Research Progress on Epigenetic Regulation in Neurodegenerative Diseases

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Abstract. Neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), are characterized by the progressive loss of neurons or deterioration in their structure and function, posing significant burdens on both society and affected families. Increasing evidence suggests that their pathogenesis is closely associated with epigenetic regulatory mechanisms, including DNA methylation, histone modifications, and non-coding RNAs. epigenetic regulation refers to molecular mechanisms that modulate gene expression without altering the DNA sequence, such as dynamic changes in DNA lamentation and gene silencing mediated by non-coding RNAs. These mechanisms influence neuronal differentiation, apoptosis, and functional status, thereby impacting the development and maintenance of the nervous system. An expanding body of research has highlighted the associations between various epigenetic factors and Neurodegenerative diseases, supporting the clinical translation of circulating non-coding RNAs as non-invasive diagnostic biomarkers. These findings provide potential targets for early intervention and the development of novel therapeutic strategies. This review aims to systematically summarize recent advances in the study of epigenetic regulation in human Neurodegenerative diseases. Through a comprehensive analysis of the relevant literature, we elucidate the key mechanistic roles of epigenetic regulation in disease onset and progression, offering a theoretical basis for identifying potential diagnostic markers and therapeutic targets. Ultimately, this review seeks to contribute new insights and strategies for delaying neurodegeneration and improving the prevention and treatment of Neurodegenerative disorders.

Keywords: Epigenetic Regulation; DNA Lamentation; Histone Modification; Non-Coding RNA; Neurodegenerative Diseases; Alzheimer's Disease; Parkinson's Disease.

1. Introduction

Epigenetics is a discipline that explores heritable changes in gene expression that occur without alterations to the underlying DNA sequence [1]. Since its emergence in the mid-20th century, epigenetics has undergone significant enrichment and development. In 1942, Conrad Waddington first introduced the term "epigenetics," defining it as "a branch of biology concerned with the causal interactions between genes and their products that bring the phenotype into being," thereby establishing a conceptual link between developmental biology and genetics [2, 3]. Between 1869 and 1928, foundational concepts such as nucleic acids, chromatin, and histones were introduced by Miescher and others [4]. Subsequent studies by Muller and McClintock on transposition further revealed the existence of non-Mendelian patterns of inheritance [5]. The characterization of X-chromosome inactivation [6] and genomic imprinting [7] demonstrated that identical genetic material within the same nucleus can exhibit distinct activity states. By the 1980s, the role of DNA methylation in regulating gene expression was identified [4]. The nucleosome model was subsequently proposed [8], and the association between histone modifications—particularly histone acetylation—and gene activity was further elucidated. In 1996, multiple enzymes responsible for histone modifications were identified [9-11], providing molecular insight into the formation of heterochromatin. Between 1999 and 2000, the "histone code hypothesis" was proposed [12], positing that specific combinations of histone modifications result in distinct biological outcomes. In 2002, studies revealed that small RNAs can direct chromatin-modifying activities to specific genomic loci, participating in transcriptional gene silencing [13]. From 2004 to 2006, the concept of bivalent chromatin—characterized by the coexistence of activating and repressive marks on the same nucleosome—was

introduced, and genome-wide analyses of histone modifications began to reveal distinctive epigenomic landscapes. Between 2009 and 2010, ten-eleven translocation (TET) enzymes, a class of α-ketoglutarate- and Fe^{2+}-dependent dioxygenases, were discovered [14, 15]. These enzymes catalyze the demethylation of DNA, indicating that epigenetic marks may be reversible. It was also discovered that CpG islands can influence the methylation status of DNA[4]. In summary, current research on epigenetic regulation primarily focuses on four major areas: DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs.

