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Epigenetic Regulation in Parkinson's Disease: Cutting -Edge Insights into miRNAs, lncRNAs and Chromatin Modifiers

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Abstract **Review Article**

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by dopaminergic neuronal loss and abnormal aggregation of α-synuclein. While genetic mutations contribute to disease susceptibility, accumulating evidence highlights the pivotal role of epigenetic regulation in modulating gene expression and disease progression. The epigenetic mechanisms, including DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA-mediated regulation, dynamically influence neuronal function, neuroinflammation, mitochondrial homeostasis, and protein aggregation in Parkinson's disease. Recent studies have revealed that microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are critical regulators of α-synuclein expression, dopaminergic neuron survival, and inflammatory signaling pathways. In parallel, chromatin modifiers such as histone acetyltransferases and deacetylases orchestrate transcriptional programs that determine neuronal vulnerability and resilience. The intricate crosstalk among miRNAs, lncRNAs, and chromatin-modifying complexes underscores the complexity of epigenetic networks in PD pathogenesis. Furthermore, epigenetic alterations have emerged as promising biomarkers for early diagnosis and disease monitoring, as well as attractive therapeutic targets for disease-modifying interventions. Advances in epigenetic-based therapies, including histone deacetylase inhibitors and RNA-based strategies, offer new opportunities for precision medicine in Parkinson's disease. This review critically summarizes current insights into the roles of miRNAs, lncRNAs, and chromatin modifiers in Parkinson's disease, discusses their potential as biomarkers and therapeutic targets, and highlights key challenges and future perspectives in translating epigenetic discoveries into clinical applications.

Keywords: Parkinson's disease; Epigenetics; microRNAs (miRNAs); Long non-coding RNAs (lncRNAs); Chromatin modifiers; α-Synuclein (SNCA); Neurodegeneration.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide and one of the fastest-growing neurological diseases. In 2023, an estimated 11.67 million people were living with PD globally, with approximately 427,000 deaths attributed to the disease. The age-standardized prevalence rate increased from 93.76 to 128.46 per 100,000 population between 1990 and 2023, reflecting a substantial rise in disease burden. According to the Global Burden of Disease Study 2021, this increase is largely driven by population ageing, and projections suggest that the number of individuals living with PD may reach 25.2 million by 2050[1–3]. Pathologically, PD is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra and the accumulation of α-synuclein-rich Lewy bodies in the brain. Clinically, the disease manifests with motor symptoms including bradykinesia, resting tremor, rigidity, and postural instability, which are often preceded by non-motor symptoms such as sleep disturbances, hyposmia, constipation, and depression [4]. Despite extensive research efforts, currently available therapies, including levodopa, dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors, and catechol-O-methyltransferase (COMT) inhibitors, primarily provide symptomatic relief without altering disease progression[5]. This limitation highlights the urgent need for mechanism-based therapeutic strategies that target upstream molecular processes involved in PD pathogenesis.

Although familial forms account for less than 10% of PD cases, the majority of cases are sporadic and arise from complex interactions between genetic susceptibility and environmental influences [6,7]. Genome-wide association studies have identified numerous risk-associated variants, supporting a multifactorial etiology rather than a purely genetic basis for the disease [8]. In this context, epigenetic regulation serves as a critical interface linking environmental exposures, ageing, and cellular stress to gene expression changes. Epigenetics encompasses heritable alterations in gene expression that occur without changes in the underlying DNA sequence and is mediated by mechanisms such as DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs. Accumulating evidence indicates that epigenetic dysregulation contributes to PD pathogenesis through altered expression of key genes, including alpha-synuclein (SNCA), Microtubule-Associated Protein Tau (MAPT), Parkin RBR E3 Ubiquitin Protein Ligase (Parkin)(PARK2), and Leucine-Rich Repeat Kinase 2 (LRRK2), thereby promoting selective vulnerability of dopaminergic neurons [9]. Importantly, epigenetic abnormalities have been detected during the early stages of PD and are believed to actively drive disease onset and progression through mechanisms that facilitate neuronal dysfunction and loss [10]. The reversible nature of epigenetic modifications further underscores their potential as promising targets for disease-modifying interventions [11].

Therefore, this review provides a comprehensive overview of the emerging roles of microRNAs, long non-coding RNAs, DNA methylation, histone modifications, and chromatin remodelling in the molecular pathogenesis of PD. Furthermore, it examines the interplay among these epigenetic regulators, evaluates their potential as diagnostic and prognostic biomarkers, and discusses innovative therapeutic approaches, including nanotechnology-based drug delivery systems and artificial intelligence-driven multi-omics strategies for precision medicine in Parkinson's disease.

2. Overview of Epigenetic Mechanisms in Neurodegeneration

Epigenetic regulation comprises a group of dynamic and reversible mechanisms that control gene expression without altering the underlying DNA sequence. These mechanisms play essential roles in neuronal development, differentiation, synaptic plasticity, and maintenance of neuronal homeostasis throughout life. Increasing evidence suggests that disruption of epigenetic regulation contributes to the pathogenesis of neurodegenerative disorders, including Parkinson's disease (PD), by influencing pathways involved in α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, and neuronal cell death. Recent advances in epigenomic and multi-omics technologies have further highlighted the importance of epigenetic alterations in disease initiation and progression, making them attractive targets for biomarker discovery and therapeutic intervention [10,12,13] The major epigenetic mechanism involved in neurodegeneration are summarized in Figure 1

The major epigenetic mechanisms involved in neurodegeneration include:

- DNA methylation
- Histone modifications
- Chromatin remodelling
- MicroRNAs (miRNAs)
- Long non-coding RNAs (lncRNAs)
- Crosstalk among epigenetic mechanisms

