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Epigenetic Modifications: A Therapeutic Approach in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disease that has affected millions of people worldwide, marked by memory loss and cognitive deficits. Currently, treatments only attempt to alleviate symptoms rather than reversing neuronal damage or cognitive deficits. However, epigenetic therapies correlated with their subsequent epigenetic modifications have been shown to show potential in pre-clinical trials, prompting researchers to focus more on this subject matter. By examining many credible sources, this paper aims to highlight potential epigenetic modifications in Alzheimer's disease patients and shed light on their subsequent epigenetic therapy. Ultimately, many pre-clinical trials have reiterated the potential these therapies have for reversing Alzheimer's disease pathology and progression. The three primary epigenetic therapies highlighted include DNA methylation inhibitors, histone deacetylase (HDAC) inhibitors, and non-coding RNA-based therapies. Altogether, with further advances in pre-clinical trials and a transition into human clinical trials, the potential of these therapies can be utilized as a novel approach to reversing the damage that occurs from epigenetic modifications in Alzheimer's patients.

Introduction

Alzheimer's disease, which is one of the most common neurodegenerative diseases in the United States, is currently inherited by and affects millions of people throughout the world. At the moment, an estimated 6.9 million Americans aged 65 years or older are experiencing the severity of Alzheimer's disease, with this number set to be projected as high as 13.8 million by 2060 in the absence of prevention or cure for this prevalent disease (Alzheimer's Association, 2024). The leading hypothesis for the cause of Alzheimer's disease concentrates on the abnormal surplus of proteins, such as amyloid-beta plaques and tau tangles in the brain, which leads to the neurodegeneration of the brain. Unfortunately, despite a surplus of research on Alzheimer's disease, there is currently no cure for treating this disease. Furthermore, there are currently more therapeutic solutions attempting to relieve the symptoms of AD and slow the progression rather than addressing and reversing any potential neuronal damage. With no current cure for Alzheimer's disease, much progress has been made in identifying epigenetic changes in patients who have Alzheimer's disease; therefore, there are treatments such as histone modifications, DNA methyltransferase inhibitors (DNMT), and microRNA modulators that are aimed at reversing the epigenetic changes to cure and find therapy at the epigenetic level for the disease (Bufill et al., 2020). As epigenetics does not directly alter the DNA sequence but rather alters the activity of genes through chemical mechanisms on the DNA or histone proteins, these chemical mechanisms can take in environmental influences and alter gene expression, thus influencing the progression of Alzheimer's disease. However, as these therapies are in pre-clinical trials, much research is still required to determine whether epigenetic therapies are a viable approach to treating AD.

On the international level, China has about 9.83 million people aged 60 years or above who have contracted or are diagnosed with Alzheimer's disease (Ren et al., 2022). The amount of Alzheimer's diagnosed patients in China is projected to be as high as 40 million people by 2050 (Lobanov-Rostovsky et al., 2023). With a large number of people in China being diagnosed with Alzheimer's disease, there has been a solid call to halt the severe progression

of aging and AD in China. Therefore, multiple studies have emphasized epigenetic markers' roles and their corresponding therapies' impacts in treating Alzheimer's disease. A review by Wang et al. (2013), conducted in China, focuses on how epigenetic modification, such as DNA methylation, histone modification, and non-coding RNA, play a pivotal role in Alzheimer's disease development and pathogenesis (Wang et al., 2013). For example, there have been many abnormal histone modifications that play a huge factor in the progression of many brain disorders, such as Alzheimer's disease. Therefore, histone deacetylase inhibitors (HDACs), which were previously used to treat cancer, now has been identified as a possible therapy for slowing the progression of AD in the human brain by regulating the homeostasis of histone acetylation (Xu et al., 2011). Altogether, promising epigenetic therapies have gathered international attention from countries such as China, emphasizing the possibility of epigenetic therapies being promising for Alzheimer's disease.

