The influence of epigenetic factors on the development of Alzheimer’s and Parkinson’s diseases

Kuat Sultan¹, Gantsa Andrei², Shomanov Arkhat³, Saulet Otebek⁴, Kerimova Aray Erzhanovna⁵

¹ Master of the first year of study in the specialty «Molecular Biology and Genetics»; Istinye University; Republic of Turkey
² School of Medicine, Faculty of Medicine; Kazakh National Medical University named after S.D. Asfendiyarov (KazNMU); Republic of Kazakhstan
³ School of Medicine, Faculty of Medicine, the 5th course; NJSC «Astana Medical University»; Republic of Kazakhstan
⁴ School of Medicine, Faculty of Medicine, the 5th course; NJSC «Astana Medical University»; Republic of Kazakhstan
⁵ Bachelor of Medicine, the 5th course; Kazakh-Russian Medical University; Republic of Kazakhstan

Abstract.
Alzheimer’s and Parkinson’s diseases continue to pose significant challenges in the field of neurodegenerative disorders, affecting millions of individuals worldwide. Over the past decades, it has become evident that epigenetic mechanisms, such as DNA methylation, histone modifications, and microRNA regulation, play a pivotal role in the pathogenesis of these diseases. In this article, we discuss recent scientific advancements in the study of epigenetic changes associated with Parkinson’s and Alzheimer’s diseases. We explore alterations in DNA methylation and their impact on the expression of genes related to neurodegeneration. Histone modifications, including acetylation and methylation, and their role in the regulation of genes associated with inflammation and amyloid proteins are also elucidated. Furthermore, we delve into the influence of microRNAs and non-coding RNAs on the pathogenesis of these diseases. Understanding the epigenetic mechanisms in Parkinson’s and Alzheimer's diseases may shed light on new prospects for diagnosis, treatment, and prevention of these neurodegenerative disorders.

Keywords:
epigenetic
Alzheimer
Parkinson
DNA methylation
histone modifications
microRNA
Introduction:
Parkinson's and Alzheimer's diseases are two of the most prevalent neurodegenerative disorders, contributing significantly to the global burden of morbidity and disability. Despite years of research, the precise molecular mechanisms underlying these diseases remain poorly understood. However, in recent decades, it has become evident that epigenetic mechanisms play a crucial role in the pathogenesis and development of these conditions. In this article, we will examine two key epigenetic mechanisms—DNA methylation and histone modifications—and their roles in the development of Parkinson's and Alzheimer's diseases. We will also discuss the role of microRNAs and non-coding RNAs in these processes.

Materials and Methods:
To conduct a literature review and organize the obtained data, a search was performed for scientific articles, reviews, and meta-analyses in medical databases such as PubMed, MEDLINE, and other relevant sources. The studies included in the review covered the period from 2018 to 2023 and were limited to publications in the English language. Keywords and phrases such as "Alzheimer's disease," "Parkinson's disease," "epigenetics," "DNA methylation," and "histones" were used for searching and selecting relevant research.

Results:
I. Epigenetic Mechanisms in Alzheimer's Disease
A. DNA Methylation
DNA methylation is an epigenetic process in which methyl groups are added to cytosine bases of deoxyribonucleic acid (DNA), regulating gene activity and, consequently, cellular functions [1]. The primary factors involved in this process include genetic predisposition and environmental factors [2]. Individuals with genetic variations, such as mutations in genes predisposing to changes in epigenetic markers like DNA methylation, are at an increased risk of developing Alzheimer's disease (AD). As highlighted in a study [3], hypermethylation, an excessive methylation process, occurs in certain gene regions, suppressing gene activity. This leads to the suppression of gene expression responsible for neuronal functions and amyloid protein metabolism, contributing to
their accumulation in the brain. Conversely, hypomethylation [4], resulting from decreased DNA methylation, activates genes associated with inflammation and amyloid proteins, also contributing to the development of Alzheimer's disease.