Over the past several decades, epigenetic regulation has emerged as a prominent focus in biomedical research. In oncology, aberrant DNA methylation has been closely associated with the silencing of tumor suppressor genes. For instance, hypermethylation-induced loss of expression of tumor suppressor genes has been observed in colorectal cancer[16]. In approximately 25% of patients with acute myeloid leukemia (AML), recurrent mutations in the DNA methyltransferase gene *DNMT3A* have been identified [17]. Histone modifications also contribute to tumorigenesis; in leukemia, for example, chimeric fusion proteins can recruit histone deacetylases (HDACs), leading to abnormal gene silencing and facilitating leukemic progression [18]. Despite these advances, the role of epigenetic regulation in neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) remains insufficiently explored and understood.

The incidence and prevalence of dementia, particularly AD, increase significantly with age, making it a growing global public health concern [19]. Currently, no effective curative therapies are available. According to reports, the number of people living with dementia worldwide reached 43.8 million in 2016, marking a 117% increase since 1990[20]. It is estimated that by 2050, the global population affected by AD and other forms of dementia will rise to 152 million[21]. Therefore, in-depth investigation of epigenetic mechanisms involved in these disorders holds substantial relevance for global health initiatives.

Epigenetic regulation presents considerable potential for application in neurodegenerative disease research. Several drugs targeting epigenetic-modifying enzymes have already entered clinical trials. For example, HDAC inhibitors have shown promise in preclinical and clinical studies for the treatment of neurodegenerative diseases[22]. Given the reversible nature of epigenetic modifications, they are regarded as promising therapeutic targets for these conditions.

This review aims to provide a comprehensive summary of recent advances in the study of epigenetic regulation in human neurodegenerative diseases. It highlights the key mechanisms by which epigenetic factors contribute to disease onset and progression, and provides a theoretical basis for identifying potential diagnostic biomarkers and therapeutic targets. Ultimately, this work seeks to inform new strategies for delaying neurodegeneration and improving the prevention and treatment of neurodegenerative disorders.

2. Molecular Mechanisms of Epigenetic Regulation

Epigenetic regulation enables differential gene expression without altering the DNA sequence and plays a vital role in cellular growth, development, and the pathogenesis of various diseases. Among the diverse epigenetic mechanisms, DNA methylation, histone modifications, and non-coding RNAs have been the most extensively studied and well-characterized.

2.1 DNA Methylation

Since its initial discovery in bacteria in 1925, DNA methylation has been widely investigated across various species and has been implicated in numerous biological processes, particularly gene regulation, making it one of the most thoroughly studied epigenetic mechanisms [23]. In 1988, DNA methyltransferase 1 (DNMT1) was first cloned. Subsequent studies demonstrated that DNMT1 plays a key role in transposon silencing, X-chromosome inactivation, and the regulation of imprinted genes. It also maintains DNA methylation patterns following DNA replication, thereby ensuring the faithful transmission of epigenetic marks during cell division[24-27]. The maintenance of methylation is

achieved through DNMT1's preferential activity on hemimethylated CpG sites, where it methylates the corresponding sites on the newly synthesized DNA strand. This mechanism ensures the propagation of both methylated and unmethylated CpG sites; however, its fidelity is relatively low. Interestingly, studies have shown that even in the absence of DNMT1—the only known maintenance DNA methyltransferase—methylation at CpG islands can remain stable, although the underlying mechanisms are yet to be fully elucidated [28].

In 1998, DNMT3A and DNMT3B were identified as de novo DNA methyltransferases capable of establishing DNA methylation independently of replication. These enzymes are critical for regulating gene expression during embryonic development and are involved in the aberrant gene silencing observed in various diseases, including cancer[29]. Between 1989 and 1998, members of the 5-methylcytosine (5mC) binding protein family, including MeCP2 and MBD1–4, were successively discovered[23]. MeCP2 recognizes and binds to methylated CpG sites to mediate transcriptional repression. Mutations that impair MeCP2's ability to bind methylated DNA are associated with Rett syndrome, highlighting the important link between DNA methylation and human disease[30].

DNA methylation can lead to the permanent silencing of previously inactive genes, thereby enhancing the stability of gene repression[28]. For instance, treatment of somatic cells with demethylating agents can reverse X-chromosome inactivation[31]. Moreover, DNA methylation levels show a strong positive correlation with aging in different brain regions[32]. Integrative genetic and epigenetic analyses of DNA methylation hold promise for uncovering the molecular pathways that link aging to neurodegenerative diseases. With the advancement of omics technologies, it may be possible to identify novel therapeutic targets aimed at delaying aging and the onset or progression of related neurodegenerative conditions[33].