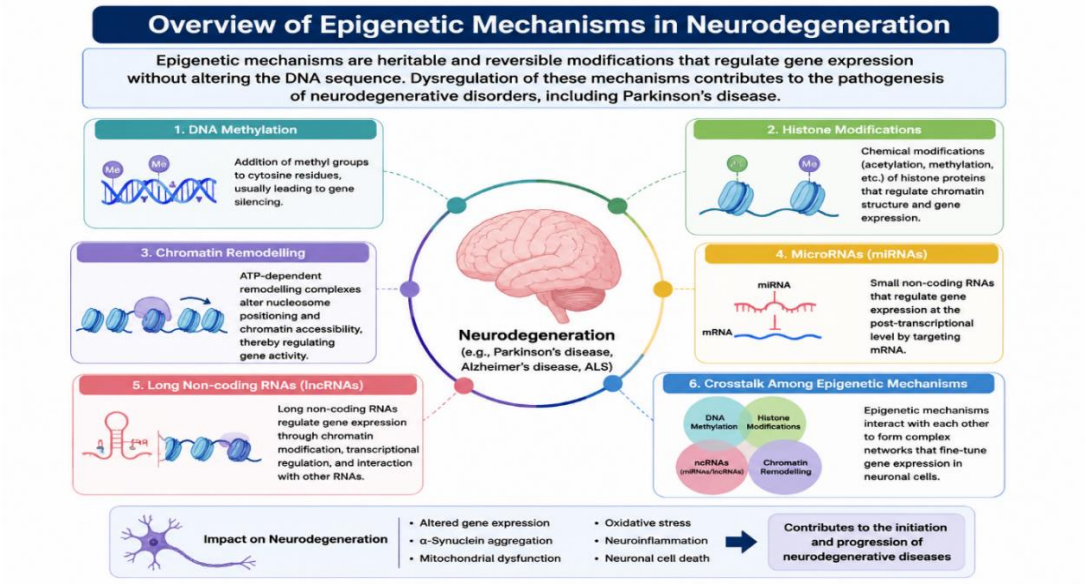

Figure 1: Overview of Epigenetic Mechanisms in Neurodegeneration

3. DNA Methylation in Parkinson's Disease

3.1 DNA Methyltransferases and DNA Methylation in PD

DNA methylation is a significant epigenetic mechanism that regulates gene expression through the addition of methyl groups to cytosine residues, primarily at cytosine-phosphate-guanine sites. Catalyzed by DNA methyltransferases, this process supports normal cellular functions by controlling gene activity. Alterations in DNA methylation patterns have been widely reported in Parkinson's disease, suggesting that epigenetic dysregulation contributes to disease pathogenesis[14].Genome-wide Associations studies have identified abnormal methylation patterns in several genes associated with neuronal function, oxidative stress, and inflammation, indicating that DNA methylation plays a significant role in PD development and progression[15].In addition to DNA methyltransferase (DNMT)-mediated methylation, ten-eleven translocation methylcytosine dioxygenase 2 (TET2) regulates DNA demethylation. Notably, loss of TET2 activity has been shown to exert neuroprotective effects in experimental models of PD, highlighting its potential importance in disease regulation[16]. The key mechanism by which DNA methylation regulates gene expression and contributes to Parkinson`s disease pathogenesis illustrated in Figure 2.

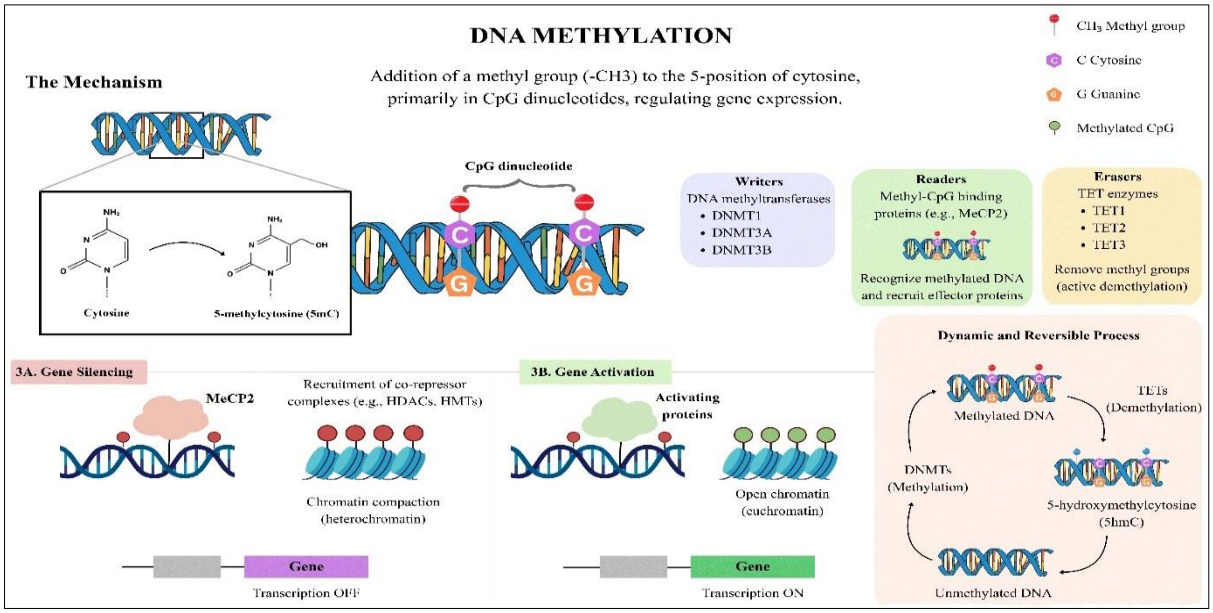

Figure 2: DNA Methylation

3.2 SNCA Gene Methylation

Among the methylation changes reported in PD, alterations in the alpha-synuclein gene (SNCA) are the most consistently observed. The SNCA gene encodes α-synuclein, the major protein component of Lewy bodies, which are pathological hallmarks of PD. Several studies have demonstrated reduced methylation within regulatory regions of SNCA, particularly in intron 1, in brain tissues and peripheral blood samples from patients with PD[17].Hypomethylation of this region is associated with increased α-synuclein expression, which may promote protein aggregation and neuronal toxicity[18].Furthermore, altered methylation of the SNCA promoter has been linked to disease susceptibility and progression, suggesting that SNCA methylation may serve as a potential biomarker for PD[19].

3.3 Environmental Factors Affecting DNA Methylation

Environmental exposures are thought to contribute to PD risk through epigenetic mechanisms, particularly DNA methylation changes. Factors such as pesticide exposure, physical activity, ageing, and other environmental stressors can influence methylation patterns and modify the expression of genes involved in neuronal survival and neurodegeneration[20].Epigenome-wide association studies have identified differentially methylated regions in genes including SLC7A11 (solute carrier family 7 member 11), which encodes a cystine–glutamate antiporter involved in antioxidant defence and cellular redox balance, and other PD-related loci, supporting the interaction between environmental and genetic risk factors in disease development[21].In addition, treatment-related factors may influence DNA methylation profiles. For example, levodopa (L-DOPA), the most commonly used therapy for PD, has been shown to alter DNA methylation patterns, including increased methylation of the SNCA gene, which may affect the interpretation of methylation-based biomarkers in treated patients[22].Emerging evidence also suggests that mitochondrial DNA methylation may contribute to mitochondrial dysfunction in PD, further linking environmental influences, epigenetic regulation, and neuronal degeneration[23].

