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OPINION ARTICLE

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Neurodegenerative Diseases and Epigenetics: Impact of Non-Coding RNAs on Disease Progression

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About the Study

The science of epigenetics, which analyzes heritable modifications in gene expression without affecting the underlying DNA sequence, has become more important in a variety of biological processes, such as the etiology of neurodegenerative disorders. Neurodegenerative illnesses, including Amyotrophic Lateral Sclerosis (ALS), Huntington's Disease (HD), Parkinson's Disease (PD), and Alzheimer's Disease (AD), are distinguished by a progressive loss of neuronal structure or function that results in the death of the affected neurons. The complexity of these diseases is identified by the multifactorial nature of their etiology, which involves genetic, environmental, and epigenetic factors. Epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs, play a significant role in the regulation of gene expression in neuronal cells.

DNA methylation, the addition of a methyl group to the fifth carbon of the cytosine ring, typically occurs at (5'—C—phosphate—G—3') Cytosine-Guanine (CpG) dinucleotide and is a key regulator of gene expression. For instance, in AD, global hypomethylation and locus-specific hypermethylation are common. Hypomethylation can lead to genomic instability, while hypermethylation of promoter regions of specific genes, such as those involved in Amyloid Precursor Protein (APP) processing, can result in decreased expression of neuroprotective genes and increased amyloid-beta production. Similarly, in PD, the methylation status of genes related to dopamine synthesis and degradation, such as alpha-synuclein and Ttyrosine Hydroxylase (TH), is modified, leading to impaired dopaminergic function.

Histones are the proteins that cover DNA, and their post-translational modifications, such as acetylation, methylation, phosphorylation, and ubiquitination, influence chromatin structure and gene expression. Histone Acetyl Transferases (HATs) and Histone De Acetylases (HDACs) regulate histone acetylation, which is generally linked to gene activation. In neurodegenerative diseases, dysregulation of histone acetylation is a common feature. For example, in AD, reduced acetylation of Histone H3 at lysine 9 and lysine 14 has been linked to the repression of memory-related genes. Inhibitors of HDACs have shown potential in restoring cognitive functions in AD models by enhancing the expression of genes involved in synaptic plasticity and memory.

Non-coding RNAs, such as Long Non-Coding RNAs (LncRNAs) and MicroRNAs (miRNAs) are essential for controlling gene expression at the post-transcriptional level. MiRNAs are short RNA molecules that bind to complementary sequences in target mRNAs, leading to their degradation or translational repression. LncRNAs, which are longer RNA molecules that do not code for proteins, also play significant roles in the regulation of gene expression and have been implicated in neurodegeneration. The lncRNA *BACE1* antisense transcript (*BACE1*-AS) increases the expression of *BACE1* mRNA in AD, hence enhancing the formation of amyloid-beta. Similarly, in HD, the lncRNA Nuclear Enriched Abundant Transcript1 (*NEAT1*) is upregulated and contributes to the pathogenesis by modulating the expression of genes involved in neuronal survival and inflammation.

The communication between different types of epigenetic modifications adds an additional layer of complexity to gene regulation in neurodegenerative diseases. Methylated DNA can recruit Methyl-CpG-binding domain proteins, which in turn recruit HDACs, leading to histone deacetylation and chromatin condensation.

Epigenetic modifications also interact with signaling

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pathways and transcription factors to influence neuronal function and survival. In neurodegenerative diseases, aberrant activation of Nuclear Factor kappa B (NF-κB) has been linked to chronic neuroinflammation and neuronal damage. Modulating the epigenetic regulation of NF-κB could potentially mitigate inflammatory responses and neuronal loss in these diseases. Non-coding RNAs also represent potential therapeutic targets. Strategies to modulate miRNA levels, such as miRNA mimics or antagomirs, can restore normal gene expression patterns. For example, increasing the levels of microRNA-29 or microRNA-107 could potentially reduce amyloid-beta production in AD. Targeting lncRNAs that stabilize disease-related mRNAs, such *BACE1*-AS in AD, provides an additional therapeutic approach.