2.2 Histone Modifications

Histone modifications represent a key mode of epigenetic regulation. By targeting specific amino acid residues on histone proteins, these modifications influence chromatin structure and function, thereby regulating gene expression. Various types of modifications, including methylation, phosphorylation, and acetylation, constitute what is referred to as the "histone code," which modulates the interaction between histones and DNA, governs chromatin remodeling, and impacts fundamental biological processes such as transcription and replication[34].

(1) Histone Acetylation

Histone acetylation was first proposed in 1964 by Allfrey and colleagues[35], who demonstrated that acetylation of lysine residues is a highly dynamic process regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs, using acetyl-CoA as a cofactor, catalyze the transfer of acetyl groups to the ε-amino group of lysine side chains. This neutralizes the positive charge on lysine, weakens the interaction between histones and DNA, and facilitates gene expression. Conversely, HDACs reverse this process, restoring the positive charge and stabilizing the local chromatin structure to suppress transcription[36].

Studies have shown that HATs play essential roles in both developing and mature brains[37]. For instance, PCAF, a member of the GNAT family of HATs, is critically involved in memory formation following stress and anxiety in adult mice[38]. In aging mice, dysregulated acetylation can impair the expression of genes involved in memory consolidation, ultimately leading to cognitive deficits[39]. Additionally, various HATs are indispensable for brain development, neuronal differentiation, and the maturation of neural progenitor cells.

(2) Histone Phosphorylation

Histone phosphorylation is another highly dynamic modification, predominantly occurring on serine, threonine, and tyrosine residues, especially within the N-terminal tails of histones. The phosphorylation status is tightly regulated by kinases (which add phosphate groups) and phosphatases (which remove them) [36, 40].

Identified histone kinases can transfer phosphate groups from ATP to specific amino acid side chains, introducing a negative charge that alters chromatin structure[36]. For example, during mitosis,

hyperphosphorylation of histone H1 and phosphorylation of histone H3 facilitate chromatin condensation into chromosomes[41]. Normally, heterochromatin protein 1 (HP1) dissociates from chromosomes during mitosis, aiding spindle attachment[36]. However, inhibition of H3 Ser-10 phosphorylation prevents this dissociation, causing HP1 to remain bound throughout mitosis, which impairs proper chromosome segregation[42].

Compared with histone kinases, the roles of histone phosphatases are less well understood. Among the few known, phosphatase PP1 is antagonistic to the mitotic kinase Aurora B. The PP1γ isoform can be recruited to mitotic chromosomes by its regulatory subunit Repo-Man, while Aurora B phosphorylates Repo-Man to disrupt its interaction with PP1γ, thereby promoting the dissociation of PP1γ from chromatin[43-45]. The antagonistic regulation between kinases and phosphatases is critical for modulating chromatin condensation and decondensation during mitosis.

The interplay between different histone modifications, known as histone crosstalk, adds further complexity to chromatin regulation and facilitates fine-tuned control of gene expression. At the molecular level, histone crosstalk primarily occurs through five mechanisms: (1) different modifications may compete for the same residue; (2) one modification may depend on the presence of another; (3) the binding of effector proteins to one modification may be disrupted by neighboring modifications; (4) modification of the substrate may influence the activity of modifying enzymes; and (5) synergistic interactions between modifications may enhance the recruitment of specific regulatory factors. Together, these mechanisms form a highly coordinated and intricate network that governs gene expression[36].

2.3 Non-coding RNAs

Non-coding RNAs (ncRNAs), as vital contributors to epigenetic regulation, modulate gene expression either by forming chromatin modification complexes or by directly targeting mRNAs. They play significant roles in human development, aging, and disease pathogenesis.

