

Review

Epigenetic Gene-Environment Interactions in Parkinson's Disease

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Abstract

Background: Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by the progressive loss of dopaminergic neurons in the substantia nigra. While genetic mutations and environmental exposures have both been established as risk factors for PD, emerging evidence has implicated epigenetic modifications as key mediators of gene-environment interactions involved in the pathogenesis of PD. **Objective:** This review aims to systematically characterize the epigenetic regulatory mechanisms that bridge the effects of environmental neurotoxins and genetic susceptibility in PD, providing a comprehensive synthesis of the current understanding of their functional crosstalk at a molecular level. **Key Findings:** Environmental factors drive the pathogenesis of PD through abnormal DNA methylation, dynamic imbalances in histone modification, and non-coding RNA regulatory networks. Here, we detail the mechanisms by which environment-induced epigenetic shifts give rise to the dysregulation of key PD-associated genes, including *SNCA*, *PRKN* (*PARK2*), *PARK7* (*DJ-1*), and *LRRK2*. This epigenetic dysregulation subsequently exacerbates downstream pathological events, such as mitochondrial dysfunction, impaired autophagy, endoplasmic reticulum stress, and neuroinflammation. **Conclusion:** Systematically exploring epigenetic gene-environment interactions offers detailed insight into the etiology of PD. Given the potential reversibility of specific epigenetic modifications, targeting these pathways may offer a prospective avenue for neuroprotective research. However, further rigorous investigation remains essential to evaluate the clinical viability of these mechanisms as reliable biomarkers or therapeutic targets.

Keywords: Parkinson's disease; gene-environment interaction; DNA methylation; histone code; non-coding RNAs

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder globally, and its highly complex and multifactorial etiology has thus far hindered any efforts to develop curative therapies. Age is a primary risk factor for PD, as while rare in individuals under 50, the prevalence of this disease increases exponentially with age, rising from roughly 107 per 100,000 among individuals in their 50 s to 1087 per 100,000 among those in their 70 s [1,2]. For this reason, the rapid aging of the global population has significantly amplified the public health impact of this disease.

The onset of PD is attributable to the combined effect of multiple factors, including genetic and environmental determinants [3]. Genetic factors have been firmly established as key drivers of PD, with mutations or duplication of the *SNCA* gene, for instance, directly contributing to the occurrence of familial PD [4,5]. However, the vast majority of PD cases are sporadic, suggesting that environmental factors may affect disease risk through mechanisms independent of DNA sequence changes. Environmental exposures to pesticides, smoking, heavy metals, and certain dietary components have all been linked to PD risk in epidemiological studies [6,7,8]. Rather than acting independently,

genetic susceptibility and environmental factors interact in a synergistic fashion to potentiate disease risk. In this conceptual model, epigenetic regulatory mechanisms serve as the central molecular link connecting these two domains [9].

Epigenetic processes, including DNA methylation, histone modification, and the actions of non-coding RNAs, allow for the regulation of gene expression without altering the underlying DNA sequence [10,11,12,13]. Unlike irreversible genetic mutations, epigenetic modifications are highly dynamic and environmentally responsive [11,14]. As such, environmental toxins can act as exogenous triggers that induce aberrant epigenetic remodeling, in turn altering the expression of vulnerability genes associated with neuronal survival [9,15]. In this way, epigenetic changes effectively translate transient environmental exposures into persistent neurodegenerative processes on a susceptible genetic background. More than simply an additional risk factor or disease, the disruption or dysregulation of these epigenetic mechanisms is thus a core integrating event in early PD pathogenesis, highlighting their promise as potential targets for preventative or therapeutic interventions [16,17].



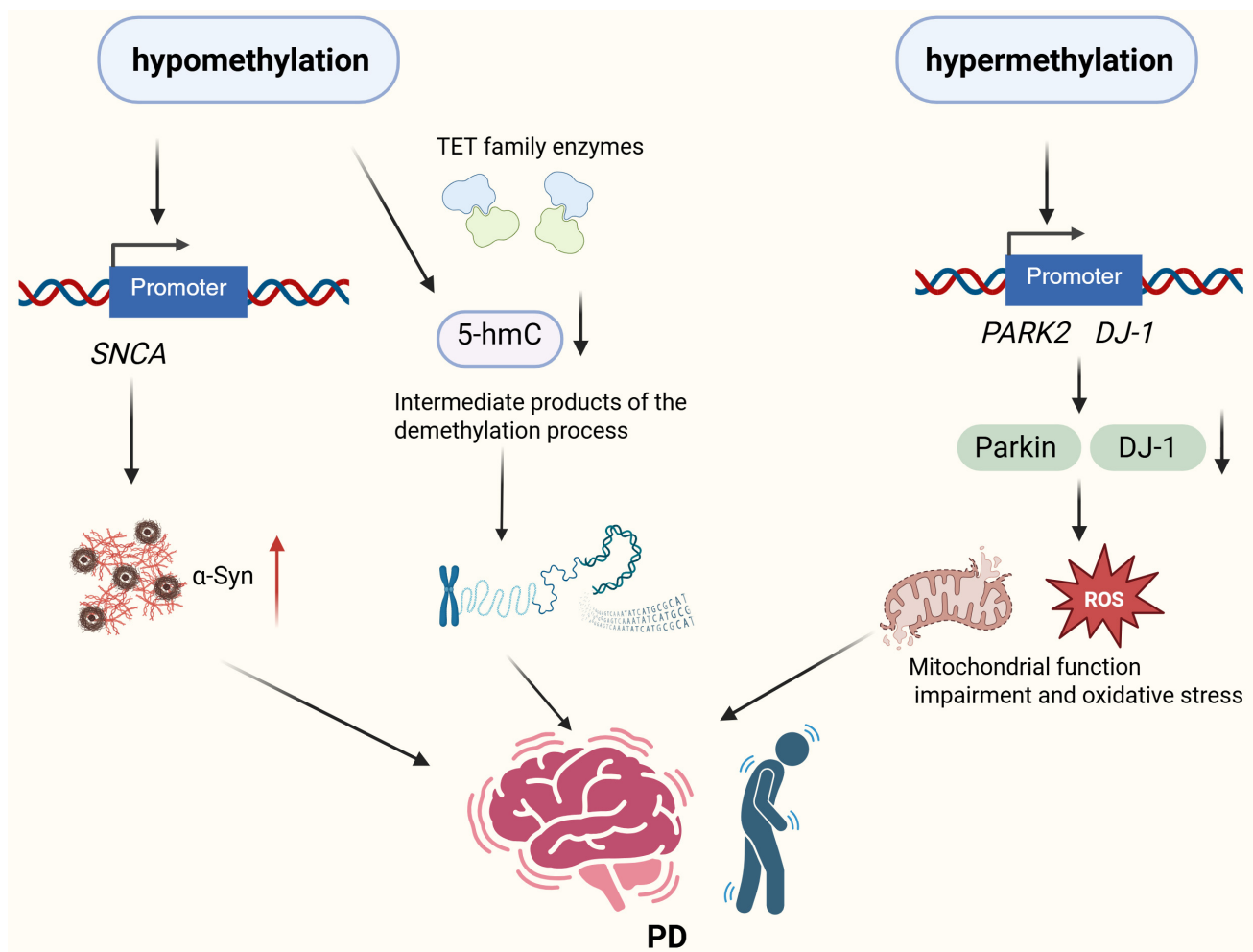


Fig. 1. The effects of altered gene methylation and DNA hydroxymethylation on PD. *SNCA* promoter hypomethylation upregulates α -Syn expression, while hypermethylation of the *PARK2* and *DJ-1* promoters reduces the expression of Parkin and DJ-1, impairing mitochondrial function and inducing oxidative stress. Concurrently, decreased DNA 5-hmC promotes dopaminergic neurodegeneration. Collectively, these epigenetic shifts drive PD pathogenesis. Figure created with BioRender.com (UQ2A9POXVA). 5-hmC, 5-hydroxymethylcytosine; PD, Parkinson's disease; ROS, reactive oxygen species; TET, ten-eleven translocation; α -Syn, α -synuclein.

2. Epigenetic Regulatory Mechanisms in PD

2.1 Abnormal DNA Methylation and Hydroxymethylation

DNA methylation is one of the most extensively studied epigenetic modifications, and it plays a crucial role in the pathogenesis of PD [18]. Under physiological conditions, DNA methylation regulates gene expression through the addition of methyl groups to the cytosine residue of CpG dinucleotides, with this modification most commonly being associated with gene silencing [19]. Notably, significant changes in the methylation status of multiple key genes have been noted in the brain tissues of PD patients [20,21]. For instance, hypomethylation of the promoter region of the *SNCA* gene is closely associated with increased α -synuclein (α -Syn) expression (Fig. 1) [22], and this phenomenon is particularly evident in the substantia nigra tissue of patients with sporadic PD [13,23]. Abnormal α -Syn is a major pathological feature of PD, and abnormal epige-

netic regulation of the *SNCA* gene may thus be an important driving force for the occurrence of this disease [4].

Recent advances employing fluorescence-activated nuclear sorting have highlighted profound cell-type specificity with respect to disease-related methylation patterns. For instance, the hypomethylation of the *SNCA* gene is predominantly observed in isolated dopaminergic/frontal neuronal nuclei rather than in glial cells [24]. While this neuron-specific hypomethylation is structurally correlated with increased α -Syn expression [13,22,23], whether these epigenetic alterations are true causal drivers of pathogenesis or merely secondary epiphenomena accompanying neurodegeneration remains a critical unresolved question in the field. Resolving this causality necessitates future longitudinal tracking and Mendelian randomization studies to definitively delineate which epigenetic shifts serve as initiating events and which are late-stage consequences of neuronal loss [25].

