MicroRNA* (*miR*) Single hairpin RNA strand precursor of ~70 bp (black strand in A) located in exons or introns of RNAs that are processed sequentially by the Drosha ribonuclease and the Dicer enzyme into a ~22 mature nucleotide (red strand in A) with incomplete complementary sequence that can regulate the expression of multiple target mRNAs.
- *Short interfering RNA* (*siRNA*) Double RNA strand with perfect complementary sequence which can regulate a



limited number of target mRNAs. However, siRNAs can also have microRNA-like off-target effects (B).
- *Mirtron* Special type of miR (A) located in the introns of pre-mature RNA coding genes. They are generated during the splicing process by bypassing the Drosha maturation step and act as mRNA expression regulators.

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