(1) microRNAs (miRNAs)

miRNAs are endogenous single-stranded RNAs approximately 21–25 nucleotides in length. In animals, primary miRNA transcripts (pri-miRNAs) are initially processed in the nucleus by the Drosha enzyme into ~70 nucleotide stem-loop precursors (pre-miRNAs). These pre-miRNAs are subsequently transported to the cytoplasm via Exportin-5 and cleaved by Dicer to generate mature miRNAs[46]. Mature miRNAs typically bind to target mRNA 3’ untranslated regions (3’ UTRs) through a seed sequence (~10 nucleotides), forming an Argonaute 2 (AGO2)-mediated RNA-induced silencing complex (RISC) to achieve post-transcriptional regulation. In plants, miRNAs exhibit near-perfect complementarity with target mRNAs, leading to mRNA cleavage via RNA interference; conversely, animal miRNAs generally display partial complementarity, repressing gene expression primarily through translational inhibition [46, 47].

In neurodegenerative disease research, notable differences in miRNA expression have been observed in cerebrospinal fluid-derived exosomes from Parkinson’s disease (PD) and Alzheimer’s disease (AD) patients compared with healthy controls[48]. Several miRNAs abundantly expressed in the central nervous system—including miRNA-7, miRNA-9, miRNA-34a, miRNA-125b, miRNA-146a, and miRNA-155—are significantly upregulated in AD brains. These upregulated miRNAs downregulate multiple immune and neuronal function-related mRNAs, contributing to AD-associated pathological features. For example, miRNA-34a and miRNA-125b suppress the expression of TREM2 (triggering receptor expressed on myeloid cells 2) in microglia and myeloid cells, resulting in impaired phagocytosis, deficient microglial activation, and dysregulated neuroinflammation, thereby promoting AD progression. These findings suggest that miRNAs may serve as promising biomarkers for early AD diagnosis and therapeutic intervention[49].

(2) tRNA-derived small RNAs (tsRNAs)

tRNAs, typically 70–90 nucleotides in length, possess a cloverleaf secondary structure and L-shaped tertiary structure, functioning as amino acid carriers to ribosomes for protein synthesis[50]. Transcribed by RNA polymerase III as precursor tRNAs (pre-tRNAs), they undergo processing and

modifications to mature tRNAs[51]. Recently identified, tsRNAs are non-coding RNAs generated by the enzymatic cleavage of mature or precursor tRNAs [52]. Based on cleavage sites, tsRNAs are categorized into tRNA fragments (tRFs) and tRNA-derived stress-induced RNAs (tiRNAs). These molecules regulate gene expression at transcriptional and translational levels and are implicated in the pathogenesis of diverse diseases[51].

In mammals, tiRNAs are produced by angiogenin (ANG) cleavage within the anticodon loop of mature tRNAs. Their biogenesis is typically induced by stressors such as heat shock, cold shock, hypoxia, and oxidative stress, though tiRNAs are also present under physiological conditions[51]. According to whether the tiRNA contains the 5' or 3' anticodon sequence, tiRNAs are further divided into 5'-tiRNAs and 3'-tiRNAs [53,54]. tRFs can associate with Argonaute proteins and repress gene expression via binding to target mRNA 3' UTRs [55]. Moreover, tRFs compete with oncogenic transcripts for binding to the RNA-binding protein YBX1, disrupting YBX1-oncogene mRNA complexes and promoting their degradation, thus inhibiting oncogene expression [56]. Pseudouridine synthase 7 (PUS7) modifies the uridine at position 8 (U8) of specific 5'-tRFs containing a TOG motif (originating from tRNA-Ala, tRNA-Cys, and tRNA-Val) to pseudouridine (Ψ), generating mTOG-Ψ8. This modified tsRNA binds poly(A)-binding protein 1 (PABPC1) and inhibits mTOG-dependent translation initiation in stem cells, thereby repressing translation[57].