In addition to the altered methylation of gene promoters, alterations in DNA methylation patterns across the entire genome are also involved in the pathogenesis of PD. Widespread region-specific DNA hypomethylation has been noted in the brain tissue of PD patients, which may contribute to genomic instability and the abnormal expression of repetitive sequences [13,14]. Conversely, the hypermethylation of specific genes has also been discovered to be associated with PD. For instance, hypermethylation in the promoter regions of known PD-associated genes, including *PARK2* and *DJ-1* may lead to the functional loss of the proteins they encode, thereby affecting mitochondrial function and oxidative stress responses (Fig. 1) [14,26]. Notably, these altered patterns of DNA methylation are not confined to neurons. The abnormal methylation of certain genes has also been detected in the peripheral blood of PD patients, providing potential opportunities for the development of epigenetic diagnostic markers for PD [4]. However, while aberrant methylation patterns in the peripheral blood have been extensively investigated in the context of diagnostic biomarker development, these peripheral signatures—such as altered methylation in CD14⁺ monocytes [27]—predominantly reflect systemic immune and inflammatory responses rather than directly mirroring the neurodegenerative epigenome of the brain. As such, directly extrapolating central nervous system pathology from peripheral blood samples requires stringent critical validation.

DNA hydroxymethylation (5-hmC) is a recently discovered epigenetic modification that has gradually attracted attention for its role in PD [28]. 5-hmC is an intermediate product of the DNA demethylation process, catalyzed by TET family enzymes. It is abundant in the nervous system and is associated with gene activation. The overall level of 5-hmC in the brain tissue of PD patients has been shown to be significantly upregulated [8]. These 5-hmC abnormalities may be involved in the degeneration of dopaminergic neurons by influencing gene expression programs and chromatin stability (Fig. 1) [29]. Importantly, current research lacks a comprehensive understanding of the temporal dynamics of these modifications. Because epigenetic landscapes remodel continuously with disease progression, future studies must evaluate methylation and 5-hmC profiles from the prodromal phase to advanced PD in order to definitively delineate which epigenetic shifts are initiating events and which are late-stage consequences of neuronal loss.

2.2 Dynamic Histone Modification Imbalances

Histone modification is another important epigenetic process that regulates the transcriptional activity of genes by altering chromatin structure. Its abnormal regulation in PD has received extensive attention in recent years [10]. Histone modifications include acetylation, methylation, and phosphorylation, with the dynamic balance of histone acetylation and methylation being particularly crucial in the pathogenesis of PD. Histone acetylation is usually associ-

ated with chromatin opening and gene activation, whereas histone deacetylation leads to chromatin condensation and gene silencing. A significant increase in the activity of histone deacetylases (HDACs) has been reported in the brain tissue of PD patients, including pronounced increases in HDAC2 and HDAC6 expression. Mechanistically, the pathogenic functions of HDACs are multifaceted, extending beyond transcriptional repression in the nucleus. For instance, preclinical studies suggest that the nuclear accumulation of HDAC2 is associated with the transcriptional suppression of critical neurotrophic and survival genes, such as those encoding brain-derived neurotrophic factor (BDNF), heat shock protein 90 (Hsp90), and c-fos [30,31]. Furthermore, cytoplasmic HDAC6 actively participates in PD pathology by deacetylating α -tubulin, which severely impairs microtubule-dependent axonal transport. This transport defect, combined with the high affinity of HDAC6 for polyubiquitinated misfolded proteins, forces the aberrant accumulation of α -Syn into aggresomes, thereby overwhelming and paralyzing the autophagic-lysosomal clearance pathway (Fig. 2) [32,33]. The regulation of histone methylation is more complex, with the effects of these modifications depending on the modified site and the degree of methylation. In the postmortem brain tissue of patients with PD, researchers have reported decreased lysine 4 trimethylation of histone H3 (H3K4me3), together with increased H3K27me3 levels. This change is closely related to the abnormal expression of genes associated with neurodegeneration. Epigenetic dysregulation of α -Syn plays a key role in PD, with *SNCA* promoter analyses conducted using the ENCODE database revealing the presence of abundant histone post-translational modifications (PTMs), including transcription-promoting markers H3K4me3 and H3K27ac, as well as inhibitory H3K27me3 [34]. However, the current conclusion is still in the research stage and has not been more accurately verified in clinical trials.

PD pathogenesis is also shaped by an imbalance in the activity of histone methyltransferases (HMTs) and demethylases (HDMs), which are key enzymes that regulate chromatin dynamics and gene expression by adding and removing methyl groups from histones [35]. H3K27me3 modifications have been found to be crucial for activating microglial polarization. Reductions in the level of JMJD3, an important HDM, in microglia lead to elevated H3K27me3 levels, driving the polarization of these cells (Fig. 2), and simultaneously intensifying the inflammatory response, leading to extensive neuronal death [36]. Furthermore, recent mechanistic studies have revealed that pathological α -Syn aggregates, including preformed fibrils, can directly trigger the upregulation of euchromatic histone methyltransferases 1 and 2 (EHMT1/2). This overactivation dramatically increases the levels of repressive H3K9 dimethylation (H3K9me2) at the promoters of crucial synaptic-related genes (e.g., *SNAP25*, *PSD95*, and *SYN1*). *In vitro* experiments indicate that the HMT-

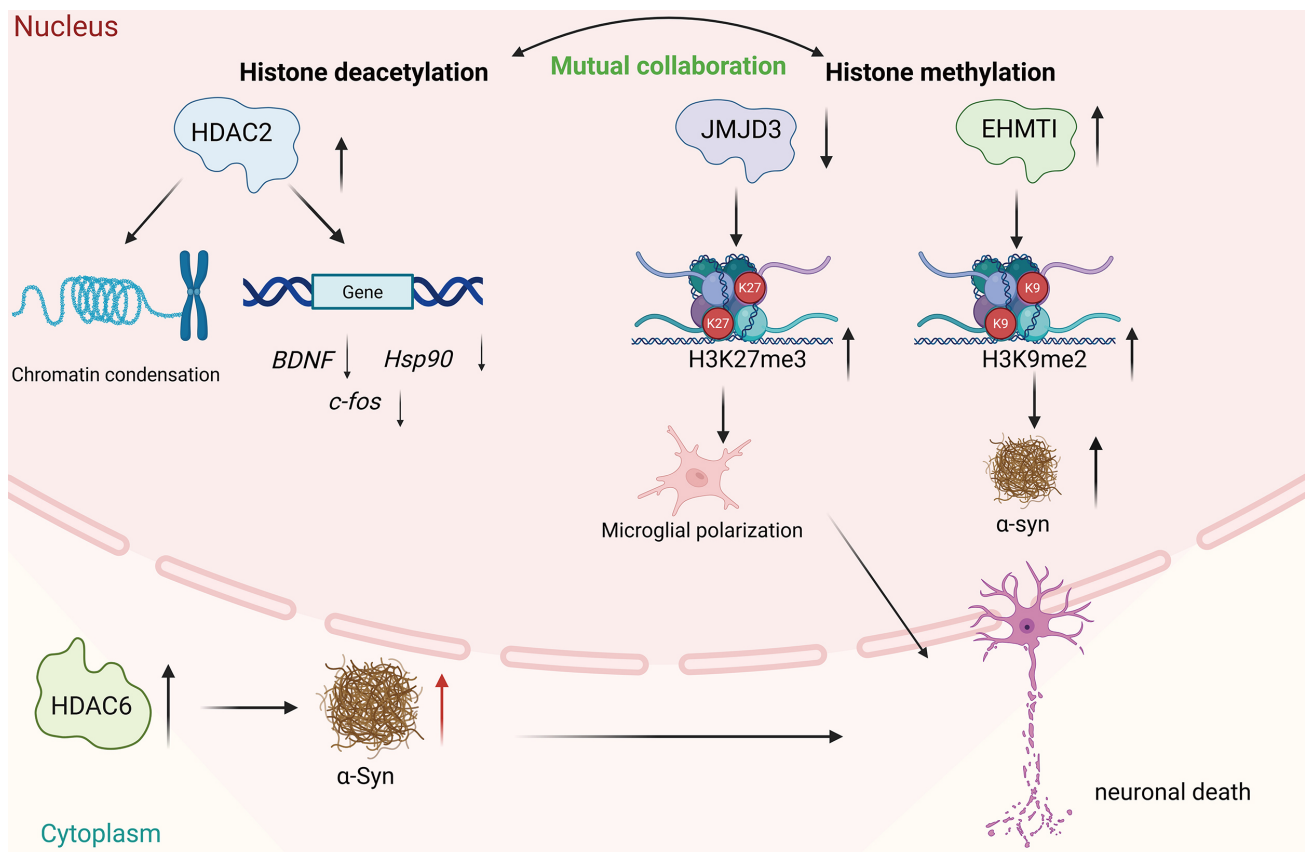


Fig. 2. The impact of the interaction between histone deacetylation and histone methylation on PD. HDAC2 suppresses the expression of genes encoding BDNF, Hsp90, and c-fos, while HDAC6 activation promotes α -Syn aggregation and aberrant degradation. Concurrently, decreased levels of histone demethylases (HDMs) such as JMJD3 increase H3K27me3 levels and activated histone methyltransferases (HMTs) including EHMT1 elevate H3K9me2 levels, worsening microglial activation and α -Syn accumulation. This synergistic interplay between histone deacetylation and methylation ultimately exacerbates PD pathogenesis. Figure created with BioRender.com (MG29P99L8R). BDNF, brain-derived neurotrophic factor; EHMT1, euchromatic histone lysine methyltransferase 1; H3K27me3, trimethylation of histone H3 lysine 27; H3K9me2, dimethylation of histone H3 lysine 9; HDAC, histone deacetylase; Hsp90, heat shock protein 90; JMJD3, Jumonji domain-containing protein 3; α -Syn, α -synuclein. Upward arrow means upregulation and down arrow means downregulation.

mediated epigenetic repression of these structural proteins may contribute to synaptic stripping and subsequent motor impairment [37]. Rather than simply responding to neurodegeneration, HMTs thus actively propagate synaptic failure and neurotoxicity in PD. Crucially, direct validation of these specific HMT-driven pathways in human clinical cohorts or post-mortem patient brain tissues remains currently unavailable, highlighting a critical translational gap that warrants cautious interpretation regarding human pathophysiology. Increasing evidence indicates that epigenetic dysregulation interacts with glial-mediated inflammatory pathways in PD. Microglia and astrocytes respond to α -synuclein accumulation and contribute to neuroinflammatory cascades, suggesting that immune-related epigenetic remodeling represents an important component of PD progression [38].