4. Histone Modifications and Chromatin Remodelling in Parkinson's Disease

4.1 Histone Acetylation, Methylation, histone deacetylases (HDACs) and histone acetyltransferases (HATs)

Histone modifications are important epigenetic mechanisms that regulate gene expression by altering chromatin structure and DNA accessibility. Among these modifications, histone acetylation and methylation are the most extensively studied in Parkinson's disease (PD). Histone acetylation is controlled by histone acetyltransferases (HATs), which generally promote gene transcription, whereas histone deacetylases (HDACs) remove acetyl groups and often suppress gene expression[24].Studies have shown that α-synuclein can interact with histones in the nucleus and disrupt normal histone acetylation, contributing to neuronal dysfunction and toxicity. Altered histone acetylation patterns have also been observed in the brains of patients with PD, indicating widespread changes in transcriptional regulation. In addition, members of the sirtuin family of HDACs play important roles in PD. Sirtuin 2 (SIRT2) has been associated with α-synuclein toxicity, and inhibition of SIRT2 has demonstrated neuroprotective effects in experimental models.In contrast, Sirtuin 1 (SIRT1) appears to protect neurons by reducing oxidative stress and promoting cell survival[25–28].Together, these findings suggest that dysregulated histone modifications contribute to PD pathogenesis and may represent potential therapeutic targets.

4.2 Chromatin Remodelling Complexes

Chromatin remodelling refers to the dynamic reorganization of chromatin structure that regulates the accessibility of DNA to transcription factors and other regulatory proteins. Thisprocess is mediated by ATP-dependent chromatin remodelling complexes, which can reposition or restructure nucleosomes. Among these complexes, the SWI/SNF (switch/sucrose non-fermentable) family plays an important role in neuronal development, differentiation, and maintenance[29].Emerging evidence suggests that abnormalities in chromatin remodelling may contribute to neurodegenerative disorders, including PD, by altering gene expression patterns required for normal neuronal function [30].In addition, defects in chromatin regulatory pathways may disrupt neuronal gene-expression programs and reduce neuronal resilience, thereby contributing to PD progression[31].

4.3 Role of Histone Modifications and Chromatin Remodelling in Neuronal Survival and Inflammation

Proper regulation of histone modifications and chromatin remodelling is essential for neuronal survival and maintenance of cellular homeostasis. In PD, epigenetic alterations can affect the expression of genes involved in neuronal protection, mitochondrial function, and stress responses[32].Dysregulation of these processes may increase neuronal vulnerability to oxidative stress and α-synuclein accumulation, ultimately contributing to dopaminergic neuron loss. Furthermore, epigenetic changes can influence inflammatory pathways by regulating the expression of cytokines and other immune-related genes, thereby promoting chronic neuroinflammation, a hallmark of PD progression[33,34].Therefore, histone modifications and chromatin remodelling not only regulate neuronal survival but also contribute to the inflammatory processes associated with neurodegeneration.

5. Role of MicroRNAs (miRNAs) in Parkinson's Disease

5.1 miRNA Biogenesis

MicroRNAs (miRNAs) are small non-coding RNAs (ncRNAs) approximately 19–25 nucleotides in length that regulate gene expression at the post-transcriptional level[35].miRNA biogenesis begins with the transcription of primary miRNA (pri-miRNA) molecules, which are processed into precursor miRNAs (pre-miRNAs) and subsequently into mature miRNAs. Mature miRNAs bind to complementary sequences within the 3′-untranslated region (3′-UTR) of target messenger RNAs (mRNAs), resulting in translational repression or mRNA degradation[36].Through this mechanism, miRNAs regulate numerous cellular processes, including neuronal development, differentiation, survival, and synaptic function. Dysregulation of miRNA expression has been widely reported in Parkinson's disease (PD), suggesting an important role in disease pathogenesis[37].

5.2 miRNAs Regulating α-Synuclein Expression

Several miRNAs directly regulate the expression of alpha-synuclein (α-synuclein), the major protein component of Lewy bodies and a key pathological hallmark of PD. Among the most extensively studied are miR-7 and miR-153, both of which bind to the 3′-UTR of the alpha-synuclein gene (SNCA) and suppress α-synuclein production. Reduced expression of these miRNAs has been observed in PD, leading to increased α-synuclein accumulation and aggregation[38]. In addition to regulating α-synuclein levels, miR-7 has been shown to exert neuroprotective effects by reducing inflammation and protecting neurons from cellular stress[39]. These findings highlight the importance of miRNA-mediated regulation of α-synuclein in PD pathogenesis

5.3 miRNAs in Dopaminergic Neuron Degeneration

miRNAs play important roles in maintaining the survival and function of dopaminergic neurons. Several miRNAs are dysregulated in PD and contribute to neuronal degeneration through effects on mitochondrial function, apoptosis, and neuroinflammation. The miR-34b/c cluster is significantly reduced in PD and has been associated with mitochondrial dysfunction and impaired neuronal survival[40].Likewise, decreased expression of miR-205 has been linked to increased levels of leucine-rich repeat kinase 2 (LRRK2), a protein associated with both familial and sporadic forms of PD [41]. The miR-

29 family regulates DNA methyltransferases (DNMTs), thereby linking miRNA activity with epigenetic regulation through DNA methylation[42,43].Another important miRNA, miR-124, promotes neuronal survival by suppressing pro-apoptotic pathways and reducing neuroinflammatory responses[44,45].In contrast, increased expression of the miR-132/212 cluster may contribute to dopaminergic neuron dysfunction by suppressing nuclear receptor-related factor 1 (NURR1), a key regulator of dopaminergic neuron development and maintenance. Additionally, reduced levels of miR-133b, which is involved in dopaminergic neuron maturation, have also been reported in PD[46].

5.4 miRNAs as Biomarkers in Parkinson's Disease

The stability of miRNAs in biological fluids has generated considerable interest in their use as non-invasive biomarkers for PD. Altered levels of several circulating miRNAs, including miR-1, miR-22, miR-29, miR-30, miR-133b, miR-153, and miR-505, have been reported in Furthermore, miRNAs can be transported within extracellular vesicles such as exosomes, which protect them from degradation and facilitate communication between cells. Because exosomal miRNAs can cross the blood–brain barrier (BBB), they may reflect molecular changes occurring within the brain and provide valuable information for early diagnosis and disease monitoring[47].Although additional validation studies are required, miRNAs represent promising biomarkers for improving the diagnosis and prognosis of PD. The potential role of circulating and exosomal miRNA as biomarkers for parkinson's disease is illustrated in figure 3