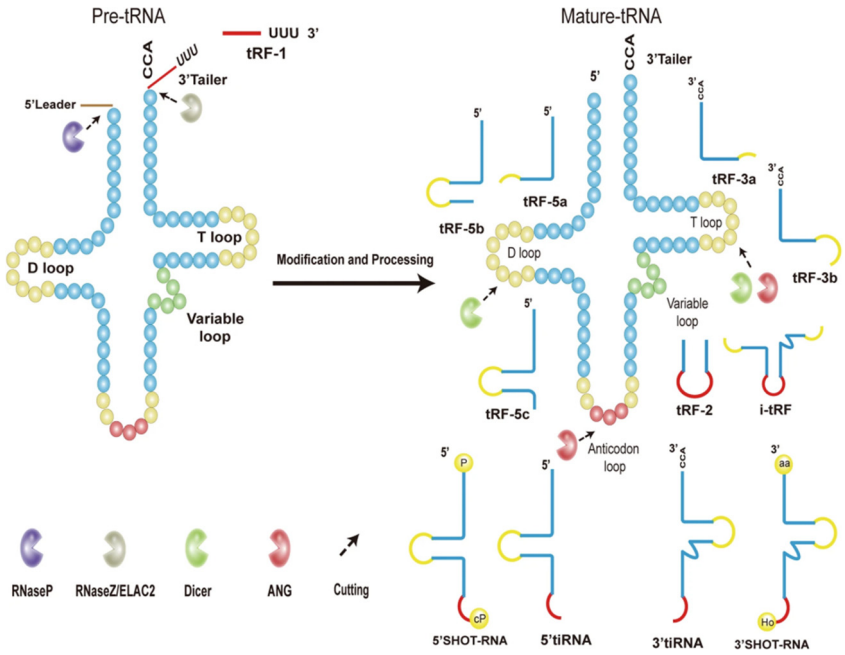

Figure 1. Biogenesis and classification of tsRNAs [51]

Emerging evidence indicates that specific tsRNAs play critical roles in the pathogenesis of various diseases. In the hippocampus of AD patients, certain tsRNAs exhibit significant expression changes. Notably, 30–40 nucleotide-long tRF-5s are the most abundant and act in a miRNA-like manner by targeting the *Rpsa* gene, which is involved in β-amyloid production and internalization, thereby participating in AD pathogenesis [58, 59]. Elevated levels of tRFs have also been detected in the prefrontal cortex, cerebrospinal fluid, and serum of PD patients, exhibiting high sensitivity (89–100%) and specificity (79–98%) for disease detection[60]. In murine brains, a tRF-5 named AS-tDR-011775 targets the *Mobp* gene, affecting axonal morphology and contributing to PD pathology [61]. Collectively, tsRNAs hold promise as novel diagnostic biomarkers and therapeutic targets for multiple neurodegenerative diseases.

3. Epigenetics and Neurodegenerative Diseases

Neurodegenerative diseases are characterized by progressive damage to neurons and their myelin sheaths, accompanied by a temporal decline in functional abilities. They are classified into acute neurodegenerative disorders—such as cerebral ischemia (CI), brain injury (BI), and epilepsy—and chronic neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), various types of spinocerebellar ataxia (SCA), and Pick's disease, among others[62]. The core pathological hallmark of these diseases is the progressive loss or degeneration of neuronal structure and function.

According to the 2023 report by the International Alzheimer's Disease Association (ADI), one new dementia case occurs every three seconds worldwide. AD accounts for 50%–60% of all dementia cases. Annually, informal care provided to dementia patients amounts to approximately 133 billion hours. Economically, the global cost of dementia exceeds 1.3 trillion USD per year and is projected to double to 2.8 trillion USD by 2030. Moreover, by 2050, low- and middle-income countries (LMICs) are expected to bear 71% of the global dementia burden[63], imposing significant financial strain on healthcare systems and socio-economic development, especially in resource-limited regions.

Recent research has highlighted epigenetic regulation as a critical factor in various neurodegenerative diseases. Epigenetic mechanisms directly influence key pathological biomarkers and demonstrate high sensitivity and specificity in disease diagnosis. Their levels vary across disease stages, offering potential for monitoring disease progression and supporting diagnostic decisions. Importantly, the reversible nature of epigenetic modifications, along with early aberrations in disease development, presents a valuable window for therapeutic intervention. Notably, non-coding RNAs (ncRNAs) detectable in peripheral blood and cerebrospinal fluid (CSF) provide minimally invasive biomarkers, circumventing the need for brain biopsies and enabling large-scale early diagnosis. Collectively, epigenetic regulation offers promising targets and strategies for the treatment of neurodegenerative disorders.