Crucially, histone modifications do not function as isolated biochemical events in the pathogenesis of PD;

rather, they are deeply integrated with DNA methylation and non-coding RNA (ncRNA) networks, forming a highly cooperative epigenetic interactome [39]. Indeed, chromatin architecture is strongly shaped by bidirectional crosstalk between histone modifications and DNA methylation. Mechanistically, DNA methylation acts as a molecular beacon to recruit specific histone-modifying enzymes. For instance, methyl-CpG-binding domain proteins, such as MeCP2, bind to methylated CpG dinucleotides and directly recruit HDAC complexes to the promoter regions [40]. This synergistic action tightly locks the chromatin in a transcriptionally silenced state. In PD, the uncoupling of this synergistic regulation triggers aberrant gene expression. A classic example of such an effect occurs at the *SNCA* gene promoter, where disease-associated DNA hypomethylation is frequently accompanied by a pathological increase in histone acetylation (e.g., H3K27ac and H3K9ac). This breakdown of normal epigenetic crosstalk simultaneously re-

moves dual repressive constraints, which appears to actively facilitate the pathological overexpression of α -Syn [41,42,43,44]. Accumulating evidence indicates that lncRNAs can act as scaffolds by providing binding surfaces to enable the assembly of selective histone-modifying enzymes, thereby specifying patterned histone modifications at target genes [45]. A holistic understanding of the epigenetic landscape of PD, therefore, necessitates deciphering this multidimensional crosstalk wherein DNA methylation establishes the foundation, histone PTMs dynamically alter chromatin structure, and ncRNAs orchestrate targeting activity.

2.3 Regulatory Roles of Non-Coding RNAs

As important participants in epigenetic regulation, ncRNAs play a key role in the occurrence and development of PD through multiple mechanisms [46,47]. The ncRNA regulatory network is extremely complex, as a single ncRNA can target multiple genes, while a single gene can also be regulated by multiple ncRNAs. These intricate regulatory interactions may become systemically dysregulated in PD, leading to abnormal activation or inhibition of disease-related pathways. In-depth analyses of ncRNA-related epigenetic regulation in PD can thus offer insight into the disease, while also informing the development of ncRNA-based diagnostic and therapeutic strategies.

2.3.1 microRNAs

microRNAs (miRNAs) are a class of small ncRNAs approximately 22 nucleotides in length that inhibit gene expression by targeting the 3'-untranslated regions (UTRs) of target mRNAs. In recent years, a large number of studies have shown that abnormal miRNA expression profiles are closely related to PD. The dysregulated miRNA transcriptome in PD predominantly converges on a highly integrated regulatory network that governs core pathogenic cascades, including α -Syn proteostasis, mitochondrial integrity, and neuroinflammation. As a representative example, brain-enriched miRNAs, including miR-7 [48] and miR-153 [49,50], serve as primary epigenetic gatekeepers by directly binding to the *SNCA* transcript, thereby playing a key role in attenuating the synthesis and neurotoxicity of α -Syn. In addition to these direct effects, there is also parallel evidence that miRNAs indirectly modulate α -Syn clearance. For instance, the increased expression of miR-224, miR-379, and miR-26b in human neuroblastoma SH-SY5Y cells impairs chaperone-mediated autophagy by decreasing the expression of essential components, including LAMP-2A and Hsc70, synergistically exacerbating the accumulation of α -Syn. While these *in vitro* cellular findings elegantly elucidate potential downstream regulatory pathways, SH-SY5Y cells possess a distinct transcriptomic background compared to mature human dopaminergic neurons. Consequently, robust validation in human-derived biological samples or induced pluripo-

tent stem cell (iPSC)-derived dopaminergic neurons is required to confirm whether this specific miRNA-mediated autophagic impairment mirrors the actual pathological processes in human PD patients (Fig. 3) [51]. Furthermore, miRNAs function as crucial upstream modulators involved in gene-environment interactions. Studies have shown that in PD-associated brain samples, pronounced miR-34b/c downregulation leads to a decrease in the expression of DJ-1 and Parkin, triggering downstream transcriptomic changes linked to mitochondrial dysfunction and oxidative stress, ultimately impairing cellular viability (Table 1, Ref. [48,49,50,51,52,53,54,55,56,57,58,59,60]).

2.3.2 Long Non-Coding RNAs

Long non-coding RNAs (lncRNAs) have also been confirmed to participate in the epigenetic regulation of PD through multiple mechanisms, although the current understanding of their functional research is still relatively limited in scope. Current functional studies suggest a universal paradigm where lncRNAs predominantly act as competing endogenous RNAs (ceRNAs), effectively serving as molecular sponges to sequester specific miRNAs, thereby alleviating their inhibitory effects on downstream target genes. Of these ncRNAs, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) has been identified as a core lncRNA involved in a range of pathways, including selective splicing, transcriptional regulation, and post-transcriptional regulation. Functioning as a broad-spectrum miRNA sponge (Fig. 3), MALAT1 engages in cross-talk with various environmental stress-induced signaling cascades. Multiple pieces of evidence suggest that it may be involved in various PD-related mechanistic processes, including the disruption of α -Syn homeostasis, apoptosis, autophagy, and neuroinflammation (Table 1) [53].

2.3.3 Other ncRNAs

In addition to miRNAs and lncRNAs, the roles of other types of ncRNAs in PD have begun to be documented, including circular RNAs (circRNAs) and piwi-interacting RNAs (piRNAs) (Table 1) [61,62]. Characterized by their covalently closed continuous loop structures, circRNAs exhibit remarkable transcriptomic stability against exonuclease degradation, making them robust epigenetic regulators and potential biomarkers for the diagnosis of PD [54]. Mechanistically, circRNAs also integrate into the RNA regulatory network to orchestrate PD pathology [55]. For example, overexpression of circ_0005654, which serves as a molecular sponge for miR-588, can simultaneously enhance the synthesis of α -Syn and inhibit its degradation (Fig. 3) [56].

piRNAs are small single-stranded ncRNAs ranging from 20 to 31 nucleotides that are derived from multiple genomic loci and function to safeguard genomic integrity by mediating transposon silencing [57]. In human studies, analysis of post-mortem brain tissues has revealed that

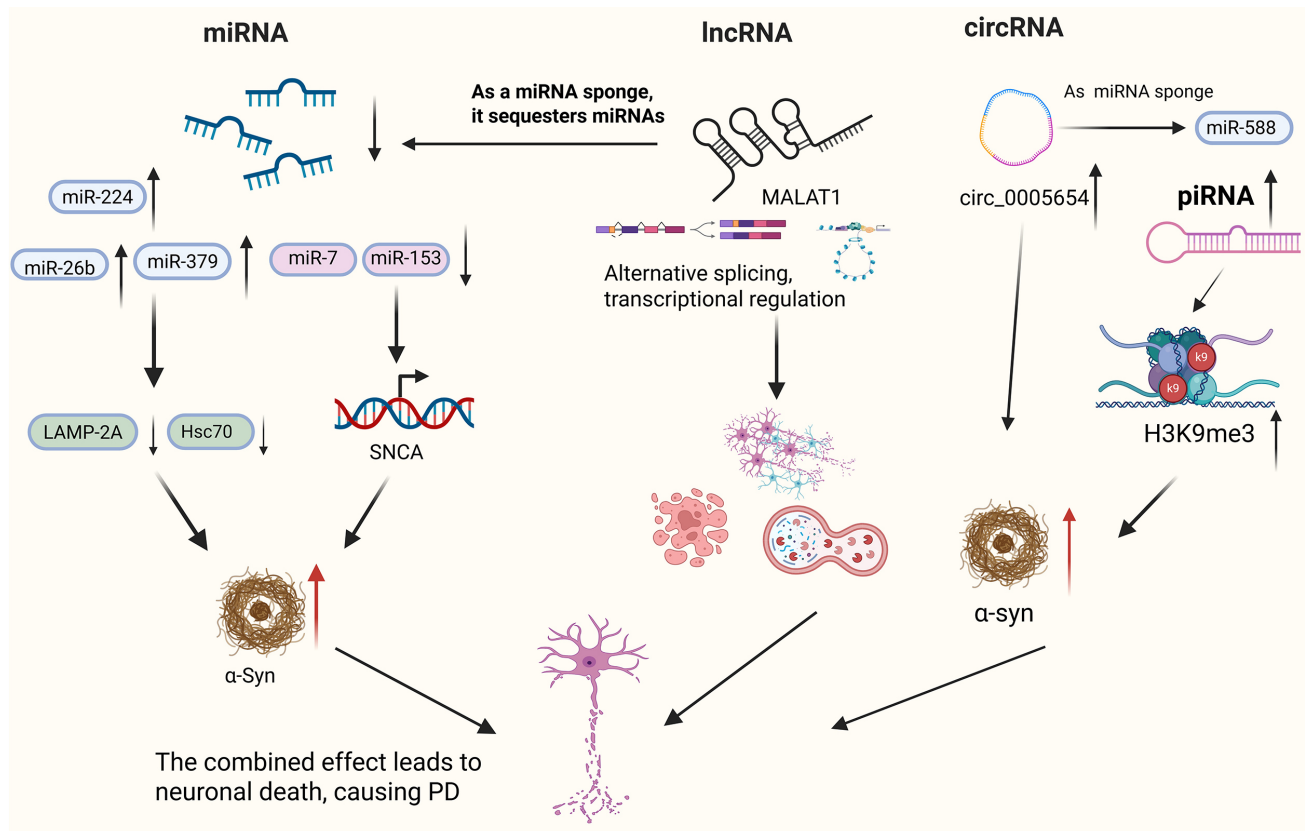


Fig. 3. Regulatory roles of ncRNAs in PD. Downregulation of miR-7 and miR-153 reduces their binding to *SNCA* transcripts, attenuating the repression of α -Syn synthesis. Conversely, upregulated miRNAs (e.g., miR-224, miR-379, and miR-26b) decrease LAMP-2A and Hsc70 expression, impairing chaperone-mediated autophagy and hindering α -Syn clearance. Furthermore, the lncRNA MALAT1 modulates transcription and alternative splicing, acting as a molecular sponge to inhibit miRNA functions. Similarly, overexpressed circ_0005654 (a miR-588 sponge) and elevated levels of piRNAs collectively promote α -Syn accumulation. Figure created with BioRender.com (PZ2A9PPOQR). circRNA, circular RNA; H3K9me3, trimethylation of histone H3 lysine 9; Hsc70, heat shock cognate 70-kDa protein; LAMP-2A, lysosome-associated membrane protein type 2A; lncRNA, long non-coding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; miRNA, microRNA; ncRNA, non-coding RNA; piRNA, PIWI-interacting RNA; α -Syn, α -synuclein. Upward arrow means upregulation and down arrow means downregulation.