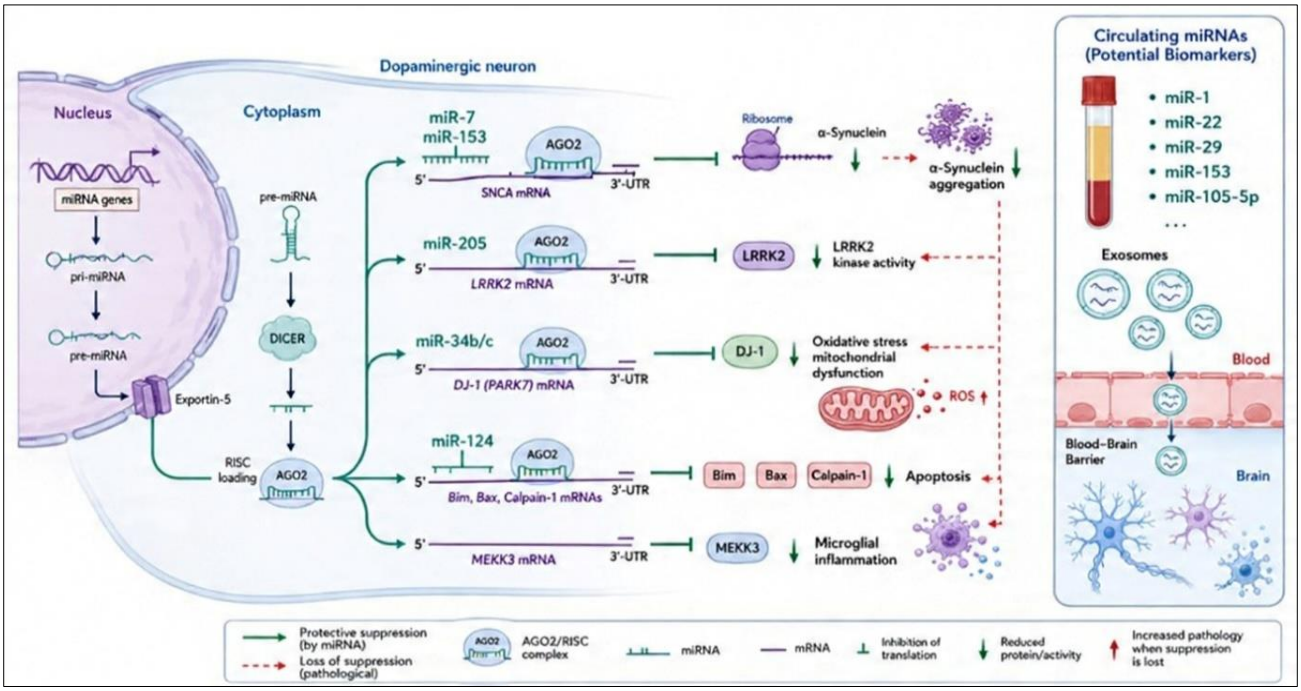

Figure 3: MiRNA Mediated Pathways in Parkinson's Disease

6. Role of Long Non-Coding RNAs (lncRNAs) in Parkinson's Disease

6.1 Mechanisms of Long Non-Coding RNA Action

Long non-coding RNAs (lncRNAs) are RNA molecules longer than 200 nucleotides that do not encode proteins but play important roles in regulating gene expression. Depending on their mode of action, lncRNAs can function as molecular scaffolds, guides, decoys, or competing endogenous RNAs (ceRNAs) that interact with microRNAs (miRNAs) and other regulatory molecules. Through these mechanisms, lncRNAs influence transcription, chromatin organization, RNA stability, and protein expression. Increasing evidence suggests that dysregulation of lncRNAs contributes to the pathogenesis of neurodegenerative diseases, including PD [48,49].

6.2 lncRNAs in Neuroinflammation and Mitochondrial Dysfunction

Neuroinflammation and mitochondrial dysfunction are two major pathological features of PD, and several lncRNAs have been implicated in these processes. Nuclear-enriched abundant transcript 1 (NEAT1) is involved in the regulation of mitochondrial quality control and has been reported to influence PTEN-induced kinase 1 (PINK1)-mediated mitophagy in experimental models of PD [50,51].Altered expression of NEAT1 may therefore contribute to impaired mitochondrial function and neuronal damage. In addition, certain lncRNAs participate in inflammatory signaling pathways by interacting with miRNAs and other regulatory molecules, thereby influencing neuronal survival and disease progression[52]. These findings

suggest that lncRNAs are important modulators of cellular stress responses in PD.

6.3 Key lncRNAs in Parkinson's Disease

Several lncRNAs have been identified as important regulators of PD pathogenesis. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is one of the most extensively studied lncRNAs and is upregulated in PD models. MALAT1 can regulate neuronal apoptosis through interactions with miR-124 and other signalling pathways[53,54]. HOX transcript antisense RNA (HOTAIR) has also been implicated in PD by modulating the expression of genes associated with neuronal survival and disease progression[55].Small nucleolar RNA host gene 1 (SNHG1) promotes α-synuclein accumulation and toxicity through interactions with miR-15b-5p, suggesting a role in Lewy body pathology Conversely, some lncRNAs exhibit protective effects. For example, H19 has been shown to reduce neuronal injury and improve cell survival in experimental PD models[56].Other lncRNAs, including ubiquitin carboxyl-terminal hydrolase L1 antisense RNA 1 (UCHL1-AS1) and antisense Uchl1 (AS-Uchl1), regulate genes involved in protein degradation pathways that are important for neuronal homeostasis[57].Collectively, these findings indicate that lncRNAs participate in multiple aspects of PD pathogenesis and may represent promising biomarkers and therapeutic targets. The diverse mechanisms by which key lncRNAs regulate neuroinflammation, mitochondrial dysfunction, α-synuclein accumulation, and neuronal survival in Parkinson's disease are summarized in Figure 4.