3.1 Alzheimer's Disease (AD) and Epigenetics

AD is characterized by age-related cognitive decline and distinctive neuropathological changes[64]. Its two primary pathological hallmarks are extracellular amyloid plaques composed of β-amyloid protein (Aβ) deposits and intracellular neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau protein, accompanied by granulovacuolar degeneration, Hirano bodies, and cerebrovascular alterations[65]. The classical amyloid cascade hypothesis attributes AD pathogenesis to abnormal processing of amyloid precursor protein (APP), where β-secretase (BACE1) plays a pivotal role in APP cleavage[66]. Increased BACE1 levels and enzymatic activity have been observed in sporadic AD brains, implicating BACE1 overexpression in disease initiation and progression.

Clinically, early AD manifests as episodic memory impairment, frequently accompanied by visuospatial and language deficits. Genetic factors contribute to 60%–80% of AD risk, with over 40 risk loci identified; among them, *APOE* alleles show the strongest association[67]. Currently approved treatments, including cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists, offer only modest symptomatic relief and do not halt disease progression[68].

Epigenetic mechanisms have emerged as crucial dimensions in understanding AD pathogenesis. Elevated DNA methylation of LINE-1 retrotransposons has been reported in AD patients[69]. Environmental exposures (e.g., lead) and cellular stress can induce hypomethylation of AD risk genes[70], while modulation of dietary methionine bioavailability (e.g., supplementation with vitamin B12 and folate) can reverse hypomethylation of promoters such as APP, *PSEN1*, and *MAPT*[68]. Thus, future epigenetic therapies targeting DNA methylation may involve manipulating methionine metabolism and employing specific DNMT and TET enzyme inhibitors to regulate methylation at AD risk loci[68].

As described, multiple miRNAs are dysregulated in the brain, blood, and CSF of AD patients, participating in pathological processes including Aβ accumulation, tau pathology, inflammation, and neuronal death. Several miRNAs modulate BACE1 and APP expression, contributing to Aβ peptide

accumulation and disease progression. Decreased levels of these miRNAs in AD brains lead to aberrant BACE1 protein upregulation, promoting toxic Aβ generation[71]. ncRNAs, especially miRNAs, hold promise as diagnostic biomarkers and therapeutic targets for AD. Detectable in peripheral fluids, they enable non-invasive, cost-effective early diagnosis. Additionally, RNA interference (RNAi) technologies aimed at reducing target gene expression provide novel therapeutic avenues[71].

3.2 Parkinson's Disease (PD) and Epigenetics

PD, or tremor paralysis, is the second most prevalent neurodegenerative disease after AD, marked by progressive, multifocal, and insidious onset. Clinical features include bradykinesia, muscle rigidity, resting tremor, and postural instability. Pathologically, PD is characterized by dopaminergic neuron loss in the substantia nigra, degeneration of the nigrostriatal pathway, and cytoplasmic Lewy bodies containing α-synuclein (α-syn) [72,75]. Genetic factors play a significant role in PD pathogenesis, with *LRRK2* (PARK8) mutations being the most common hereditary cause identified to date[73]. Diagnosis primarily relies on clinical observation, with definitive diagnosis requiring anatomical confirmation, which poses limitations.

Research shows that in PD, α-syn interacts with DNA methyltransferase 1 (DNMT1), sequestering it in the cytoplasm and reducing its nuclear levels, resulting in global hypomethylation—including in CpG island regions upstream of genes such as *SNCA*, *SEPW1*, and *PRKAR2A*. Hypomethylation of the *SNCA* first intron CpG island leads to α-syn overexpression, further enhancing DNMT1 cytoplasmic sequestration and establishing a pathological feedback loop[74]. Restoring *SNCA* methylation may thus help regulate α-syn expression in sporadic PD. Histone acetylation also plays a key role in PD. α-syn aggregation forming Lewy bodies is a pathological hallmark; glutathione S-transferase pull-down assays indicate α-syn directly binds histone H3, impeding histone acetyltransferase (HAT) binding, and resulting in decreased H3 acetylation. This hypoacetylation may suppress transcription of neuroprotective genes, contributing to neuronal dysfunction[75].