piRNA expression is elevated during the late motor stages of PD [58]. *In vitro* cellular studies have further indicated that in sporadic PD patient-derived neurons, piRNA dysregulation impairs the epigenetic silencing of retrotransposons such as SINEs and LINEs, leading to the repression of metabolic target genes, including *PPARGC1A* [63]. *In vivo*, *C. elegans* models overexpressing human α -Syn demonstrate that dysregulated piRNAs interact with RNA-binding proteins (e.g., tdp-1) to influence neurodegeneration [59]. Mechanistically, inhibiting piRNA synthesis reduces the levels of repressive histone methylation (e.g., H3K9me3). This alteration in chromatin state reactivates protein degradation systems, facilitating the clearance of α -Syn aggregates and improving motor phenotypes [58]. Collectively, piRNAs participate in PD epigenetic regulation primarily by affecting transposon silencing and histone modification pathways.

3. Environmental Factors Influence the Risk of PD Through Epigenetic Mechanisms

3.1 Chemical Substance Exposure and Epigenetic Alterations

Exposure to environmental chemicals is an important risk factor for the onset of PD, and epigenetic mechanisms are regarded as the key bridge connecting environmental exposure and abnormal gene expression.

3.1.1 Pesticide Exposure

Pesticide exposure, especially to organochlorine pesticides and pyrethroid pesticides, has been confirmed in multiple epidemiological studies to be associated with an increased risk of PD [64,65]. Mechanistically, rather than simply inducing general cytotoxicity, these environmental toxicants actively remodel the cellular epigenome, triggering intracellular oxidative stress and mitochondrial dysfunction, which serve as upstream

Table 1. Key non-coding RNAs and their functional effects in the pathogenesis of PD.

ncRNA type	Specific ncRNA	Target/Epigenetic mechanism	Pathological effect/Functional outcome
miRNA	miR-7, miR-153	Directly bind to <i>SNCA</i> 3'-UTR [48,49,50]	Repress the synthesis and neurotoxicity of α -Syn; downregulation attenuates this repression [48,49,50]
	miR-224, miR-379, miR-26b	Target essential autophagy components (LAMP-2A and Hsc70) [51]	Impair chaperone-mediated autophagy, synergistically exacerbating α -Syn accumulation [51]
	miR-34b/c	Regulate expression of <i>DJ-1</i> and <i>Parkin</i> [52]	Downregulation triggers downstream transcriptomic changes linked to mitochondrial dysfunction and oxidative stress [52]
	miR-205	Post-transcriptional repression of <i>LRRK2</i> [60]	Promoter hypermethylation causes miR-205 loss, releasing LRRK2 from repression and causing its overexpression [60]
lncRNA	MALAT1	Acts as a broad-spectrum miRNA sponge (ceRNA) [53]	Cross-talks with environmental stress cascades; disrupts α -Syn homeostasis, apoptosis, and neuroinflammation [53]
circRNA	circ_0005654	Functions as a molecular sponge for miR-588 [54,55,56]	Enhances the synthesis of α -Syn and simultaneously inhibits its degradation [56]
piRNA	Somatic piRNAs	Mediate transposon silencing; interact with RNA-binding proteins [57,59]	Dysregulation impairs epigenetic silencing of retrotransposons, represses PPARGC1A, and influences neurodegeneration [58,59]

3'-UTR, 3' untranslated region; ceRNA, competing endogenous RNA.

signals to alter the functional state of epigenetic enzymes. Specifically, rotenone treatment has been shown to cause an abnormal increase in the activity of DNA methyltransferases (DNMTs) in the substantia nigra of rats. This toxicant-induced enzymatic shift leads to hypermethylation of the promoter regions of crucial neuroprotective genes such as *PARK2* and *PARK7*, thereby inhibiting their expression [66]. In addition, pesticide exposure can also alter chromatin state by influencing the activity of histone modification enzymes. For instance, rotenone can induce the expression of HDAC2, leading to the silencing of neurotrophic factor genes (Fig. 4) [67]. Furthermore, exposure to the herbicide paraquat impairs total HDAC activity, driving abnormal histone H3 acetylation that specifically activates apoptotic pathways in dopaminergic cells [68]. These pathways collectively highlight how environmental factors compromise neuronal survival by persistently altering epigenetic markers (Table 2, Ref. [26,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90]).

3.1.2 Heavy Metal Exposure

Heavy metal exposure is also an important environmental risk factor for PD [91]. Manganese (Mn) exposure is particularly closely associated with PD-like neuropathy [92]. Studies have found that long-term manganese exposure can lead to alterations in genome-wide DNA methylation patterns, especially in the promoter regions of genes

related to oxidative stress and apoptosis (Table 2) [69]. Elevated Mn levels in mitochondria restrict oxidative respiration, leading to ROS production and ultimately inducing mitochondrial dysfunction [70]. The potential of Mn to enhance oxidative stress arises from the change in its oxidation state from Mn^{2+} to Mn^{3+} , which further enhances its pro-oxidative properties [93] and triggers α -Syn aggregation [94]. Accumulation of Mn in neurons primarily occurs in the globus pallidus of the basal ganglia, the substantia nigra, and the subthalamic nucleus, followed by the striatum, leading to progressive neuronal degeneration [95]. These studies suggest that manganese can affect the risk of PD through distinct epigenetic mechanisms, and the clarification of these mechanisms is of great significance for the prevention of PD related to occupational and environmental heavy metal exposure (Fig. 4).

3.1.3 Air Pollution

Particulate Matter 2.5 (PM2.5, with a diameter of less than 2.5 micrometers) exposure can induce epigenetic changes, such as DNA hypomethylation, which may be involved in the pathogenesis of certain CNS injuries [70]. Analyses of human blood samples have shown that PM2.5 exposure inhibits the normal binding of DNMTs to DNA, leading to hypomethylation of cytosine residues at CpG sites and alterations in the DNA methylation machinery (Table 2) [71]. Furthermore, in animal models, PM2.5 exposure has been found to exacerbate dopaminergic neu-