Similarly, in the United States, many studies have concentrated on the epigenetic potential of treating and slowing the progression of Alzheimer's disease. For instance, a study highlights the use of HDAC inhibitors in reversing cognitive deficits such as memory loss, problems concentrating, and difficulty speaking in mouse models of Alzheimer's disease as well as other neurodegenerative diseases (Graff et al., 2013). The essential use of HDAC inhibitors is to restore the acetylation levels of histones that regulate gene transcription, which is responsible for the functionality of cognitive functions. Therefore, the successful use of animal models to reverse the loss of cognitive functions in instances such as Alzheimer's disease shows the potential of epigenetic therapies for Alzheimer's disease.

On the local aspect, many researchers from the University of Buffalo identified and looked at whether epigenetic therapies may have the potential to reverse the damage resulting from Alzheimer's disease. Within their research, they identified that there was an abnormal epigenetic process in animal models they had previously studied, as well as postmortem tissue from patients who were diagnosed with Alzheimer's disease (Yan, 2019). In addition, researchers identified that epigenetic therapy has the potential to correct a network of genes and simultaneously restore cell normality, therefore restoring any cognitive function and behavior loss (Yan, 2019). Altogether, the efforts of many local hospitals and universities have focused on how epigenetic therapies can reverse any epigenetic process that has been observed in AD patients and target those changes to restore standard functionality and processes.

Given the impacts Alzheimer's disease has had on copious quantities of people diagnosed with the disease internationally and nationally, there is a solid call to find an effective and long-lasting treatment for such disease. Therefore, many studies and research have aimed to find epigenetic modifications and alterations in patients with Alzheimer's disease. With the identification of many alterations in epigenetic mechanisms, there is a need to test epigenetic therapies such as histone modification, DNA methyltransferase inhibitors (DNMT), and microRNA modulators. These therapies potentially could reverse any damage that occurred because of epigenetic modifications, particularly of those observed in Alzheimer's disease, therefore presenting a possibility to prevent, manage, and cure this prevalent disease. Hence, the necessity of this study lies in addressing the potential to slow and reverse the progression of Alzheimer's disease through epigenetic therapies that work to reverse epigenetic modification in the human genome.

Methodology

The main goal of this study was to identify the epigenetic modifications parallel to Alzheimer's disease and to accentuate the potential of epigenetic therapies in curing this disease. The type of research conducted in this study is a secondary literature review using many primary sources and other scholarly articles focusing on epigenetic biomarkers and their subsequent therapies identified in Alzheimer's disease. The research methodology implemented in the multistep approach started with literature searches in databases, which are comprised of many primary and scholarly sources focused on epigenetic biomarkers and therapeutics solutions for Alzheimer's disease. Subsequently, the selected articles from a wide range of search engines and databases were screened according to the authenticity and relevance of the article in connection with Alzheimer's disease. Within those articles and studies, specific primary sources and studies were used to direct attention to epigenetic modifications in Azheimer's patients and models. Then, a qualitative

analysis method was used to review all the studies and scholastic articles to identify patterns and ideas resonating across the literature. These studies were used to ultimately get a better understanding of each of the three major epigenetic modifications concerning Alzheimer's disease and the subsequent epigenetic therapy reversing any damages as a result of the disease. There were no ethical considerations throughout the study as it relied mainly upon primary literature and sources; therefore, it did not involve any physical tools or intervention in this study. Furthermore, any research biases or opinion-based articles were avoided by incorporating various sources and studies conducted worldwide.