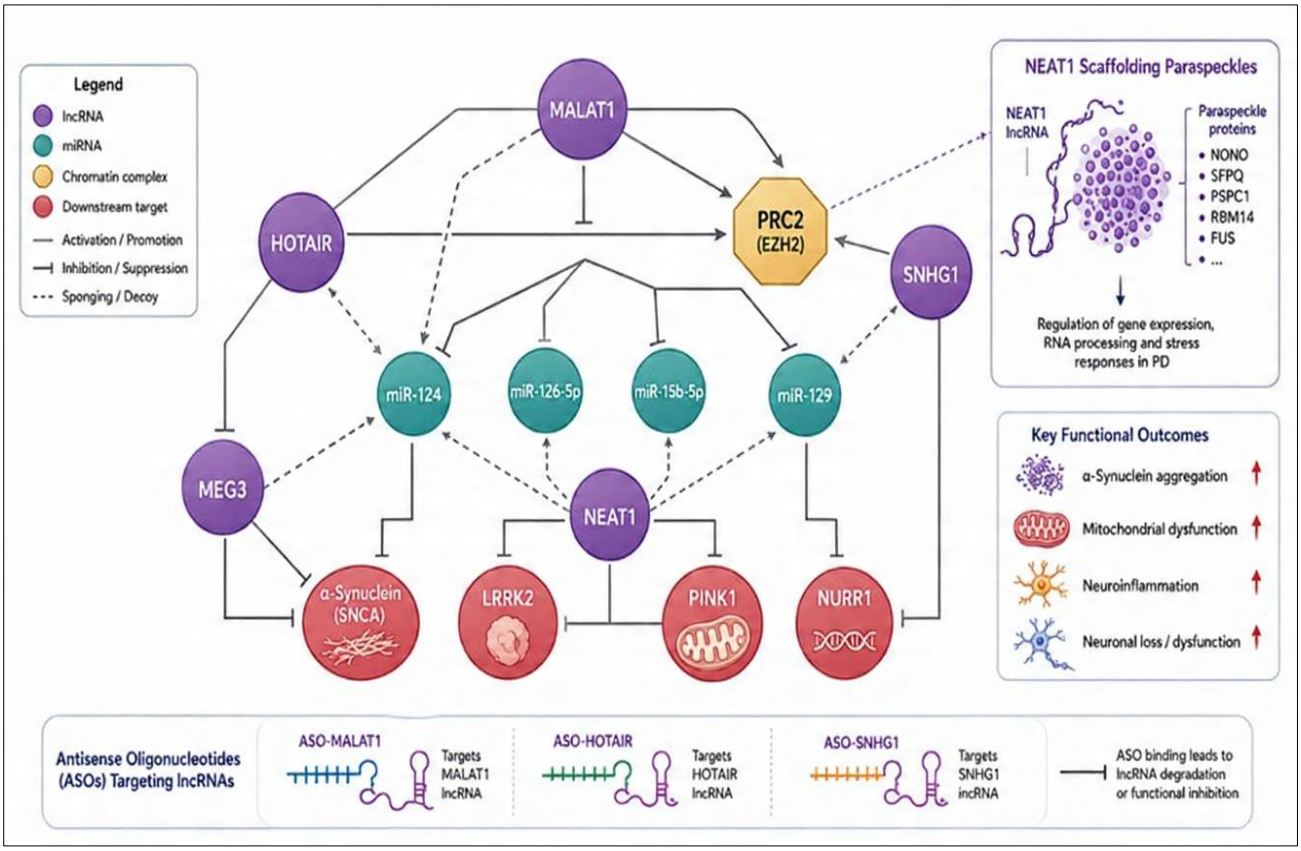

Figure 4: lncRNA Regulatory Network in Parkinson Disease

7. Crosstalk Between miRNAs, lncRNAs, and Chromatin Modifiers in Parkinson's Disease

Non-coding RNAs (miRNAs and lncRNAs) do not function independently. They interact with chromatin modifiers such as DNA methyltransferases (DNMTs), histone-modifying enzymes, and chromatin-remodelling proteins to regulate gene expression. These interactions form complex epigenetic networks that influence α-synuclein accumulation, mitochondrial dysfunction, neuroinflammation, and dopaminergic neuron loss in PD[58–60].

7.1 Interaction Between Epigenetic Mechanisms

Epigenetic regulation in PD involves continuous communication between miRNAs, lncRNAs, and chromatin-modifying enzymes. This interaction helps control the expression of genes involved in neuronal survival and disease progression. One important example is the lncRNA HOTAIR, which recruits the chromatin modifier EZH2, a component of the Polycomb Repressive Complex 2 (PRC2). EZH2 adds the repressive histone mark H3K27me3 to neuroprotective genes, reducing their expression and promoting neuronal vulnerability[61,62].Another

example involves the miR-29 family, which normally suppresses the DNA methyltransferases DNMT3A and DNMT3B. Reduced levels of miR-29 in PD increase DNMT activity, leading to abnormal DNA methylation and altered expression of genes required for mitochondrial function and neuronal survival[43,63].Histone deacetylases (HDACs) also interact with miRNAs. Increased HDAC activity can suppress the expression of protective miRNAs such as miR-7. Since miR-7 normally inhibits α-synuclein production, its reduction contributes to α-synuclein accumulation and neurodegeneration[39].

7.2 Regulatory Networks in PD Pathology

The interaction between miRNAs, lncRNAs, and chromatin modifiers forms regulatory networks that contribute to PD pathology. Recent studies shows reduced miR-7 expression increases α-synuclein production. At the same time, lncRNAs such as SNHG1 promote α-synuclein aggregation by sponging protective miRNAs, further enhancing neuronal toxicity[64]. Similarly, lncRNAs such as NEAT1 and HOTAIR influence mitochondrial function and cell survival through interactions with chromatin modifiers and miRNAs. These networks affect pathways involved in oxidative stress, mitophagy, and inflammation, all of which contribute to dopaminergic neuron degeneration[55,64,65].The combined effects of altered miRNA expression, lncRNA activity, and chromatin modifications ultimately lead to:

- Increased α-synuclein accumulation
- Mitochondrial dysfunction
- Neuroinflammation
- Oxidative stress
- Loss of dopaminergic neurons

Understanding these interconnected pathways may help identify new therapeutic targets for PD by modulating multiple epigenetic mechanisms simultaneously[66,67]. The integrated interactions among miRNAs, lncRNAs, DNA methylation, histone modifications, and chromatin-remodelling complexes that regulate Parkinson's disease pathogenesis are summarized in Figure 5.