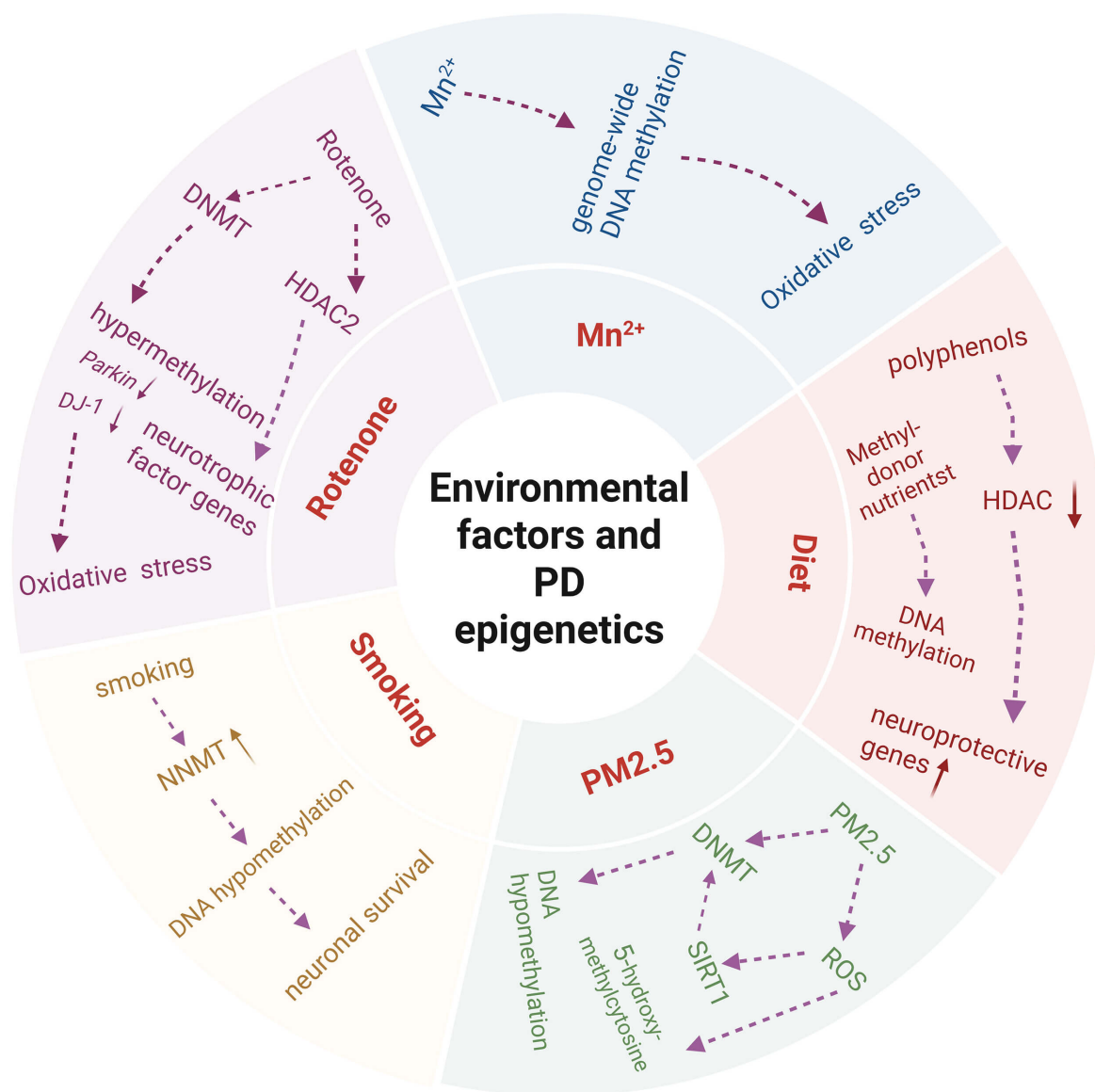


Fig. 4. Environmental factors and epigenetic regulation of PD. Rotenone overactivates DNMTs and HDAC2, hypermethylating the promoters of the genes encoding Parkin and DJ-1 and silencing neurotrophic genes. Chronic manganese exposure alters genome-wide DNA methylation, triggering oxidative stress. PM2.5 exposure drives DNA hypomethylation by inducing oxidative stress, oxidizing 5-hmC, and impairing DNMT binding. ROS biogenesis further alters methylation levels by promoting SIRT1-DNMT1 interactions. These effects can also be modulated by lifestyle factors, as dietary methyl donors regulate methylation via one-carbon metabolism, polyphenols upregulate neuroprotective genes by inhibiting HDACs, and smoking upregulates NNMT, causing DNA hypomethylation that may increase neuronal survival. Figure created with BioRender.com (AA29P9B6LI). DNMT, DNA methyltransferase; DNMT1, DNA methyltransferase 1; NNMT, nicotinamide N-methyltransferase; PM2.5, particulate matter with an aerodynamic diameter of ≤ 2.5 μm ; SIRT1, sirtuin 1.

ron loss through the downregulation of the genes encoding PINK1 and DJ-1 due to CpG hypermethylation [26]. These findings highlight the association between PM2.5 exposure and epigenetic changes in PD (Fig. 4).

3.2 Epigenetic Regulatory Roles of Lifestyle Factors

Lifestyle factors are also closely related to PD pathogenesis, highlighted the promise of lifestyle factors as mod-

ifiable environmental exposures capable of influencing the risk of PD through epigenetic mechanisms.

3.2.1 Diet

Diet is a key lifestyle factor with epigenetic regulatory effects relevant to the prevention of PD [96]. Studies have shown that multiple dietary components can regulate gene expression by influencing the activity of epigenetic mod-

Table 2. Environmental exposures and associated epigenetic alterations in PD.

Environmental factor	Specific agents	Principal epigenetic alterations	Downstream functional consequences
Pesticides	Rotenone	Overactivates DNMTs; induces HDAC2 expression [66,67]	Hypermethylation of <i>PARK2</i> and <i>PARK7</i> (<i>DJ-1</i>) promoters; silencing of neurotrophic factors [66,67]
	Paraquat	Impairs total HDAC activity [68]	Drives abnormal histone H3 acetylation, activating apoptotic pathways in dopaminergic cells [68]
Heavy Metals	Manganese (Mn)	Alters genome-wide DNA methylation; disrupts homeostatic histone acetylation [69,84,85,86,87]	Influences genes related to oxidative stress and apoptosis; induces mitochondrial dysfunction [69,70]
Air Pollution	PM2.5	Induces DNA hypomethylation; alters methylation of pro-inflammatory genes [71,88,89,90]	Promotes neuroinflammation and downregulates <i>PINK1</i> and <i>DJ-1</i> via CpG hypermethylation [26]
Diet (Lifestyle)	Folate, Vitamin B12	Alters intracellular SAM availability for DNMTs [72,73]	Hypomethylation of <i>SNCA</i> promoter, leading to α -Syn transcription upregulation [74,75]
	Polyphenols (EGCG)	Acts as a natural inhibitor of specific HDACs (e.g., HDAC6) [76,77,78,79]	Disrupts α -Syn the protofibril [79]
Physical Activity (Lifestyle)	Exercise	Elevates beta-HB (HDAC inhibitor); modifies <i>SNCA</i> and <i>GP-NMB</i> methylation [80,81,82,83]	Promotes hyperacetylation of neuroprotective genes (BDNF and GDNF) and mitigates neuroinflammation [80,81]

β -HB, β -hydroxybutyrate; CpG, cytosine-phosphate-guanine; EGCG, epigallocatechin gallate; GDNF, glial cell line-derived neurotrophic factor; SAM, S-adenosylmethionine.

ification enzymes or the availability of substrates. For instance, methyl-donor micronutrients such as folate, vitamin B12, and choline are essential precursors in the one-carbon metabolism cycle. This pathway is critical for the synthesis of S-adenosylmethionine (SAM), the primary methyl donor for DNMTs. A dietary deficiency in these precursors can diminish the intracellular SAM pool, thereby restricting substrate availability for DNMTs and potentially leading to altered maintenance of DNA methylation [72,73]. In the context of PD, this metabolic restriction has been associated with the hypomethylation of the *SNCA* promoter, which may contribute to the upregulation of α -Syn transcription [74,75]. Certain plant-derived polyphenols, such as epigallocatechin gallate (EGCG), have also been shown to exhibit inhibitory effects on specific chromatin-modifying enzymes, particularly HDACs, within *in vitro* screening assays and preclinical rodent models. Mechanistically, EGCG can competitively bind to the zinc-dependent catalytic pocket of HDACs, attenuating their enzymatic activity [76,77,78]. By inhibiting cytoplasmic HDAC6, EGCG may help preserve α -tubulin acetylation in a process thought to facilitate microtubule-dependent autophagic flux (Table 2). Consequently, this may aid in the lysosomal clearance of α -Syn aggregates, potentially mitigating neurotoxicity. Although these mechanistic extrapolations offer a compelling theoretical basis for nutritional epigenetics, current evidence remains largely confined to cellular

and animal models. The clinical translation of these findings is severely limited by human pharmacokinetic barriers, and definitive evidence from human clinical trials, demonstrating that dietary polyphenols can induce direct epigenetic modifications in the brains of PD patients is currently lacking (Fig. 4) [79].

3.2.2 Physical Activity

Physical activity serves as a systemic physiological stressor capable of profoundly remodeling the neuro-epigenome, effectively translating mechanical and metabolic exertion into neuroprotective chromatin alterations. Mechanistically, prolonged exercise drives the robust systemic production of specific intermediate metabolites, including β -hydroxybutyrate (β -HB) and lactate, which readily cross the blood-brain barrier (BBB) to act as potent endogenous epigenetic modulators. Specifically, β -HB functions as a direct, natural inhibitor of class I HDACs. By actively suppressing HDAC activity in the brain, exercise-induced β -HB promotes a transcriptionally permissive state (hyperacetylation) at the promoters of critical neuroprotective genes (*BDNF*, *GDNF*) [80,81]. This targeted epigenetic remodeling directly facilitates synaptic plasticity and dopaminergic neuron survival in PD models. Furthermore, physical exertion dynamically shifts homeostatic DNA methylation, likely by modulating the intracellular availability of one-carbon metabolites and alter-

ing the catalytic efficiency of DNMTs and TET enzymes in response to metabolic demand [97]. Clinical epigenomic profiling substantiates this mechanism, demonstrating that sustained exercise significantly modifies the methylation landscape of specific PD-associated risk loci. For instance, physical activity induces targeted DNA methylation changes at the *SNCA* intron 1 (*SNCAII*) [82] and appears to remodel the methylation status of the *GPNMB* locus (e.g., CpG site cg17274742), a critical neuro-immune modulator [83]. By biochemically fine-tuning the epigenetic signatures of these pathogenic targets, exercise establishes a resilient chromatin environment that actively mitigates neuroinflammation and synucleinopathy (Table 2).

3.2.3 Smoking

There is a large amount of epidemiological data supporting a so-called “smoking paradox” associated with the pathogenesis of PD [98,99,100,101], with nicotine potentially reducing the risk of developing PD through epigenetic mechanisms. Some evidence showed that nicotine may function as a robust pharmacological epigenetic modulator. Systemic nicotine exposure may influence the neuronal chromatin landscape by inhibiting HDAC activity, thus potentially shifting the epigenetic balance toward histone acetyltransferase (HAT)-mediated hyperacetylation [102]. This transcriptionally permissive chromatin state is not stochastic; rather, it is highly targeted toward crucial neuroprotective loci. Specifically, chronic nicotine exposure induces persistent and localized epigenetic remodeling at the promoter regions of key neurotrophic genes, such as BDNF, establishing a stable, highly acetylated, and transcriptionally active configuration [103]. In the context of PD, this coordinated epigenetic transition ensures the sustained overexpression of BDNF and other essential survival factors. Consequently, this persistent neurotrophic signaling may enhance the resilience of dopaminergic neurons against pathological stressors and preserve striatal synaptic plasticity, potentially offering an epigenetic and molecular basis for the epidemiological observation that tobacco exposure reduces PD risk.

Epidemiological studies have consistently reported an inverse association between tobacco consumption and PD risk. However, it is imperative to emphasize that this statistical correlation does not imply causality, nor does it provide any clinical justification for tobacco use. Tobacco consumption is well-established as a major risk factor for various life-threatening pathologies, including cardiovascular diseases and numerous malignancies. Critically, there is currently no clinical or translational evidence to advocate for smoking or nicotine administration as a therapeutic or preventative strategy for PD.