Genetic predisposition, which plays a significant role in AD development, is associated with mutations in the APP, PSEN1, and PSEN2 genes for early-onset disease, as well as the APOE gene polymorphism for late-onset disease [5]. DNA hypomethylation, as previously described, and reduced levels of S-adenosylmethionine (SAM) [6], leading to changes in homocysteine and folate levels in the blood [7], are linked to the activation of genes involved in amyloid protein (Aβ) formation. Furthermore, hypermethylation of genes such as ANK1, RPL13, RHBDF2, DUSP22, and SORL1 contributes to the progression of pathological processes, such as Aβ and tau protein formation [8,9,10].

B. Histone Modification and Its Influence on Chromatin Conformation

Acetylation and deacetylation of histones are crucial epigenetic modification processes that regulate gene activity. Histones are protein molecules around which DNA is wound, forming a structure known as chromatin. These histone modifications affect DNA accessibility for transcription (the process of reading genetic information) and, consequently, gene expression [11]. For instance, some studies indicate that the level of histone H3 and H4 acetylation may be elevated in Alzheimer's disease patients, potentially leading to increased expression of genes associated with inflammation and amyloid pathology. On the other hand, histone deacetylation may reduce gene activation, playing a role in regulating neuroplasticity and memory [12-14]. Histone acetylation plays a crucial role in various mechanisms, such as cognitive functions, memory, stress response, synaptic plasticity, DNA repair, and neuronal death [15-17].

Some studies have shown an increase in the level of H3K9me2 (an epigenetic modification to the DNA packaging protein Histone H3) in the prefrontal cortex of laboratory mice with Alzheimer's disease and in patients. This, in turn, leads to an increase in the levels of proteins responsible for H3K9 methylation. Inhibiting these enzymes reversed the
changes in H3K9me2 and prevented the reduction in NEP gene expression, indicating a potential role of histone methylation in AD [18-19]. An increase in H3K9me2 has also been observed in the neurons of the cortex and hippocampus in mice subjected to hypoxia and in AD patients. This was associated with reduced NEP gene expression, which may contribute to beta-amyloid accumulation. The controlled targeting of the G9a enzyme, catalyzing H3K9me2 methylation, resulted in reversible changes in H3K9me2 and prevented the decrease in NEP [20].

C. The Role of Non-Coding RNAs in Alzheimer's Disease Pathogenesis

MicroRNAs (miRNAs) are short non-coding RNA molecules that play a role in regulating gene expression. The formation and functioning of miRNAs involve several stages, starting from miRNA gene transcription and ending with the regulation of gene expression by interacting with messenger RNAs. These processes play a significant role in regulating various biological processes and are essential for understanding the molecular mechanisms of various diseases, including Alzheimer's disease.

MiRNAs can interact with molecular targets involved in AD pathogenesis, such as S100A8, IGFBP-2, miR-146a-5p, and miR-132-3p [21-23]. All of these factors can amplify inflammatory processes in the pathogenesis of this disease.

II. Epigenetic Mechanisms in Parkinson's Disease

A. DNA Methylation

As previously described, DNA methylation is a modification in which a methyl group (-CH3) is added to cytosine, forming 5-methylcytosine. This process typically occurs on cytosines adjacent to guanines in CpG islands. DNA methylation plays a crucial role in gene regulation, cell differentiation, and development. DNA methylation acts as a "switch" for genes, where heavily methylated genomic regions are usually less active at the transcriptional level (gene expression is turned off), while regions with lower methylation are more active (gene expression is turned on). For example, the SNCA gene (alpha-synuclein) codes for the alpha-synuclein protein, which plays a central role in the pathogenesis of Parkinson's disease. Demethylation of a CpG island in the SNCA gene's intron 1 leads to increased gene
expression. Patients exhibit reduced methylation of the CpG island in several brain regions, such as the substantia nigra, putamen, and cortex, which is associated with increased SNCA expression [24-25]. The level of methylation of the SNCA gene promoter polymorphism in patients correlates with the dosage of L-dopa (a medication for Parkinson's disease). Patients receiving higher doses of L-dopa have higher methylation levels, resulting in lower SNCA gene expression [26].