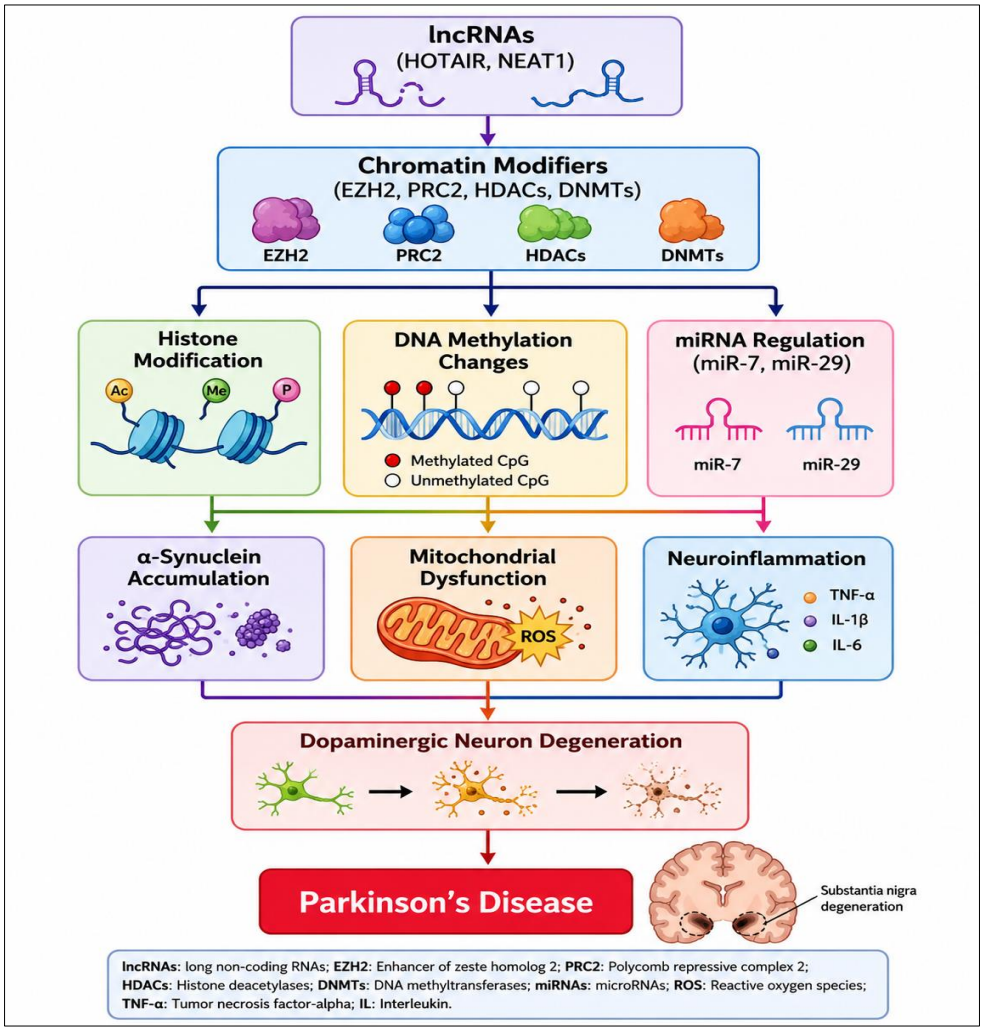

Figure 5: Crosstalk Between miRNAs, lncRNAs, and Chromatin Modifiers in Parkinson's Disease

Figure Legend:

This schematic illustrates the interaction between long non-coding RNAs (lncRNAs), including HOTAIR and NEAT1, and chromatin modifiers such as EZH2, PRC2, HDACs, and DNMTs. These regulators influence key epigenetic mechanisms, including histone modifications, DNA methylation changes, and miRNA regulation (e.g., miR-7 and miR-29). The coordinated dysregulation of these pathways promotes α-synuclein accumulation, mitochondrial dysfunction, and neuroinflammation, ultimately leading to dopaminergic neuron degeneration and the progression of Parkinson's disease.

8. Epigenetic Control of SNCA Expression and α-Synuclein-Mediated Neurodegeneration

8.1. Epigenetic Regulation of SNCA Expression

The *SNCA* gene, which encodes α-synuclein, represents a central convergence point through which multiple epigenetic mechanisms contribute to Parkinson's disease (PD) pathogenesis. At the DNA level, hypomethylation of the *SNCA* intron 1 CpG island reduces transcriptional repression and enhances α-synuclein expression. This epigenetic alteration has been observed in the substantia nigra, cerebral cortex, and peripheral blood of PD patients and correlates with disease severity[18,68].Genome-wide methylation studies further support the importance of DNA methylation abnormalities in regulating PD-associated genes and neuronal vulnerability[69].post-transcriptional regulation of *SNCA* is mediated by several non-coding RNAs. Among these, miR-7 and miR-153 directly bind to the 3′-untranslated region (3′-UTR) of *SNCA* mRNA and suppress α-synuclein translation. Reduced expression of these miRNAs in the PD substantia nigra removes an important regulatory checkpoint, resulting in increased α-synuclein synthesis and accumulation [70].Experimental evidence further demonstrates that loss of miR-7 regulation promotes α-synuclein accumulation and dopaminergic neuronal loss *In vivo*[71]Long non-coding RNAs (lncRNAs) provide an additional regulatory layer through competing endogenous RNA (ceRNA) networks. In experimental PD models, SNHG1 promotes α-synuclein accumulation by sequestering miR-15b-5p, leading to upregulation of SIAH1, impaired protein clearance, and increased neurotoxicity. Similarly, MALAT1 acts as a molecular sponge for miR-124, thereby reducing miR-124 availability and promoting DAPK1-mediated dopaminergic neuronal apoptosis and motor deficits; silencing MALAT1 rescues apoptosis and improves behavior. Together, these findings indicate that DNA methylation, microRNAs, and lncRNA-mediated ceRNA networks cooperate to regulate SNCA expression and related pathways, and to influence disease progression[51,52,72].

8.2. Role of α-Synuclein in Protein Aggregation, Chromatin Dysregulation, and Dopaminergic Neurodegeneration

Beyond being an epigenetically regulated protein, α-synuclein actively participates in pathogenic feedback mechanisms that exacerbate neuronal dysfunction. Elevated α-synuclein levels promote protein misfolding and aggregation, leading to the formation of Lewy bodies, a pathological hallmark of PD that contributes directly to dopaminergic neuron degeneration[73].The relationship between α-synuclein and chromatin is bidirectional. Following overexpression, α-synuclein trans locates to the nucleus, where it directly interacts with histone H3 and suppresses histone acetylation, resulting in transcriptional dysregulation and enhanced neurotoxicity[25,26].This effect can be reversed by histone deacetylase (HDAC) inhibition, highlighting the therapeutic potential of chromatin-targeted interventions[74,75].In addition, α-synuclein associates with nucleosomes and ATP-dependent chromatin-remodelling complexes, thereby altering chromatin accessibility and global gene expression patterns[76] .Post-translational modifications further influence α-synuclein toxicity. SIRT2-mediated deacetylation of α-synuclein at lysine residues 6 and 10 enhances its aggregation propensity and neurotoxic effects [28,77,78]. Pharmacological inhibition of SIRT2 reduces α-synuclein-mediated toxicity and provides neuroprotection in several experimental PD models. These observations demonstrate that α-synuclein functions not only as a downstream target of epigenetic dysregulation but also as an active regulator of chromatin structure and gene expression. Consequently, the *SNCA* locus and its associated regulatory RNA networks represent promising therapeutic targets for epigenetic interventions aimed at slowing dopaminergic neurodegeneration in Parkinson's disease[79,80]. The integrated epigenetic regulation of *SNCA* expression and the downstream consequences of α-synuclein-mediated neurodegeneration are illustrated in Figure 6.