4. Epigenetic Regulation of Key PD-Associated Genes

Epigenetic research has revealed that PD-related genes, including *SNCA*, *PARK2*, *DJ-1*, *LRRK2*, *MAPT* [104], and *GBA* [105], are subject to epigenetic regulation. This section focuses on the epigenetic regulatory mechanisms of several key genes in PD (Table 3, Ref. [19,34,69,72,73,74,75,76,77,83,97,98,103,104,105]).

4.1 *SNCA*

The precise epigenetic regulation of the *SNCA* gene is pivotal, as its aberrant transcriptional activation may contribute to α -Syn accumulation. Current evidence explicitly links environmental neurotoxin exposure to the dysregulation of *SNCA* through targeted epigenetic shifts. In human epidemiological and post-mortem studies, specific hypomethylation of *SNCA* regulatory regions (such as intron 1) has been observed in the brains and peripheral blood of PD patients with a history of pesticide exposure [106]. In *in vitro* and animal models, exposure to mitochondrial complex I inhibitors such as rotenone directly impairs DNMT function. This functional deficit is thought to guide the direction of epigenetic changes by promoting targeted hypomethylation of the *SNCA* promoter, an event highly correlated with the pathological overexpression of α -Syn.

In addition to their effects on DNA methylation, environmental toxins also disrupt the histone landscape to synergistically upregulate *SNCA*. Specifically, in experimental models, exposure to neurotoxins (e.g., MPTP/MPP⁺ and rotenone) alters cellular metabolites such as the NAD⁺/NADH ratio. This metabolic shift functionally inhibits the activity of metabolite-dependent HDACs (e.g., sirtuins), leading to a pathological accumulation of activating histone marks, such as elevated H3 acetylation at the *SNCA* promoter, thereby hyperactivating gene transcription [6,106,107,108]. While modulating the *SNCA* histone landscape presents a theoretical strategy to reduce α -Syn expression [34], a critical evaluation reveals that most definitive mechanistic evidence originates from highly controlled cellular models. Consequently, extrapolating these specific epigenetic dynamics to the complex, multifactorial etiology of human PD requires cautious interpretation.

4.2 *PARK2*

In addition to *SNCA*, emerging evidence has demonstrated that other PD-associated genes are subject to epigenetic regulation, contributing to the disease’s pathogenesis. The *PARK2* gene encodes the Parkin protein, which is an E3 ubiquitin ligase that plays a core role in mitochondrial autophagy, mitochondrial biogenesis, and the maintenance of mitochondrial homeostasis [109]. Homozygous or compound heterozygous *PARK2* mutations are the main cause of early-onset autosomal recessive PD [110]. However, an increasing body of evidence indicates that in sporadic PD patients without known genetic mutations, the

Table 3. Epigenetic modification of key genes related to PD.

Gene	Core function	The relevant epigenetic mechanisms	Reference
<i>SNCA</i>	α -synuclein production	DNA hypomethylation, histone acetylation, miRNA regulation	[34,72,73,74,75,76,77]
<i>PARK2/DJ-1</i>	Mitochondrial quality and antioxidant	Promoter methylation and induction of oxidative stress-related epigenetic changes	[19,83,97,98]
<i>LRRK2</i>	Kinase signaling, membrane transport	Promoter methylation as an upstream signal of epigenetics	[69,103]
<i>MAPT</i>	Tau protein pathology	Haplotype-specific methylation	[104]
<i>GBA</i>	Degradation of glycolipids	DNA methylation	[105]

function of *PARK2* may also be dysregulated through epigenetic mechanisms, with environmental factors potentially acting as modulators for these alterations. In human clinical research, genome-wide methylation analysis was conducted on blood and saliva samples from individuals with a history of long-term caffeine intake. CpG residues identified in these individuals were located proximal to genes associated with familial PD, including *GBA*, *PARK2*, and *PINK1* [111]. Environmental factors have predominantly been found to impact the *PARK2* gene via inducing the hypomethylation of its promoter, with patients affected by early-onset PD exhibiting significantly lower levels of *PARK2* promoter methylation as compared to healthy controls [112]. However, DNA methylation patterns in peripheral blood or saliva samples do not offer direct insight into the true epigenetic pathological state within the central nervous system, particularly in the dopaminergic neurons of the substantia nigra.

4.3 *DJ-1*

The *DJ-1* (*PARK7*) gene is another important recessive PD pathogenic gene. *DJ-1* exerts neuroprotective effects through multiple mechanisms, including antioxidant activity and the regulation of mitochondrial function [112,113,114,115]. Because monogenic PD cases driven by *DJ-1* mutations are exceedingly rare, establishing robust cohorts to study non-genetic modifiers remains challenging [105]. However, there is evidence that hypermethylation of the promoter region of the *DJ-1* gene is associated with an increased risk of PD. In a related animal model hypermethylation of *DJ-1* has been observed [26]. This epigenetic alteration can lead to a decrease in *DJ-1* protein expression and weaken the antioxidant capacity of cells [26]. Due to the extreme rarity of monogenic PD cases driven by *DJ-1* mutations and the consequent lack of sufficient clinical samples, the specific mechanisms by which *DJ-1* influences PD remain to be elucidated.

4.4 *LRRK2*

As the most common pathogenic gene in cases of autosomal dominant PD, the epigenetic regulation of the *LRRK2* gene in sporadic PD has also begun to attract attention. Although *LRRK2* gene mutations primarily give

rise to familial PD, the expression of this gene is also dysregulated in sporadic PD patients [116]. From an epidemiological perspective in human cohorts, caffeine intake exhibits a significant gene-environment interaction in carriers of the *LRRK2* Arg1628Pro mutation. Specifically, human clinical data indicate that caffeine consumers carrying this mutation have a lower risk of PD compared to non-consuming carriers, with this effect being partly attributed to trigonelline, an alkaloid found in coffee [117]. However, a critical evaluation of available human data indicates that, while a gene-environment interaction is evident, direct evidence specifically linking caffeine's protective effect to the epigenetic modulation of *LRRK2* in the human central nervous system remains insufficient and requires further investigation. In contrast, mechanistic insights from *in vitro* cell models provide concrete evidence of epigenetic regulation, specifically via miRNAs. Studies demonstrate that in SH-SY5Y neuroblastoma PD models, the miR-205 promoter region is hypermethylated. The direction of this epigenetic change leads directly to the transcriptional silencing and decreased levels of miR-205 expression. Crucially, treatment with 5-azacytidine—a DNMT inhibitor that induces DNA demethylation—reverses this promoter hypermethylation, restores miR-205 levels, and consequently decreases *LRRK2* expression. Target prediction analysis confirms that the 3'-UTR of *LRRK2* contains specific binding sites for miR-205. Functionally, the overexpression of miR-205 in HEK293T cells directly inhibits both the transcription and translation of *LRRK2*, whereas miR-205 inhibitors elevate *LRRK2* levels [60]. These experimental results elucidate a clear functional effect wherein the hypermethylation-induced loss of miR-205 releases *LRRK2* from post-transcriptional repression, leading to the pathogenic overexpression of the *LRRK2* protein. While reversing this methylation axis represents a highly promising mechanistic pathway *in vitro*, caution is warranted when extrapolating this as an immediately accessible therapeutic target for PD [103]. Indeed, these dynamic cellular findings require rigorous validation in complex *in vivo* mammalian models before therapeutic claims can be substantiated.

Table 4. Comparison of epigenetic modifications in PD across human studies and experimental models.

Epigenetic mechanism	Target	Human studies: source & findings	Animal/ <i>in vitro</i> models: source/findings	Divergence and limits
DNA Methylation	<i>SNCA</i>	Brain Tissue (Substantia Nigra/Frontal Cortex): Global promoter hypomethylation [13,20,21,23,106]. FANS-sorted Neurons: Confirmed neuron-specific hypomethylation [24].	<i>In vitro</i> Cell Models: Exposure to mitochondrial complex I inhibitors (e.g., paraquat, rotenone) directly impairs DNMT function, inducing targeted <i>SNCA</i> hypomethylation. [6,34,106,107,108].	Animal models define the causal link between environment and <i>SNCA</i> dysregulation.
DNA Methylation	<i>PARK2</i>	Peripheral Blood/Saliva: Altered CpGs near <i>PARK2</i> in long-term caffeine consumers [111]. Clinical Patients: Promoter hypomethylation in early-onset PD [112].	<i>In vivo</i> Rat Models: Rotenone treatment induces promoter hypermethylation of the <i>PARK2</i> gene [66].	Directional discrepancies (brain vs. blood) highlight the limits of peripheral biomarkers.
DNA Methylation	<i>DJ-1</i>	Clinical Patient Samples: Promoter hypermethylation, leading to decreased protein expression and attenuated antioxidant capacity [26].	<i>In vivo</i> Rat and SH-SY5Y Cell Models: High PM2.5 exposure induces CpG hypermethylation and downregulates <i>DJ-1</i> expression [26]. Rotenone Models also confirm hypermethylation [66].	High consistency between toxin models and clinical data validates environmental toxicology.
Histone Marks	Multi-gene	PD Patient Brain Tissue: Significantly increased HDAC2/6 activity, inhibiting neurotrophic genes [30,31]. ENCODE Database: Confirmed H3K4me3 and H3K27ac marks on <i>SNCA</i> [34].	Toxin/Exercise Models: HDAC6 in the cytoplasm participates in the pathological process of PD by deacetylating α -tubulin [32,33]. Exercise-induced β -HB inhibits HDACs and activates BDNF [80,81].	Reveals “metabolite-histone” axis, but extrapolation to chronic human PD requires caution.
Crosstalk	<i>LRRK2</i>	Epidemiological Cohorts: Caffeine intake shows a protective gene-environment interaction in <i>LRRK2</i> mutation carriers [117], but lacks direct evidence of central epigenetic mechanisms in humans.	SH-SY5Y Neuroblastoma: Promoter hypermethylation of miR-205 downregulates its expression, releasing post-transcriptional repression on <i>LRRK2</i> and directly causing target protein overexpression [60].	Fills molecular gaps in epidemiology; necessitates <i>in vivo</i> validation.
Non-coding RNA	α -Syn / Transposons (miRNA, piRNA)	Post-mortem Brain Tissue: Significant downregulation of miR-34b/c triggers mitochondrial dysfunction [52]. Abnormally elevated piRNA expression in the brain during late motor stages of PD [58].	<i>In Vitro</i> / <i>C. elegans</i> Models: Elevated miR-224 etc. impair autophagy [51]. piRNA dysregulation impairs the epigenetic silencing of retrotransposons such as SINEs and LINEs, leading to the repression of metabolic target genes including <i>PPARGC1A</i> [63].	Human tissues reflect end-stage changes; models are better for early dynamic evolution.

