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FROM METHYLATION TO miRNAs: THE EPIGENETIC LANDSCAPE OF NEURODEGENERATIVE DISEASES AND ITS THERAPEUTIC POTENTIAL.

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ABSTRACT

Background: In the pathobiology of neurodegenerative diseases (NDDs), including Huntington's, Parkinson's, and Alzheimer's, epigenetic dysregulation has become a significant factor. Neuronal dysfunction and degeneration have been linked to dysregulated non-coding RNAs, aberrant DNA methylation, and histone changes. Environmental pollutants, which cause oxidative stress, inflammation, and genomic instability, frequently make these changes worse. Reversing epigenetic abnormalities might provide a way to mitigate neurodegeneration and restore brain systems. **Objective:** To synthesize current knowledge on the epigenetic mechanism", "Epigenetic Alterations in Neurodegenerative Diseases", "epigenetic therapy in neurodegeneration", and challenges, limitations in epigenetics of neurodegenerative disorders. **Methodology**: A narrative review was conducted through a structured search of PubMed, Scopus, Web of Science, and Google Scholar, focusing on articles published on role of epigenetic landscape of Neurodegenerative Diseases and Its Therapeutic Potential. Keywords related to epigenetic mechanism", "Epigenetic Alterations in Neurodegenerative Disorders", "epigenetic therapy in neurodegeneration", and challenges, limitations in epigenetics of neurodegenerative disorders. **Results:** The review emphasizes the critical role of epigenetic landscape of neurodegenerative diseases and its therapeutic potential in the wide range. It identifies A revolutionary

strategy for tackling the underlying mechanisms of NDDs is the use of epigenetic modulators. These treatments have the ability to reverse the epigenetic dysregulation brought on by environmental pollutants and genetic predispositions by focusing on reversible alterations in gene expression. **Conclusion:** As the concluded remarks a revolutionary strategy for tackling the underlying mechanisms of NDDs is the use of epigenetic modulators.

1. INTRODUCTION

The term "epigenetics" refers to meiotically and/or mitotically heritable modifications in gene expression that are influenced by environmental variables and interoceptive processes rather than nucleotide sequences in DNA. Epigenetic modifications include changes in both coding and non-coding RNAs, DNA methylation, and histones that affect how the genome is expressed (Xylaki et al., 2019). Without changing DNA sequences, all of these changes have an impact on how genes and proteins are expressed. Epigenetic alteration may have catastrophic consequences in the degeneration of brain cells. A major global health concern, neurodegenerative disorders (NDDs) are typified by the progressive death of neurons along with the breakdown of the brain's connectome and functions. The illnesses cause crippling cognitive and motor deficits that have a significant negative influence on a person's quality of life, which includes their relationships, thoughts, feelings, and behaviors (Alkahtani et al., 2023). Because environmental variables have a significant impact on neurodegenerative disorders like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Prion disease, and others, modifications in the epigenome are involved. As life expectancy has increased, so too has the prevalence of NDDs, placing an increasing strain on healthcare systems around the globe. By 2030, one out of every six people on the planet is expected to be 60 years of age or older. Life expectancy is gradually rising above 80 years in wealthy nations (Kakoti et al., 2022). Neuroepigenetics is the word used to describe the study of neuronal epigenetics. Neuroepigenetic changes are not inherited, in contrast to standard epigenetics. Epigenetic pathways are crucial for circuit control and information storage. Neuroepigenetics can affect how the central nervous system develops and functions (Hwang et al., 2017). The essential role that epigenetic processes play in neurogenesis (Yao et al., 2016) reflects the significant role that their dysregulation plays in the etiology of neurological conditions. Although not directly brought on by genetic abnormalities, faulty epigenetic pathways have been connected to Parkinson's disease (PD) and Alzheimer's disease (AD).

2. METHODOLOGY

To uncover, assess, and incorporate pertinent results from preclinical and clinical research, the review employs a systematic methodology.