B. The Role of Histone Modifications in Parkinson's Disease Regulation

Chromatin remodeling, responsible for histone modifications, represents a dynamic process that regulates essential physiological functions, including gene expression. Post-translational modifications of histones, such as methylation and acetylation, play a pivotal role in altering chromatin structure and regulating DNA for transcription. Histone acetylation is typically associated with gene transcriptional activity. Interestingly, Parkinson's disease patients exhibit increased histone acetylation levels in the midbrain dopaminergic neurons compared to control subjects. This suggests the crucial role of histone modifications in this neurodegenerative disease. Alpha-synuclein, the primary protein underlying Parkinson's disease, is an interesting aspect to discuss. It is regulated by histone acetylation and, conversely, influences histone acetylation, possibly through feedback mechanisms. Studies have shown that alpha-synuclein interacts with histones in cell nuclei, accelerating its fibrillation and brain toxicity [27]. It has been identified that alpha-synuclein directly binds to histones, inhibiting histone H3 acetylation through interaction with SIRT2, a deacetylase enzyme [28]. Furthermore, mutations of alpha-synuclein (p.A30P and p.A53T) exhibit increased nuclear localization, which is associated with Parkinson's disease [29-30].

Moreover, genes and molecules associated with Parkinson's disease, such as SNCA, MAPT, and PINK1, are also regulated through histone modifications. For instance, the MAPT H1 haplotype is associated with activating histone modification H3K4me3, while the H2 haplotype is linked to repressive modification H3K27me3. The PINK1 protein regulates HDAC3 activity through phosphorylation, impacting the deacetylase's activity and influencing p53 stability and, consequently,
neuronal apoptosis. These findings underscore the importance of histone modifications in Parkinson's disease regulation and open prospects for the use of HDAC inhibitors as neuroprotective agents against alpha-synuclein toxicity and other aspects of neurodegeneration [31-32].

**Conclusion:**

In conclusion, Parkinson's and Alzheimer's diseases remain significant medical and research challenges, necessitating a deeper understanding of their molecular mechanisms for the development of new diagnostic and treatment approaches. Epigenetic mechanisms, such as DNA methylation, histone modifications, and microRNA regulation, play a substantial role in the pathogenesis of these diseases, and their study provides us with valuable insights. Scientific research in this field continues to expand our knowledge and provides a robust foundation for the development of personalized approaches to the treatment and prevention of Parkinson's and Alzheimer's diseases. We hope that further investigations in the field of epigenetics will help us discover more effective strategies to combat these severe neurological disorders.

**References:**

[8] Alzheimer's disease pathology is associated with early alterations in brain DNA methylation at ANK1, BIN1, RHBDF2 and other loci (harvard.edu)
[10] Promoter hypermethylation of the phosphatase DUsp22 mediates PKA-dependent TAU phosphorylation and CREB activation in Alzheimer's disease - PubMed (nih.gov)
[12] The acetylation of tau inhibits its function and promotes pathological tau aggregation - PubMed (nih.gov)
[14] Sirtuin 1 reduction parallels the accumulation of tau in Alzheimer disease - PubMed (nih.gov)
[16] The emerging field of epigenetics in neurodegeneration and neuroprotection - PubMed (nih.gov)
[17] Recovery of learning and memory is associated with chromatin remodelling - PubMed (nih.gov)
[18] Inhibition of EHMT1/2 rescues synaptic and cognitive functions for Alzheimer's disease - PubMed (nih.gov)
[20] Hypoxia-induced down-regulation of neprilysin by histone modification in mouse primary cortical and hippocampal neurons - PubMed (nih.gov)
[26] L-dopa increases α-synuclein DNA methylation in Parkinson's disease patients in vivo and in vitro - PubMed (nih.gov)
[27] Nuclear localization of alpha-synuclein and its interaction with histones - PubMed (nih.gov)
[28] Alpha-synuclein acts in the nucleus to inhibit histone acetylation and promote neurotoxicity - PubMed (nih.gov)
[29] Large-scale identification of coregulated enhancer networks in the adult human brain - PubMed (nih.gov)
[31] PINK1 positively regulates HDAC3 to suppress dopaminergic neuronal cell death - PubMed (nih.gov)