ENCODE, Encyclopedia of DNA Elements; FANS, fluorescence-activated nuclear sorting; H3K4me3, trimethylation of histone H3 lysine 4; H3K27ac, acetylation of histone H3 lysine 27; LINEs, long interspersed nuclear elements; *PPARGC1A*, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; SINEs, short interspersed nuclear elements.

5. Prevention and Treatment Strategies Based on PD-Related Epigenetics

5.1 Source Control and Risk Assessment for Environmental Exposures

Epigenetic regulation-focused strategies for PD prevention should prioritize source control for relevant environmental exposures. Given that various environmental chemicals can increase the risk of PD through epigenetic mechanisms, reducing or avoiding exposure to these harmful substances is essential for effective primary preven-

tion [7,118]. As a major environmental risk factor for PD, the mitigation of pesticide exposure must be understood through its specific epigenetic impact rather than general toxicity. For instance, exposure to specific pesticides has been mechanistically linked to the aberrant hypomethylation of the *SNCA* promoter and the dysregulation of histone modification, leading to α -Syn accumulation [84,85,119]. The evidence suggests that reducing such exposure during the early stages of this process can halt the progressive accumulation of these adverse epigenetic marks. Therefore,

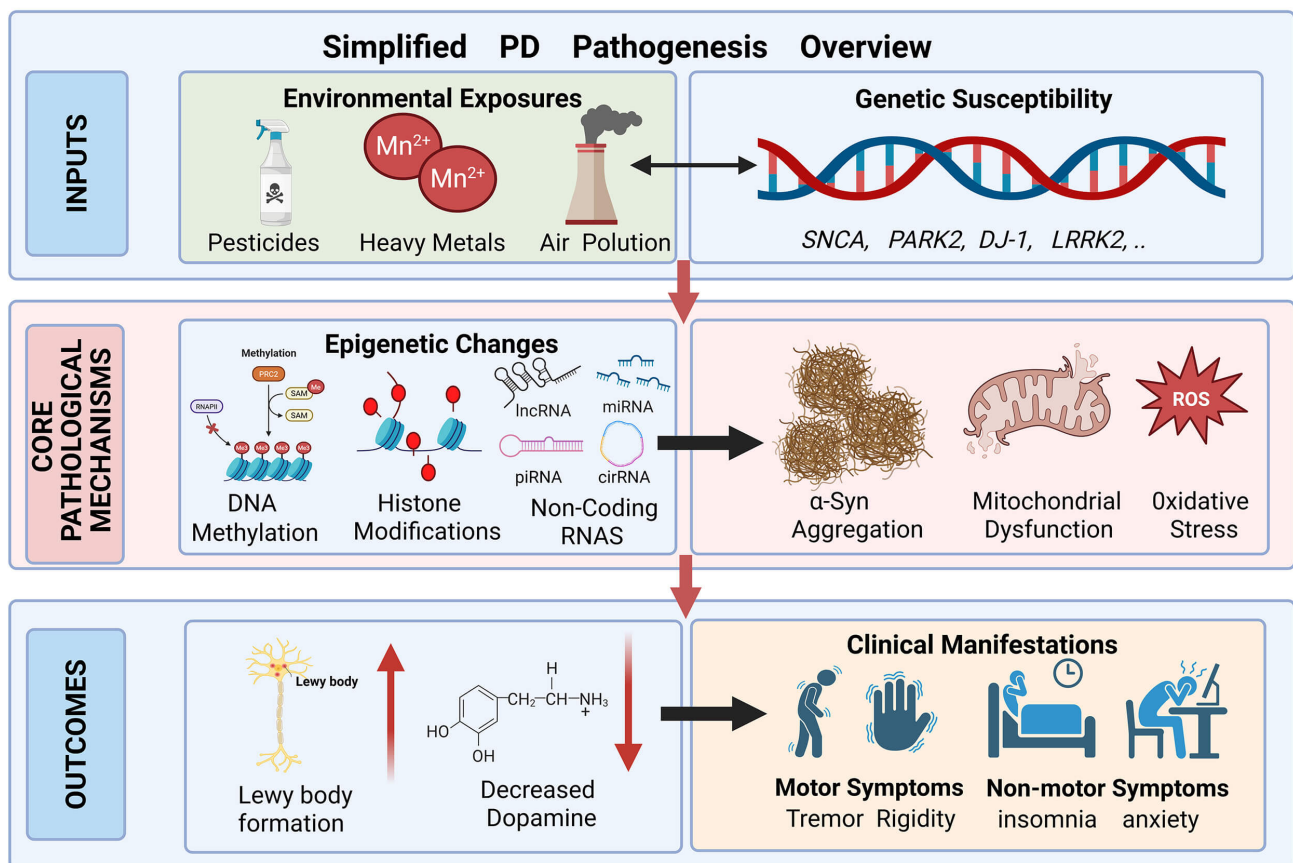


Fig. 5. Schematic overview of gene-environment interactions mediated by epigenetic mechanisms in the pathogenesis of PD. A schematic overview of a proposed three-tiered pathogenic cascade. The upper panel (Inputs) depicts the interplay between environmental exposures (e.g., pesticides, heavy metals like Mn^{2+} , and air pollution) and genetic susceptibility (e.g., mutations in *SNCA*, *PARK2*, *DJ-1*, and *LRRK2*). These upstream factors converge on the central panel (Core Pathological Mechanisms), where epigenetic changes—encompassing DNA methylation, histone modifications, and regulation by non-coding RNAs (lncRNA, miRNA, piRNA, circRNA)—act as crucial molecular interfaces. These epigenetic alterations subsequently dysregulate downstream cellular processes, leading to α -Syn aggregation, mitochondrial dysfunction, and oxidative stress, which mutually exacerbate one another. The lower panel (Outcomes) illustrates the ultimate pathological consequences of these processes in Lewy body formation and decreased dopamine levels, which clinically manifest as both motor symptoms (e.g., tremor, rigidity) and non-motor symptoms (e.g., insomnia, anxiety). Figure created with BioRender.com (DG2A9PQMRH). *LRRK2*, *Leucine-Rich Repeat Kinase 2*; PD, Parkinson's disease; α -Syn, α -synuclein.

avoiding pesticide exposure is not merely a general health precaution, but a targeted approach with the potential to help prevent the initial epigenetic triggers of dopaminergic neurodegeneration.

The control of heavy metal exposure is also an important aspect of PD prevention. Rather than simply addressing general environmental pollution, interventions must focus on the epigenetic consequences of metals like Mn and lead, which are known to disrupt homeostatic histone acetylation and alter the DNA methylation profiles of genes associated with oxidative stress and mitochondrial dysfunction [84,86,87]. Minimizing heavy metal exposure directly limits the environmental induction of these specific epigenetic lesions. Furthermore, for occupationally exposed groups, traditional biological monitoring should ideally incorporate epigenetic biomarkers. This would enable the detection of

early, potentially reversible molecular changes before irreversible neuronal damage occurs.

The control of air pollutants is also of great significance for the prevention of PD. Fine PM_{2.5} and industrial chemicals such as polychlorinated biphenyls can exacerbate PD risk by inducing neuroinflammation through epigenetic dysregulation, including the altered methylation of pro-inflammatory cytokine genes and the disruption of specific microRNA networks [88,89,90]. Experimental evidence indicates that reducing exposure to these airborne neurotoxins can attenuate these adverse epigenetic alterations, thereby suppressing microglial activation. Consequently, limiting exposure to airborne pollutants offers a direct, mechanism-based intervention suitable for helping to maintain the epigenetic stability of the neuro-immune axis [120].

Table 5. Epigenetic therapeutic strategies for PD and their current clinical limitations.

Therapeutic strategy	Specific examples/mechanisms	Intended neuroprotective effects	Current translational limitations & challenges
HDAC Inhibitors	Vorinostat; beta-HB (endogenous via exercise)	Inhibit HDAC activity to increase histone acetylation, activating expression of neuroprotective genes [80,81,132,133,134,135]	High systemic toxicity: Lacks locus specificity, inducing global epigenetic alterations and aberrant gene activation in post-mitotic neurons [136]
DNMT Inhibitors	Azacitidine	Reverse promoter hypermethylation (e.g., restoring miR-205); regulate immune responses [60]	BBB permeability restrictions: Poor delivery into the central nervous system limits efficacy. Broad-spectrum effects cause off-target toxicities [136]
Nutritional Epigenetics	Dietary methyl donors (Folate, Vitamin B12); Polyphenols (EGCG, Resveratrol)	Maintain SAM pool for normal DNA methylation; inhibit HDACs; activate SIRT1 [72,75,128,129]	Bioavailability & Metabolism: Poor systemic bioavailability, rapid metabolic processing, and restricted ability to cross the BBB [121,122]
Targeted Epigenome Editing	CRISPR-dCas9 systems fused with epigenetic effectors	Achieve highly specific locus-targeted correction of PD-associated epigenetic aberrations [137]	Early stage of development: Currently lacks <i>in vivo</i> mammalian validation; complex delivery mechanisms to the human brain are yet to be perfected [136,137]
BBB, blood-brain barrier; CRISPR-dCas9, clustered regularly interspaced short palindromic repeats–catalytically dead CRISPR-associated protein 9.			