2.1. Literature Search Strategy

A comprehensive literature search was conducted using databases such as PubMed, Scopus, Web of Science, and Google Scholar. The search included studies published between 2000 and 2025, ensuring a broad coverage of both foundational and recent advancements in the field. Keywords used in the search included “epigenetic mechanism”, “Epigenetic Alterations in Neurodegenerative Disorders”**,** “epigenetic therapy in neurodegeneration”, and challenges, limitations in epigenetics of

neurodegenerative disorders". Boolean operators (AND, OR) were applied to refine search queries and capture relevant studies. A total of 1000 records were initially identified. After removing duplicates and applying inclusion/exclusion criteria, 125 studies were included in the final qualitative synthesis.

2.2. Inclusion and Exclusion Criteria

To guarantee their quality and relevance, studies were chosen using predetermined inclusion and exclusion criteria.

• Inclusion Criteria

Research examining how epigenetic processes contribute to NDDs. Clinical and preclinical research on the role of epigenetics in neurodegenerative diseases using animals and cell cultures. Studies on the effects of the environment on NDDs' epigenetic dysregulation. Studies evaluating the effectiveness of epigenetic treatment. Articles from peer-reviewed journals that are published in English were included.

• Exclusion Criteria

Research that is primarily concerned with genetic mutations that are not connected to epigenetics. Studies involving non-mammalian models or non-neurological disorders. Opinion pieces, reviews, or commentary that lack experimental evidence. Small sample sizes without statistical significance or articles with limited methodology.

2.3. Data Extraction and Synthesis

Key themes, such as mechanisms of epigenetic dysregulation, therapeutic interventions, preclinical and clinical trial outcomes, drug delivery developments, and biomarker development, were used to comprehensively collect and categorize pertinent data from the chosen research. Where necessary, summaries of the retrieved data are provided to improve accessibility and clarity.

3. Mechanisms of Epigenetic Modification

Epigenetic mechanisms, which include DNA methylation and hydroxymethylation, post-translational modifications of histone tails and nucleosome positioning, and mechanisms mediated by long and short non-coding RNA molecules, control the chromatin structure and levels of gene expression without altering the primary DNA sequence. Human development and cell differentiation depend on these processes, which are essential for differentiated cells' biological functions and enable strict control of gene expression levels in response to environmental cues and metabolic demands. In particular, learning and memory processes depend on the neuronal epigenome, which is extremely susceptible to outside inputs (Creighton et al., 2020). The pathophysiology of neurological illnesses is significantly impacted by the dysregulation of epigenetic mechanisms, which is reflected in the basic relevance of these systems during neurogenesis (Yao et al., 2016). For instance, abnormal epigenetic pathways have been linked to Parkinson's disease (PD) and Alzheimer's disease (AD), which are not explicitly brought on by genetic changes. Chromatin Remodeling Complexes, non-coding RNAs, histone modifications, and DNA methylation all contribute to epigenetic mechanisms. The "epigenetic machinery" is a group of enzymes that add, delete, and read epigenetic marks, enabling chromatin remodeling to either promote or repress gene transcription. The reversibility of epigenetic marks, which is essential for memory formation and consolidation in neurons, is made possible by the activity of these enzymes (Creighton et al., 2020). People with major neurodegenerative diseases, such as Alzheimer's disease (AD) (Coppedè, 2021a), Parkinson's disease (PD) (Rathore et al., 2020), and amyotrophic lateral sclerosis (ALS) (Coppedè, 2020), have both global and gene-specific epigenetic changes in their blood and brain tissues.