Besides lncRNAs and miRNAs, tRNA-derived fragments (tRFs) differ significantly in abundance between PD patients and healthy controls in CSF, serum, and cortex. A panel of tRF signatures can distinguish PD patients with high sensitivity (89–100%) and specificity (79–98%) [76], highlighting tRFs as promising non-invasive diagnostic biomarkers.

AD primarily affects the hippocampus and cerebral cortex, clinically manifesting as progressive memory loss, language impairment, visuospatial dysfunction, and cognitive decline. PD mainly involves the substantia nigra–striatal pathway, presenting with resting tremor, muscle rigidity, bradykinesia, and postural instability. Although epigenetic mechanisms regulate gene expression in both diseases, their specific targets and pathways differ. Future epigenetics-based precision therapies and non-invasive biomarkers hold potential to revolutionize early diagnosis and intervention strategies for both AD and PD.

4. Challenges and Prospects

This review systematically summarizes recent advances in epigenetic regulation—including DNA methylation, histone modifications, and non-coding RNAs (ncRNAs)—in the context of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). It highlights the critical roles of epigenetic mechanisms in the pathogenesis of AD and PD, including the association of Aβ accumulation and tau hyperphosphorylation with epigenetic modifications in AD, and the epigenetic regulation of α-synuclein aggregation in PD. Furthermore, this review explores the potential applications of epigenetics-based precision diagnostics, therapeutic strategies, and non-invasive biomarkers.

Despite the significant progress achieved, the application of epigenetics in neurodegenerative diseases still faces multiple challenges. In terms of disease diagnosis, epigenetic regulation involves multidimensional mechanisms such as DNA methylation, histone modifications, non-coding RNAs,

and chromatin remodeling, with complex interactions among them. This complexity hinders the comprehensive and accurate elucidation of disease mechanisms. Moreover, the high spatiotemporal and tissue specificity of epigenetic modifications limits their real-time and dynamic tracking. Epigenetic alterations are also susceptible to both genetic and environmental influences, resulting in considerable inter-individual variability and heterogeneity in biomarker expression and therapeutic response. Additionally, common comorbidities such as metabolic disorders and inflammatory responses further complicate diagnosis, as these conditions may interact with neurodegenerative processes via epigenetic mechanisms.

On the technical front, current omics technologies face limitations in resolving cell-type-specific epigenetic heterogeneity within affected brain regions. Furthermore, due to the dynamic and reversible nature of epigenetic marks, traditional detection methods are inadequate for real-time monitoring, which hampers the identification of critical therapeutic windows.

From a therapeutic perspective, some epigenetic modifications act directly on genetic material, necessitating drugs that are reversible and exhibit high safety profiles to avoid potential risks associated with irreversible alterations. In addition, many epigenetic drugs have poor permeability across the blood–brain barrier, leading to insufficient drug concentrations in the brain. The dynamic nature of epigenetic modifications also demands sustained and stable drug levels, which are difficult to achieve with conventional delivery methods, thereby limiting treatment efficacy.

Despite these challenges, epigenetics holds substantial potential in the field of neurodegenerative disease research. With advances in epigenomic technologies, the integration of multi-omics approaches, artificial intelligence for data analysis and prediction, and precision drug delivery systems, epigenetic-based strategies may overcome current limitations and offer new avenues for early diagnosis and personalized treatment. Future efforts should focus on promoting interdisciplinary collaboration and accelerating the translation of basic research into clinical applications. The development of epigenetic biomarkers and therapeutic targets may contribute to more accurate prevention, early diagnosis, and individualized treatment of neurodegenerative diseases, ultimately improving patient outcomes and quality of life.

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