The establishment of a risk assessment system for environmental exposure is an important foundation for the prevention of PD. Given that individuals' susceptibility to environmental factors varies and that these differences are partly determined by genetic background and epigenetic status, there is clear value in establishing an environmental exposure risk assessment model based on epigenetic markers. By integrating dynamic epigenetic profiles—such as peripheral blood DNA methylation signatures—with individual environmental exposome data, such a dual-layered system would offer the opportunity to identify vulnerable populations harboring preclinical epigenetic alterations, facilitating precise, customized, and timely intervention prior to the onset of motor symptoms.

5.2 Nutritional Epigenetics and Dietary Interventions

Nutritional epigenetics offers modulatory potential as a means of managing and preventing PD. However, current claims regarding its therapeutic efficacy must be interpreted with caution, as a significant gap remains between preclinical findings and clinical realities [121,122]. The intake of dietary methyl donors is a key factor influencing the DNA methylation status through the generation of SAM, the primary universal methyl donor. Nutrients such as folic acid, vitamin B12, vitamin B6, choline, and betaine are involved in the process of methyl group transfer. Preclinical models have demonstrated that deficiencies in any of these nutrients may lead to global hypomethylation, including the hy-

pomethylation of the *SNCA* promoter, thereby exacerbating α -Syn pathology. While ensuring adequate methyl donor status is theoretically beneficial for maintaining epigenetic homeostasis, robust clinical trials demonstrating that dietary supplementation can effectively reverse established epigenetic aberrations or halt disease progression in human PD patients are currently lacking [123,124].

Polyphenols, as antioxidant compounds widely present in plant-based foods, have attracted growing levels of attention as resources for the prevention of PD due to their epigenetic regulatory effects [125,126]. Beyond their antioxidant effects, natural compounds may also influence PD progression through regulation of inflammatory signaling pathways. For example, luteolin has been reported to protect dopaminergic neurons by suppressing Toll-like receptor 4 (TLR4)-mediated microglial M1 polarization, highlighting the therapeutic potential of targeting neuroimmune mechanisms [127]. *In vitro* and in animal models, polyphenols, such as epigallocatechin gallate (EGCG) and resveratrol, not only possess antioxidant or chelating properties but can also directly interfere with intracellular signal transduction pathways through their interaction with α -Syn and the modulation of its aggregation [128]. Moreover, in animal models, resveratrol has been shown to be a potent activator of the NAD⁺-dependent HDAC SIRT1, alleviating oxidative stress and promoting neuronal survival [129]. Despite these promising results, the clinical efficacy of polyphenols remains severely constrained.

The major barriers to their more widespread utilization in humans include their poor systemic bioavailability, rapid metabolic processing, and restricted ability to cross the BBB.

Omega-3 polyunsaturated fatty acids (ω -3 PUFA) are another dietary component with neuroprotective effects that have begun to attract attention for their epigenetic regulatory effects [130]. ω -3 PUFA intake can inhibit microglial activity and neuroinflammation, protecting the function of astrocytes and enhancing the production of neurotrophic factors to regulate neural transmission and mitigate neurodegeneration. ω -3 PUFA intake may improve PD by inhibiting the release of pro-inflammatory cytokines, promoting the expression of neurotrophic factors, restoring mitochondrial function and membrane fluidity, reducing ROS production, maintaining α -Syn proteostasis, preserving calcium homeostasis, protecting axon transport, and reducing endoplasmic reticulum stress [131]. Foods rich in ω -3 PUFA include deep-sea fish (such as salmon and tuna), flaxseeds, and walnuts. The intake of moderate amounts of these foods may thus help prevent PD.

While precision nutritional interventions based on individual genomic and epigenomic profiles represent a promising theoretical frontier, dietary intervention for PD currently faces critical limitations. Individuals with different genetic backgrounds and epigenetic states exhibit high variability in their nutrient absorption and metabolic profiles. Before translating nutritional epigenetics into clinical practice, future research must prioritize well-designed, large-scale randomized controlled trials. These trials need to utilize advanced delivery systems (e.g., nanoparticles) to overcome bioavailability issues and employ reliable peripheral epigenetic biomarkers to objectively monitor the true disease-modifying effects of dietary interventions in humans.

5.3 Development and Therapeutic Application Prospects of Epigenetic Drugs

The reversibility of epigenetic modifications offers unique opportunities for the treatment of PD, and the development of drugs targeting epigenetic regulation has emerged as a promising new direction for PD drug research and development. However, the development of drugs with targeted epigenetic regulatory activity remains in its infancy and faces formidable translational hurdles. HDAC inhibitors are among the most thoroughly studied epigenetic drugs. They function by increasing histone acetylation levels through the inhibition of HDAC activity, thereby activating the expression of neuroprotective genes [132,133,134]. Currently, HDAC inhibitors, including vorinostat, and drugs that cause DNA hypomethylation, such as azacitidine, have been approved and are used for the treatment of cancer [135]. Similarly, DNMT inhibitors are hypothesized to enhance the survival and function of dopaminergic neurons. By altering the methylation

status of DNA, preclinical studies predominantly utilizing neurotoxin-induced cell cultures and rodent models suggest that DNMT inhibitors may change the expression of pro-inflammatory and anti-inflammatory genes, help regulate immune responses, and potentially reduce neuroinflammation in the brain [14]. However, directly repurposing these broad-spectrum epigenetic modifiers for PD poses severe safety concerns. Unlike actively proliferating cancer cells, neurons are post-mitotic. Systemic administration of these conventional inhibitors lacks locus specificity, inducing global epigenetic alterations that can lead to profound off-target toxicities, including aberrant gene activation and generalized cellular dysfunction. Therefore, a clear distinction must be made between pharmacological efficacy in experimental models and clinical applicability. The neuroinflammatory milieu in human PD is chronically progressive and substantially more complex than the acute toxicity modeled in laboratory settings. To date, there is no verified human clinical data corroborating that systemic administration of DNMT inhibitors yields targeted anti-inflammatory or neuroprotective benefits in PD patients without precipitating severe epigenetic toxicity.

A critical, objective analysis reveals that the clinical translation of current epigenetic drugs remains severely impeded by two major challenges: high systemic toxicity and restricted permeability across the BBB [136]. Consequently, future therapeutic strategies must pivot away from broad-spectrum inhibitors. The field is increasingly focusing on precision tools, such as targeted epigenome editing (e.g., CRISPR-dCas9 systems fused with specific epigenetic effectors) [137]. These advanced modalities aim to achieve locus-specific correction of PD-associated epigenetic aberrations, thereby avoiding global off-target effects and offering a more viable and safer path for disease-modifying therapy.

6. Conclusions, Limitations and Future Prospects

In conclusion, studies in human samples, animals, and *in vitro* models have offered detailed insight into epigenetic modifications in PD (Table 4, Ref. [6,13,20,21,23,24,26,30,31,32,33,34,51,52,58,60,63,66,80,81,106,107,108,111,112,117]). These epigenetic mechanisms serve as a key molecular bridge mediating gene-environment interactions in PD. Rather than acting in isolation, dynamic alterations in DNA methylation, histone modifications, and ncRNA activity coordinately translate environmental exposures into the persistent transcriptional reprogramming of susceptible neurons (Fig. 5). In the near future, however, the field must transition from descriptive associative studies to mechanistic causality in order to translate these insights into viable clinical strategies.

Despite the accumulating evidence linking epigenetic gene-environment interactions to PD, several critical limitations warrant cautious inter-

pretation of the current findings (Table 5, Ref. [60,72,75,80,81,121,122,128,129,132,133,134,135,136,137]). Most epigenetic analyses rely on whole-tissue homogenates or peripheral surrogate tissues, which may not fully reflect the distinct epigenetic landscapes of specific cell types, such as vulnerable dopaminergic neurons, or the complex neurobiological events within the central nervous system. Furthermore, findings are often confounded by inevitable factors including normal aging and long-term pharmacological treatments, making it difficult to isolate disease-specific signatures. The predominantly cross-sectional nature of current evidence also precludes the establishment of definitive temporal links between environmental exposures, epigenetic drift, and PD onset. Moreover, inconsistent methodologies and varied sample sizes across studies have resulted in limited reproducibility among diverse ethnic and genetic cohorts. Therefore, future research, particularly longitudinal cohort studies and the application of single-cell resolution techniques, is essential to delineate cell-type-specific alterations and validate these epigenetic insights for potential clinical translation.

Several key scientific questions remain unresolved, highlighting specific avenues for future research. First, establishing causality is paramount, as it is unclear as to whether the observed epigenetic alterations are a primary driver of PD pathogenesis or merely secondary consequences of neurodegeneration and prolonged pharmacotherapy. To address this, future research must prioritize longitudinal cohort studies integrating multi-omics data (e.g., genomics, epigenomics, and exposomics) with causal inference models, such as Mendelian randomization. Second, overcoming the barrier of cellular heterogeneity is a major research priority. Future investigations should leverage single-cell epigenomic technologies (such as scATAC-seq and single-nucleus DNA methylomics) to systematically dissect cell-type-specific epigenetic vulnerabilities, precisely delineating the distinct epigenetic responses of dopaminergic neurons versus different glial subpopulations under environmental stress.

Furthermore, while the inherent reversibility of epigenetic marks presents an attractive therapeutic target, expectations regarding drug development must be tempered with caution. The transition to clinical application requires overcoming severe limitations related to off-target toxicity and BBB permeability. Therefore, future therapeutic research should pivot away from the use of broad-spectrum epigenetic inhibitors toward the development of highly specific locus-targeted epigenome editing tools (e.g., CRISPR-dCas9 systems fused with epigenetic effectors). Ultimately, only by rigorously addressing these specific scientific challenges can epigenetic insights be reliably translated into viable, safe, and effective disease-modifying strategies for PD management.

Author Contributions

Conceptualization: XZ, JJ, KZ and GC; Writing-original draft: KZ and GC; Software: KZ; Funding acquisition: XZ and JJ; Writing-review and editing: XZ and JJ. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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