3.1 DNA Methylation

When a methyl group (CH3) is added to the fifth position of the cytosine pyrimidine ring, 5-methylcytosine (5-mC) is formed. This type of DNA methylation usually takes place in CpG islands, which are regions that are unusually enriched in the CpG dinucleotide and found in the promoter region of nearly half of human genes and comparatively absent from most other places in the genome (Fournier et al., 2012; Jones, 2012). The suppression of gene expression is caused by DNA methylation. DNA methylation has been shown to be essential for memory acquisition and retention (Miller et al., 2007). In addition to being a result of inheritance, methylation also happens in response to environmental influences, age, and illnesses. DNA methylation has been observed to occur not only at the cytosine phosphate-guanine (CpG) island but also at non-CpG (CpH) sites. Because of this limiting transcription, there are a lot of CpG methylations in the neuronal gene. DNA methylation is caused by DNA methyl transferases (DNMT), including DNMT1, DNMT3A, and DNMT3B. Research has demonstrated that mice that have both DNMT1 and DNMT3A deleted have impaired hippocampal-based learning and memory (Feng et al., 2010). Ten-eleven translocation proteins (TET) that are methylcytosine dioxygenases are responsible for the conversion of 5-methyl-cytosine (5mC) to 5-hydroxymethylcytosine (5hmC) in synaptic plasticity and memory-related genes (Tahiliani et al., 2009). TET is in charge of converting 5mC into 5-carboxy-cytosine (5caC), 5-formyl-cytosine (5fC), and 5hmC. As a result, these genes activate the memory-related genes and demethylate DNA.

3.2 Histone Modifications

Acetylation, methylation, and phosphorylation are examples of histone changes that are important (Rossetto et al., 2012). Histone acetylation is typically associated with active gene transcription, whereas deacetylation causes transcriptional repression and chromatin condensation (Shvedunova et al., 2022). Reduced histone acetylation has been found in NDDs, especially in genes involved in anti-inflammatory and neuronal repair. Neuronal damage is exacerbated by the chromatin condensation that results, which restricts the accessibility of transcription factors to target genes (Neal et al., 2018). For instance, decreased histone acetylation has been connected to defective neuroprotective gene transcription in HD, which leads to motor neuron death (Valor et al., 2015). Numerous important studies have quantified the extent of these histone alterations. In a series of investigations using postmortem brain tissues from AD patients and mouse models, Gräff et al. (2012) found that the hip pocampus had less histone H4K12 acetylation. They found 2279 genes exhibiting H4K12 deacetylation using ChIP-seq, with 91% of these genes being downregulated in AD brains (Gräff et al., 2012). According to research, AD patients have about 50% higher HDAC2 levels than controls (Gräff et al., 2012). In their analysis of histone acetylation patterns in 20 postmortem HD brains and matched controls, Klein et al. (2019) found that H3K9ac and H3K27ac at neuronal survival gene promoters were reduced by 35–40%, with the degree of reduction increasing with the stage of the disease.

3.3 Non-coding RNAs

By attaching to messenger RNAs and modifying their stability or translation, non-coding RNAs—particularly microRNAs—control gene expression post-transcriptionally. Neuronal toxicity in NDDs is a result of dysregulated microRNAs (Olufunmilayo et al., 2023). The 3 Untranslated region (UTR) of mRNAs is where non-coding RNAs like MicroRNAs (miRNA) bind to mediate post-transcriptional control, which prevents

translation or destruction. Neuronal cell development and differentiation are aided by miRNA-124. When miRNA-124 suppresses PTBP1, neuronal cells are formed, while non-neuronal cells may also arise. Additionally, it has been found that certain non-coding RNAs are necessary for dendritogenesis, synapse formation, and maturation (Schratt, 2009). The local protein synthesis required for synaptic plasticity and neuronal survival is likewise regulated by neurone-specific miRNA. In hippocampus neurons, long non-coding RNAs increase the expression of genes linked to synapses (Raveendra et al., 2018). For example, by downregulating anti-apoptotic genes, elevated levels of microRNA-34a in AD reduce neuronal survival (Li et al., 2018). In a similar vein, PDs frequently exhibit increased microRNAs linked to oxidative stress and inflammation, which exacerbates neuronal damage (Martinez et al., 2017). In a number of illnesses, specific microRNA dysregulation has been measured. To examine the hippocampus miRNA expression profiles of AD patients and mice, Zovoilis et al. (2011) used qRT-PCR and deep sequencing (Maciotta et al., 2013). In contrast to controls, they found that brains exhibiting symptoms of AD had 2.8 times higher levels of miR-34c. According to Zovoilis et al. (2011), in vitro studies showed that miR-34c directly targets SIRT1 mRNA, lowering protein levels by about 40% and causing cognitive deterioration. After examining serum samples from 30 controls and 32 PD patients, Maciotta et al. (2013) discovered a panel of 18 miRNAs that were differentially expressed. These included miR-30c and miR-148b, which were correlated with disease progression and severity scores and shown an over three-fold increase in expression in PD patients (Maciotta et al., 2013). Cerebrospinal fluid from 41 AD patients and 27 controls was miRNA profiled by Johnson et al. (2008), who found that a signature of 12 miRNAs could 93% accurately identify AD patients.