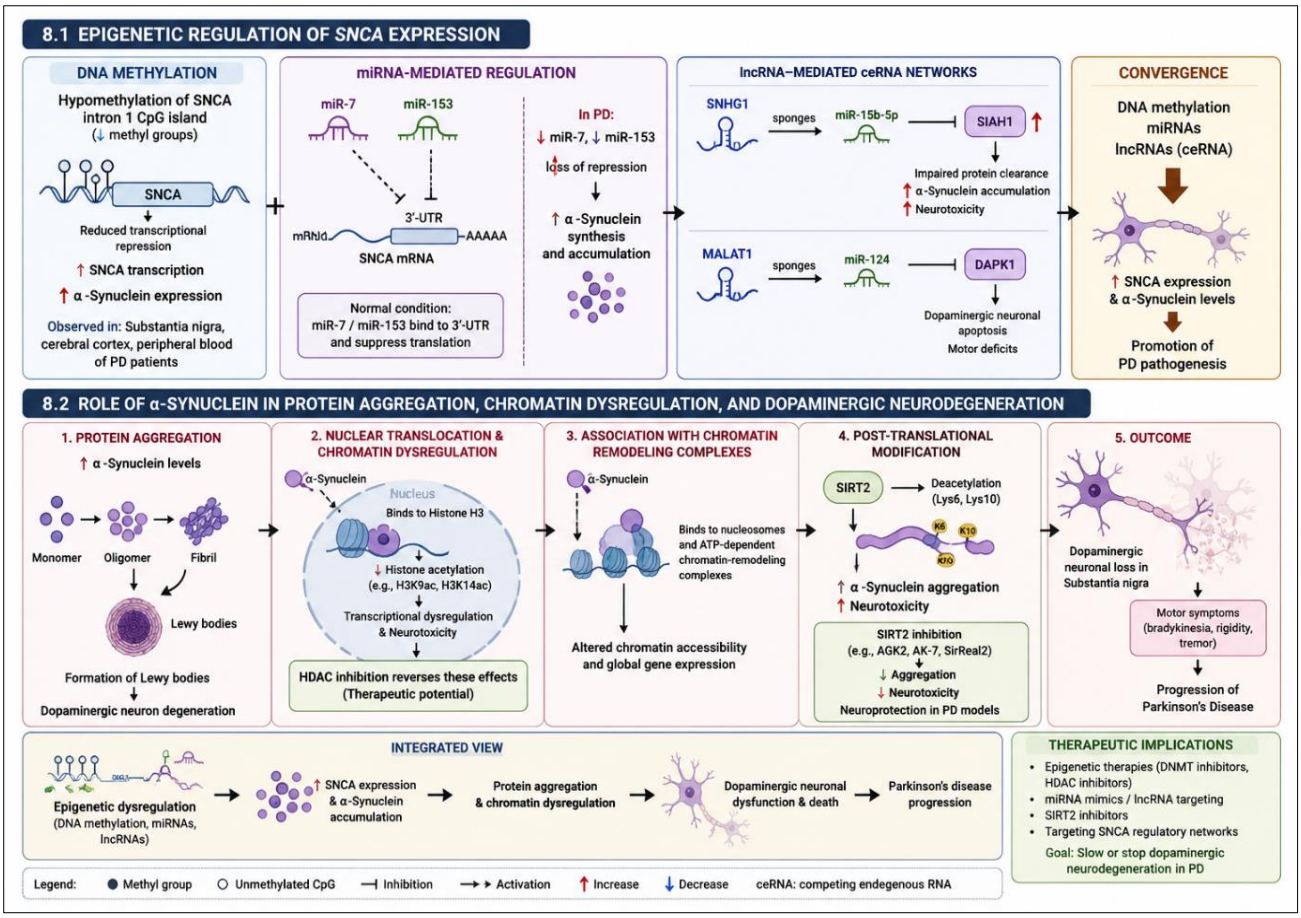

Figure 6: Epigenetic Regulation of *SNCA* Expression and α-Synuclein-Mediated Neurodegeneration in Parkinson's Disease

Figure 6.

Epigenetic mechanisms, including DNA methylation, miRNAs, and lncRNAs, regulate *SNCA* expression and α-synuclein accumulation. Increased α-synuclein promotes protein aggregation, chromatin dysregulation, and dopaminergic neurodegeneration in Parkinson's disease.

9. Epigenetic Biomarkers for Parkinson's Disease: Diagnostic and Prognostic Applications

9.1. Circulating microRNA Biomarkers

The search for minimally invasive biomarkers for Parkinson's disease (PD) has highlighted circulating microRNAs (miRNAs) as promising candidates due to their stability in biofluids and their ability to reflect disease-associated molecular alterations. Dysregulated miRNAs can be detected in serum, plasma, cerebrospinal fluid (CSF), exosomes, saliva, and other peripheral tissues, often preceding overt clinical manifestations of PD[81,82].Several studies have identified disease-associated changes in miRNAs involved in α-synuclein regulation, neuroinflammation, mitochondrial dysfunction, and neuronal survival. For example, altered levels of miR-7, miR-153, miR-29 family members, miR-124, and miR-132 have been reported in PD patients[83,84].Furthermore, circulating panels comprising miR-153, miR-409-3p, miR-10a-5p, let-7g-3p, and miR-105-5p have demonstrated encouraging diagnostic performance, achieving sensitivities of 84–92% and specificities of 80–90% across independent cohorts[85–87].Meta-analyses further support the reproducibility of several miRNA signatures as potential biomarkers for disease detection and monitoring [82,88].

9.2. DNA Methylation Markers

DNA methylation abnormalities represent another important class of epigenetic biomarkers in PD. Among the most extensively studied targets is the SNCA locus, where hypomethylation of CpG regions, particularly within intron 1, is associated with increased α-synuclein expression and disease susceptibility [89,90].Altered SNCA methylation patterns have been detected not only in post-mortem brain tissue but also in peripheral blood mononuclear cells, leukocytes, saliva, and whole-blood samples, supporting their utility as accessible biomarkers[91,92] . Beyond SNCA, epigenome-wide association studies have identified differential methylation in genes involved in oxidative stress regulation, glutamate transport, neuronal differentiation, and immune responses, including SLC7A11 and TET2-associated pathways [21].Importantly, DNA methylation signatures appear responsive to therapeutic interventions, as levodopa treatment has been shown to increase SNCA methylation

levels in patients and experimental models[93].These findings suggest that methylation markers may serve not only as diagnostic indicators but also as pharmacodynamic measures of treatment response.

9.3. Clinical Relevance and Diagnostic Potential

Epigenetic biomarkers offer several advantages over conventional clinical assessments, including the potential for early detection during the prodromal phase, accessibility through non-invasive sampling, and responsiveness to disease progression and therapeutic intervention [94].In addition to diagnosis, specific miRNAs such as CSF miR-19b and miR-24, together with peripheral SNCA methylation profiles, have been associated with rates of motor decline and disease progression, indicating prognostic value[95]. However, the molecular heterogeneity of PD limits the performance of single biomarkers. Consequently, multimodal approaches integrating epigenetic data with genomic, proteomic, metabolomic, imaging, and clinical variables have shown superior predictive accuracy compared with single-marker strategies[96]. Recent advances in machine learning and artificial intelligence have further enhanced biomarker discovery and patient stratification. Algorithms such as random forests, XGBoost, graph neural networks, and deep learning models applied to large cohorts including the Parkinson's Progression Markers Initiative (PPMI), Alzheimer's Disease Neuroimaging Initiative-PD (ADNI-PD), and Global Parkinson's Genetics Program (GP2) have identified epigenetic signatures predictive of disease phenoconversion and progression[97,98].Explainable artificial intelligence approaches, including SHAP (Shapley Additive Explanations) analyses and attention-based models, are increasingly used to improve biological interpretability and clinical trustworthiness[99].Furthermore, federated learning frameworks enable collaborative model development across institutions while preserving patient privacy, facilitating the generation of robust and generalizable epigenetic biomarkers for future clinical implementation[100].Despite these advances, several challenges remain, including variability in sample collection, RNA extraction methods, normalization procedures, and differences between RT-qPCR and sequencing platforms. The relatively small size of many validation cohorts also limits reproducibility[101]. Therefore, adherence to standardization frameworks such as the MIQE guidelines and emerging epigenetic quality-control initiatives remains essential before routine clinical adoption can be achieved.