3.4 Chromatin Remodeling Complexes

Histone and nonhistone DNA-binding proteins, genomic DNA, and related components in the cell nucleus comprise the macromolecular complex known as chromatin (Mehler, 2008; Portela and Esteller, 2010). Any component of the continuum, such as a whole genome, a chromosome, a particular gene, a chromosomal region, or a single functional genomic element, can be referred to by its chromatin state. The most fundamental repeating component of chromatin is a nucleosome. It is made up of 147 base pairs of DNA that are coiled around an octamer of histone proteins. Two of each "core" histone protein (H2A, H2B, H3, H4) or noncanonic "variant" histone protein (e.g., H2A.Z, H3.3) are found in each octamer. DNA that is folded around linker histones (i.e., H1) creates the distinctive "beads on a string" pattern that binds nucleosomes together. Different levels of compaction are represented by the sequential packaging of these chromatin fibers into higher-order structures. The nuclear machinery involved in transcription, DNA replication, DNA repair, and other processes can access the DNA when chromatin is in one of two states: highly compacted (heterochromatin) or more loose (euchromatin). The understanding that chromatin states are highly dynamic, susceptible to changes at all levels (histone, nucleosome, and higher-order configurations) in response to constantly shifting environmental and interoceptive cues, and in charge of actively modulating genomic activity has led to a great deal of interest in the postgenomic era, much like DNA methylation status. Furthermore, the dysregulation of these variables and/or related chromatin states is increasingly being linked to the pathophysiology of neurologic and psychiatric diseases. These alterations are

mediated by molecular factors that are essential to numerous neurobiologic processes.

4. Epigenetic Alterations in Neurodegenerative Disorders

4.1 Alzheimer's Disease

The most prevalent neurodegenerative illness and the main type of dementia in older adults is Alzheimer's disease (AD). Over time, the disease's symptoms worsen. Senile plaques (SP), which are extracellular amyloid deposits, and neurofibrillary tangles (NFT), which are intra-neuronal clumps of hyperphosphorylated tau protein, are observed in affected brain regions. β-secretase (BACE1) and γ-secretase, a protein complex made up of presenilins and other proteins, are responsible for the proteolytic cleavage of its precursor protein (APP), which results in the amyloid β (Aβ) peptide, the main component of SP (Overk and Masliah, 2014). A postmortem examination of AD brains revealed an enrichment of acetylated histone H3 on lysine 27 in genomic regions related to tau and β-amyloid-dependent pathology, with the resulting overexpression of the genes located within, such as APP, PSEN1 and 2, and MAPT (Marzi et al., 2018). DNA methylation is altered in several genes associated with the disease, including the amyloid precursor protein (APP), Apolipo protein E (APOE), and Ankirin 1 (ANK1) (Smith et al., 2019).

4.2 Parkinson's Disease

Parkinson's disease (PD), the second most common neurodegenerative disorder after AD, is characterized clinically by resting tremor, rigidity, bradykinesia, and postural instability, as well as non-motor symptoms like autonomic insufficiency, cognitive impairment, and sleep disorders. Pathologically, PD is characterized by a progressive and profound loss of neuromelanin-containing dopaminergic neurons in the substantia nigra with the presence of eosinophilic, intracytoplasmic inclusions called Lewybodies (LBs; containing aggregates of α-synuclein and other substances), as well as Lewy neurites in surviving neurons. Levodopa and dopaminergic therapy can help alleviate some of the symptoms, but there is no cure to stop the disease's progression (Thomas and Beal, 2011). Most occurrences of Parkinson's disease (PD) are sporadic, most likely caused by a mix of environmental exposures, polygenic inheritance, and complicated gene-environment interactions on top of gradual and persistent aging-related neuronal dysfunction (Migliore and Coppedè, 2009). Studies in PD families have identified at least 15 PD loci (PARK1-15) and many causal genes, indicating that PD is inherited as a Mendelian characteristic in a small percentage of individuals (Nuytemans et al., 2010). Analysis of promoter methylation of causative PD genes in post-mortem brains and peripheral blood cells of affected persons has been the main focus of the involvement of epigenetics in disease etiology (Coppedè, 2012). In particular, the substantia nigra and other brain regions of sporadic PD patients showed lower methylation levels of the gene coding for α-synuclein (SNCA gene), the first known causal PD gene (Jowaed et al., 2010; Matsumoto et al., 2010). Furthermore, it was demonstrated that DNMT1 is sequestered from the nucleus into the cytoplasm by α-synuclein, and post-mortem PD brains showed lower levels of DNMT1 (Desplats et al., 2011). The majority of research on histone changes in Parkinson's disease (PD) comes from studies conducted in cell cultures and animal models of the disease, such as those caused by overexpressing human α-synuclein, paraquat and rotenone, or the mitochondrial poisons 1-methyl 4-phenylpyridinium (MPP+) (Harrison and Dexter, 2013). Overall, those results showed that various HDACi are neuroprotective against α-synuclein-mediated

toxicity, and that α-synuclein interacts with his tones and inhibits histone acetylation.

4.3 Huntington's Disease

Mutant huntingtin directly interacts with HAT proteins, resulting in altered histone acetylation, according to research on Huntington's disease (HD), a neurodegenerative disease brought on by trinucleotide repeat expansion in the gene (HTT) encoding the huntingtin protein (Steffan et al., 2000; Jiang et al., 2006). In both fly and mouse models of HD, therapy with HDACi stopped the continued progressive neuronal degeneration, according to a number of research (reviewed by Gray, 2010).

5. Epigenetic Therapies

Research on the connection between human disease and epigenetics has grown in importance in recent years. As previously stated, epigenetic changes have a significant impact on gene expression, and abnormal changes have been connected to a number of illnesses, such as cancer, neurological conditions, heart disease, and, of course, the Covid-19 syndrome (Vodovotz ET AL., 2020). The development of targeted epigenetic therapeutics has become possible due to the increasing comprehension of epigenetic pathways in disease (Egger et al., 2004). DNA methyltransferase and histone deacetylase inhibitors are examples of epigenetic medications that might alter epigenetic marks and possibly reverse disease-related aberrant gene expression patterns. These therapies are presently being investigated in clinical trials for a number of illnesses, such as cancer and neurological conditions, after demonstrating promise in preclinical research.

Whereby gene-environment interactions are a result of neuronal degenerative processes and which contribute to the start of the disease by causing age-related decreases in cognitive and motor skills. Nonetheless, a number of epigenetic markers have been suggested as possible therapeutic targets to treat or postpone neurodegeneration because of their reversibility (Coppedè, 2021a). There are two ways to control DNA methylation: the first involves using substances called DNMT inhibitors to block DNMTs, and the second involves giving methyl donor substances like SAM or folates and other B-group vitamins that are necessary for the synthesis of SAM (Coppedè, 2021a). The Food and Drug Administration has approved azacitidine and decitabine as DNMT inhibitors for the treatment of hematological malignancies. Other medications are being studied for hematological and solid tumors. Unfortunately, these substances are frequently poisonous and comparatively unstable, which makes them appear to be more beneficial for cancer cells that proliferate quickly than for neurons that do not. Decitabine, for instance, has been demonstrated to increase PD-related genes and worsen neurotoxicity in cultured dopaminergic neurons. This includes demethylating the SNCA gene, which codes for α-synuclein (Wang et al., 2013). One-carbon metabolism, a crucial metabolic route that connects the folate and methionine cycles, produces SAM, the ubiquitous intracellular methyl donor molecule. Therefore, dietary folates and associated B-group vitamins are necessary for the synthesis of SAM, and their deficiency can affect the methylation capacity of cells (Coppedè, 2021b). Presenilin 1 protein, a part of the ϒ-secretase complex necessary for the synthesis of amyloid-beta peptide, the neurotoxic peptide that builds up in AD brains, is encoded by the PSEN1 gene, which is one of the genes responsible for familial AD types. In both the blood of living AD patients and post-mortem AD brain regions, we recently found decreased PSEN1 methylation levels, which led to increased gene expression. This suggests that PSEN1 may be an epigenetic biomarker of AD (Monti et al., 2020). While dietary supplementation