10. Epigenetic Therapeutic Approaches in Parkinson's Disease

10.1. HDAC Inhibitors

Histone acetylation abnormalities contribute to transcriptional dysregulation and dopaminergic neurodegeneration in Parkinson's disease (PD)[25,26,33,102].Consequently, histone deacetylase (HDAC) inhibitors have emerged as promising epigenetic therapeutics. Several compounds, including valproic acid, sodium butyrate, trichostatin A, vorinostat (SAHA), and entinostat, improve motor function, reduce α-synuclein toxicity, and enhance dopaminergic neuron survival in experimental PD models[75]. More selective inhibitors such as RGFP966, which targets HDAC3, may reduce adverse effects associated with pan-HDAC inhibition. In addition, modulation of sirtuins represents a complementary strategy. SIRT2 inhibitors such as AGK2 and AK-7 reduce α-synuclein-mediated toxicity whereas activation of SIRT1 by compounds such as resveratrol promotes neuronal survival through antioxidant and autophagic mechanisms[103,104].These findings support HDAC-targeted therapies as promising disease-modifying approaches for PD.

10.2. miRNA-Based Therapies

MicroRNAs (miRNAs) regulate numerous pathways involved in PD pathogenesis, including α-synuclein accumulation, mitochondrial dysfunction, apoptosis, and neuroinflammation Therapeutic strategies involve either restoring neuroprotective miRNAs through synthetic mimics or suppressing pathogenic miRNAs using antagomirs. Among the most extensively studied candidates, miR-7 inhibits α-synuclein expression and suppresses NLRP3 inflammasome activation, thereby reducing neuroinflammation and neuronal degeneration[105,106].Similarly, miR-124 protects dopaminergic neurons by regulating apoptosis and inflammatory signalling pathways, while the miR-29 family has been implicated in neuronal survival and epigenetic regulation[42,43]. In contrast, dysregulation of miR-132 and miR-34b/c contributes to PD progression, making these molecules attractive therapeutic targets. Although most miRNA-based interventions remain at the preclinical stage, advances in nanoparticle and exosome-mediated delivery systems are enhancing their translational potential[87].

10.3. lncRNA-Targeting Strategies

Long non-coding RNAs (lncRNAs) play critical roles in regulating chromatin structure, transcription, and post-transcriptional gene expression, making them attractive therapeutic targets in PD. Several lncRNAs, including MALAT1, HOTAIR, NEAT1, and SNHG1, are dysregulated in PD and contribute to α-synuclein aggregation, oxidative stress, autophagy dysfunction, and neuronal apoptosis. Silencing pathogenic lncRNAs using antisense oligonucleotides or RNA interference strategies has demonstrated neuroprotective effects in experimental models. For example, MALAT1 suppression reduces neuronal apoptosis and α-synuclein expression. whereas inhibition of HOTAIR and SNHG1 attenuates pathogenic signalling pathways associated with disease progression. Conversely, restoration of protective lncRNAs such as H19 and Uchl1-AS may support neuronal survival and dopaminergic function[51,107,108].These findings highlight lncRNA-targeted therapies as an emerging avenue for precision epigenetic intervention in PD.

10.4. Natural Epigenetic Modulators

Naturally occurring compounds that modulate epigenetic pathways have gained attention as potential adjunctive therapies for PD. Resveratrol is one of the best-characterized examples and exerts neuroprotective effects through activation of the AMPK–SIRT1 signalling pathway, enhancement of autophagy, and reduction of oxidative stress[27,103].Furthermore, resveratrol has been shown to regulate the MALAT1/miR-129/SNCA signalling axis, thereby reducing neuronal apoptosis and α-synuclein accumulation[54].Vitamin E has also been associated with modulation of DNA methylation patterns, including methylation of the *MAPT* gene, suggesting a role in epigenetic regulation of PD-related pathways[109].In addition, β-asarone attenuates neurodegeneration by regulating MALAT1-associated signalling and reducing α-synuclein expression[110].Although these natural compounds show considerable promise in preclinical studies, further clinical investigations are required to validate their efficacy and safety in PD patients. Epigenetic dysregulation, including miRNAs, lncRNAs, histone modifications, DNA methylation, and chromatin remodelling, lies upstream of α-synuclein aggregation, mitochondrial failure, and neuroinflammation in Parkinson's disease. Its reversibility, accessibility in peripheral biofluids, and pharmacological tractability position the epigenome as both a biomarker repository and therapeutic frontier. Translational success will require standardized methodologies, cell-type-resolved data, blood-brain barrier-permeable delivery, and AI-guided patient stratification, and the next generation of PD trials should embed epigenetic readouts as a matter of course.

10. CONCLUSION

Epigenetic dysregulation, including miRNAs, lncRNAs, histone modifications, DNA methylation, and chromatin remodelling, lies upstream of α-synuclein aggregation, mitochondrial dysfunction, and neuroinflammation in Parkinson's disease. The dynamic and reversible nature of these epigenetic mechanisms, together with their detectability in peripheral biofluids, highlights their value as both diagnostic biomarkers and therapeutic targets. Collectively, the evidence reviewed demonstrates that epigenetic regulation plays a central role in the initiation and progression of Parkinson's disease by integrating genetic susceptibility with environmental influences. A comprehensive understanding of these interconnected epigenetic networks will be essential for advancing biomarker discovery, refining disease mechanisms, and facilitating the development of more effective strategies for the diagnosis and management of Parkinson's disease.

Future Perspectives

The successful clinical translation of epigenetic therapies remains challenging because of limited blood–brain barrier penetration, off-target effects, and inadequate cell-type specificity Nanotechnology-based delivery platforms, including lipid nanoparticles, polymeric nanoparticles, and engineered exosomes, are being developed to improve the delivery of miRNA mimics, antisense oligonucleotides, and epigenetic drugs to the central nervous system. Notably, exosome-mediated delivery of siRNA targeting *SNCA* has successfully reduced α-synuclein aggregation in transgenic mouse models. Translational success will require standardized methodologies, cell-type-resolved data, blood–brain barrier-permeable delivery systems, and AI-guided patient stratification. Furthermore, the next generation of Parkinson's disease clinical trials should routinely incorporate epigenetic biomarkers and molecular readouts to facilitate patient stratification, monitor therapeutic responses, and accelerate the development of precision epigenetic therapies. Future therapeutic strategies are likely to combine HDAC inhibitors, ncRNA-based therapies, and natural epigenetic modulators to simultaneously target multiple pathogenic pathways while minimizing toxicity. Such multimodal approaches may pave the way toward precision epigenetic medicine for Parkinson's disease.

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