of SAM restored PSEN1 methylation levels and improved cognitive functions in the animals, prior research in AD epigenetics showed that a diet deficient in methyl donor compounds, such as folates and other B-group vitamins, caused PSNE1 hypomethylation, which in turn led to increased amyloid-beta peptide production and AD-like symptoms in rodents. These findings suggest that SAM supplementation could be a therapeutic option for AD (Fuso et al., 2012). SAM is being investigated as a possible drug to correct AD-related epigenetic alterations and attenuate disease symptoms in recently reviewed cell culture, animal, and human trials (Coppedè, 2021a). Overall, research using animal or cell culture models of AD showed that SAM has antioxidant and epigenetic qualities, which lessen the burden of amyloid-beta peptide buildup and strengthen antioxidant defenses. Nutraceuticals such alpha-tocopherol, N-acetyl cysteine, and acetyl-L-carnitine, as well as formulations containing SAM, folic acid, and vitamin B12, have also been studied in AD patients and have demonstrated some improvement in cognitive symptoms. Unfortunately, human trials did not assess changes in DNA methylation levels, therefore it is impossible to assess these formulations' epigenetic qualities (Coppedè, 2021a). Since SAM affects the methylation levels and function of several enzymes involved in dopamine metabolism, such as dopamine receptors and transporters, it has been demonstrated that intracranial injection of SAM causes PD-like changes in rodents, such as striatal dopamine depletion, tremors, and hypokinesia (Lee et al., 2004). Thus, rather than focusing on DNA methylation, epigenetic treatments in PD animal models mostly targeted histone tail alterations (Coppedè, 2014). Targeting reversible alterations in gene expression to restore neural function, epigenetic modulators offer a possible treatment strategy for NDDs (Babar et al., 2022). Due to their ability to reverse epigenetic dysregulation, two major families of modulators—HDAC inhibitors and DNMT inhibitors—have attracted a lot of interest (Didonna et al., 2015). These substances have the potential to lessen neuronal degeneration by reactivating dormant neuroprotective genes and lowering neuroinflammation (Ye et al., 2024).

5.1 HDAC Inhibitors

Enzymes called HDACs remove acetyl groups from histones, which causes chromatin condensation and inhibits the transcription of genes. Overactive HDACs suppress genes essential for neuronal survival and repair in NDDs. According to Rogge et al. (2013), HDAC inhibitors reopen chromatin for the transcriptional activation of neuroprotective genes by restoring histone acetylation. The ability of HDAC inhibitors to raise histone acetylation, which improves the transcription of genes involved in brain plasticity and repair, is the main mechanism of action (Kumari et al., 2024). By altering the expression of inflammatory cytokines and stress-response pathways, these substances also lessen neuroinflammation (Shen et al., 2020).

HDAC inhibitors are appealing options for reducing inflammation and neurodegenerative processes in AD, PD, and HD because of their dual effect. HDAC inhibitors have shown promise in neurodegenerative models in preclinical research (Romoli et al., 2019). In mouse models of AD, valproic acid (VPA), a broad-spectrum HDAC inhibitor, has demonstrated effectiveness in enhancing memory and synaptic plasticity (Kumar et al., 2022). Similar to this, another HDAC inhibitor called Vorinostat, also known as suberoyl+anilide+hydroxamic acid (SAHA), has demonstrated efficacy in regaining motor function and minimizing neuronal loss in HD animals (Saute et al., 2018). These results demonstrate how HDAC inhibitors can restore compromised neural functions and halt the progression of illness. The process of turning these discoveries into therapeutic uses

has started with clinical trials. Early-phase trials for AD and HD are presently being conducted to examine VPA and other HDAC inhibitors (Lyko et al., 2018). Tolerability and moderate efficacy have been shown in preliminary results, which serve as a foundation for additional study. However, before these medicines can be widely used in clinical practice, issues including dosage optimization and limiting off-target effects need to be resolved. Several thorough preclinical investigations have measured the effectiveness of HDAC inhibitors. In a series of studies, Kilgore et al. (2010) used APP/PS1 transgenic mice and the HDAC inhibitor sodium butyrate (Kilgore et al., 2010). Following three weeks of therapy, they found that the hippocampus's histone H4 acetylation had increased by 47%, and that contextual fear memory and spatial learning had significantly improved as well. When compared to mice who were not treated, Morris water maze performance demonstrated a 38% decrease in escape latency (Kilgore et al., 2010). In a transgenic mice model of AD, Thomas et al. (2008) gave valproic acid (VPA) for four weeks, which reduced the generation of amyloid-β and the burden of plaque by 65% (Thomas et al., 2008). According to their molecular studies, VPA administration dramatically decreased tau hyperphosphorylation and stimulated neurite outgrowth in cultured neurons by 40%, inhibiting GSK-3β activity (Thomas et al., 2008).

5.2 DNMT Inhibitors

The addition of methyl groups to DNA is catalyzed by DNMTs, which usually silences gene expression (Chistiakov et al., 2017). Neuroprotective genes' decreased expression in NDDs is exacerbated by their hypermethylation, which increases neuronal susceptibility (Mohd et al., 2022). By reactivating dormant genes and resuming their beneficial roles, DNMT inhibitors provide a means of reversing this hypermethylation (Lyko, 2018). According to Ciechomska et al. (2019), DNMT inhibitors work by demethylating CpG islands in promoter regions, which enables the reactivation of genes essential for brain survival and repair. These inhibitors have the potential to stop or reverse the progression of disease by focusing on abnormal DNA methylation patterns (Rasmi et al., 2022). Figure 2 illustrates how a CpG island's methylation status functions as a molecular switch to regulate the methylation of gene activity, resulting in silence and a lack of methylation that permits expression. In neurodegenerative models, preclinical research has shown that DNMT inhibitors have neuroprotective benefits (Teijido et al., 2018). In PD and HD animals, two often researched DNMT inhibitors, azacitidine and decitabine, have demonstrated promise (Luo et al., 2022). These substances improved the behavioral and physiological results of treated mice by restoring the expression of genes related to neuronal development and synaptic function. Notwithstanding these positive outcomes, there are still several obstacles in the way of DNMT inhibitor clinical translation. According to Kular et al. (2019), these substances frequently have systemic effects that result in off-target toxicity and undesired alterations in non-neuronal tissues. Their therapeutic window is limited by their lack of specificity, which emphasizes the necessity of sophisticated delivery systems to guarantee brain-specific targeting. Furthermore, it is yet unclear how DNMT inhibition may affect global methylation patterns in the long run (Gladkova et al., 2023). The molecular mechanisms and quantitative effects of DNMT inhibitors have been reported in recent investigations. Zheng et al. (2019) used the APP/PS1 mice model of AD to investigate decitabine (5-aza-2′-deoxycytidine). They found that NEP and BIN1 promoters were demethylated after 4 weeks of therapy (30% and 25% decreases in methylation, respectively), which led to a

28% decrease in amyloid-beta plaques in the hippocampus and an increase in the expression of these genes (Zheng et al., 2019). In the MPTP animal model of Parkinson's disease, Wang et al. (2016) showed that 5-azacytidine therapy significantly demethylated the BDNF promoter (45% reduction), which increased BDNF expression by 2.3 times. Alongside this, there were notable improvements in motor function and a 27% increase in tyrosine hydroxylase-positive neurons in the substantia nigra (Wang et al., 2016). When 5-aza-2′-deoxycytidine was given to R6/2 HD mice, Mielcarek et al. (2013) observed notable decreases in mutant huntingtin aggregation (52% decrease) and striatal atrophy (38% decrease). These effects were especially pronounced on the genes related to synaptic function and cholesterol homeostasis.

5.3 miRNA-based Therapies

Several preclinical models have shown the effectiveness of microRNA-based strategies. By using antagomirs against miR-155 in SOD1-G93A ALS mice, Koval et al. (2013) were able to extend longevity by 15 days (10% increase) and reduce microglial activation by 40%. More than 300 dysregulated genes linked to neuroinflammation and neuronal survival showed restored expression, according to RNA-seq data (Koval et al., 2013). By lowering α-synuclein protein levels by 42%, Junn et al. (2009) discovered that miR-7 mimics MPP+-treated SH-SY5Y cells were protected against α-synuclein-mediated toxicity. Using a novel brain-penetrant nanoparticle technology, Konopka et al. (2010) administered miR-132 mimics to 3xTg-AD mice, which led to a 35% increase in novel object recognition performance and a 58% decrease in tau hyperphosphorylation (Konopka et al., 2010).

6. RESTRICTIONS, DIFFICULTIES, AND FUTURE DIRECTIONS OF EPIGENETIC DRUGS FOR NEURODEGENERATIVE DISEASES

Numerous model animal experiments have already examined the concept of employing epigenetic medications to treat neurodegenerative illnesses. Prior research has demonstrated that the use of different histone-deacetyltransferase (HDAC) inhibitors, such as sodium butyrate, trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA, Vorinostat), or valproate (VPA), significantly reversed the memory defects observed in various AD models (Fischer et al., 2007; Francis et al., 2009; Kilgore et al., 2010). In addition to restoring synaptic plasticity and memory function, oral administration of the HDAC inhibitor MS-275 (Entinostat) significantly reduced the accumulation of amyloid plaque and neuroinflammation shown in APP/PS1 AD mice (Zhang and Schluesener, 2013). Even when sodium butyrate was administered late in the course of the disease, after neuronal cell death had begun, it was surprisingly effective (Govindarajan et al., 2011). Furthermore, some investigations have demonstrated that HDAC inhibitors have a comparable therapeutic impact in models of HD and PD (Coppedè, 2010; Sadri-Vakili and Cha, 2006). S adenosyl methionine (SAM) is a methyl donor necessary for the methylation of DNA and histone proteins, and AD patients appear to have lower levels of SAM (Coppedè, 2010). Numerous investigations in mice shown that hypomethylation of PSEN1 promoters and subsequent deposition of A resulted from vitamin B deficiency, which is necessary for the manufacture of SAM (Coppedè, 2010). Consistent with these findings, there is evidence that vitamin B supplements may lessen cognitive impairments in a variety of AD model animals and patients, albeit more research is necessary (Coppedè, 2010). The fact that several HDAC proteins (among the four classes of 11 HDAC proteins) are impacted simultaneously is one

of the most important considerations when utilizing these HDAC inhibitors. In order to minimize potential adverse effects, it is unclear which of the several HDAC proteins is principally responsible and the most suitable treatment target for AD-induced memory disturbance or HD-induced locomotor impairments. The ability of these epigenetic-based treatment strategies, such as HDAC inhibitors, to alter or modify the disease pathophysiology itself is yet unknown, despite their efficacy. Furthermore, it is yet unknown if the histone acetylation alterations in AD and HD are a major contributor to the pathophysiology of the diseases or merely an effect of them.

7. CONCLUSION

In conclusion, while significant strides have been made in understanding the role of epigenetic mechanism, epigenetic Alterations in Neurodegenerative Disorders**,** epigenetic therapy in neurodegeneration, and challenges, limitations of epigenetics. The complexity of neurodegenerative diseases pathology demands further investigation. Future research should aim to elucidate the intricate mechanisms underpinning the NDDs, explore the full spectrum of epigenetic landscape, and develop targeted therapeutic interventions. Such endeavors will require the techniques in which gene editing tools like CRISPR-Cas9, leveraging advances in genetics, molecular biology, and clinical medicine to forge new pathways in the diagnosis, treatment, and prevention of neurodegenerative diseases.

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