Epigenetic Mechanisms in Alzheimer's Disease

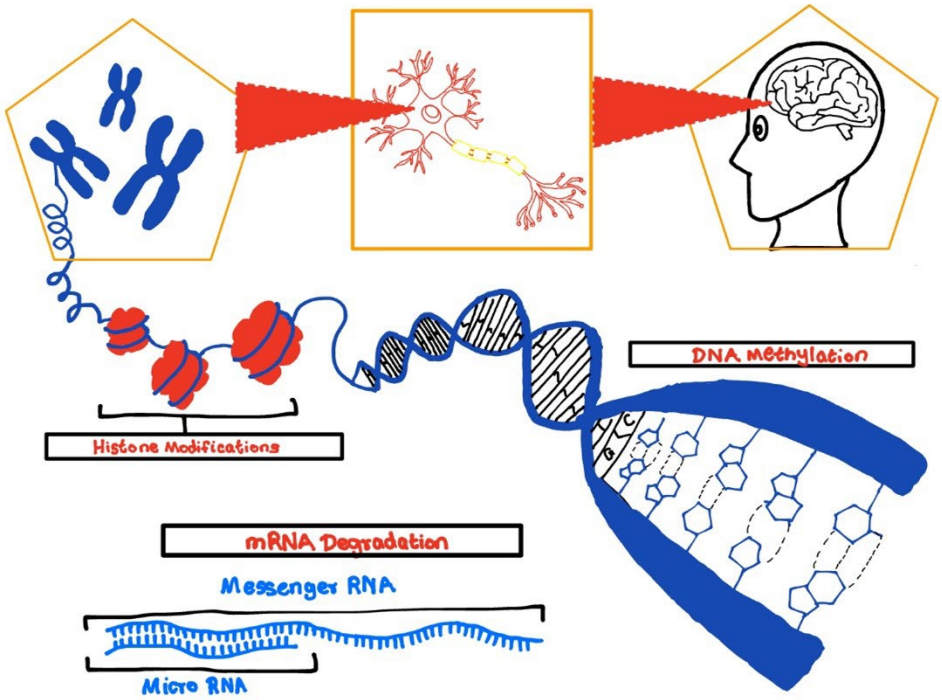

Figure 1. Epigenetic Mechanisms. Source: Pratik, 2024. Description: This figure shows the breakdown of each epigenetic modification with specific highlights on histone modifications, DNA methylations, and mRNA degradations. The image above depicts the pathways and precise location of epigenetic alterations in the human genome with a careful breakdown starting with the human brain to the double helix DNA strand.

Epigenetic mechanisms are crucial in developing neurodegenerative diseases as they regulate gene expression without directly altering or processing the original DNA sequence. These mechanisms are essential in controlling what proteins are produced by determining which genes should be turned on or off. Epigenetics is particularly important in the brain's functioning and has been shown to play a role in aging; therefore, any changes or disruptions to these processes could contribute to the development of neurodegenerative diseases. Within the brain, epigenetic mechanisms ensure the expression of specific genes necessary for neuronal processes, brain development, and memory formation. However, any modification to these gene expressions could significantly alter its processes, potentially initializing or progressing neurodegenerative diseases such as Alzheimer's disease. Furthermore, epigenetic modifications can be triggered by various factors, such as environmental stimuli like diet, stress, and exposure to toxic pollutants (National

Library of Medicine, 2021). Additionally, even intrinsic factors such as aging and hereditary issues contribute to epigenetic modifications, thus influencing the development of neurodegenerative diseases in the brain.

The three main identifiable mechanisms are DNA methylation, histone modifications, and non-coding RNA interactions. In Alzheimer's disease, these modifications are highly prevalent and have contributed to many neurological problems and deficits. For example, DNA methylation modification has been shown to alter gene expression and protein production, exacerbating Alzheimer's disease. Multiple genome-wide studies have shown at least two hundred seventy uniquely different modified regions distinctively associated with Alzheimer's disease in comparison to standard control (Wang et al., 2023). The many modifications identified make DNA methylation a potential biomarker and therapeutic target for Alzheimer's disease. Similarly, histone proteins help stabilize DNA and control gene transcription. In Alzheimer's disease, several studies have linked many modifications, such as the acetylation of the histone H4 at lysine 12 (H4K12ac) and alterations at H3K27me3 and H3K4me3 to Alzheimer's disease (Sharma et al., 2020). Therefore, histone modifications serve as a prospective biomarker for Alzheimer's disease and have been targeted for therapeutic approaches alongside therapies targeting DNA methylation. Finally, non-coding RNAs control gene expression and play a considerable role in chromatin modifications, mRNA stability, X-chromosome inactivation, and other biological processes (Olufunmilayo, 2023). In Alzheimer's, modifications in non-coding RNA affect the disease pathology, similar to other epigenetic modifications, promoting neurodegeneration and deterring gene expression (Olufunmilayo, 2023). Altogether, there have been severe connections highlighting the impacts of epigenetic modifications in Alzheimer's disease pathology, prompting further investigation and consideration of epigenetic therapeutics.

DNA Methylation

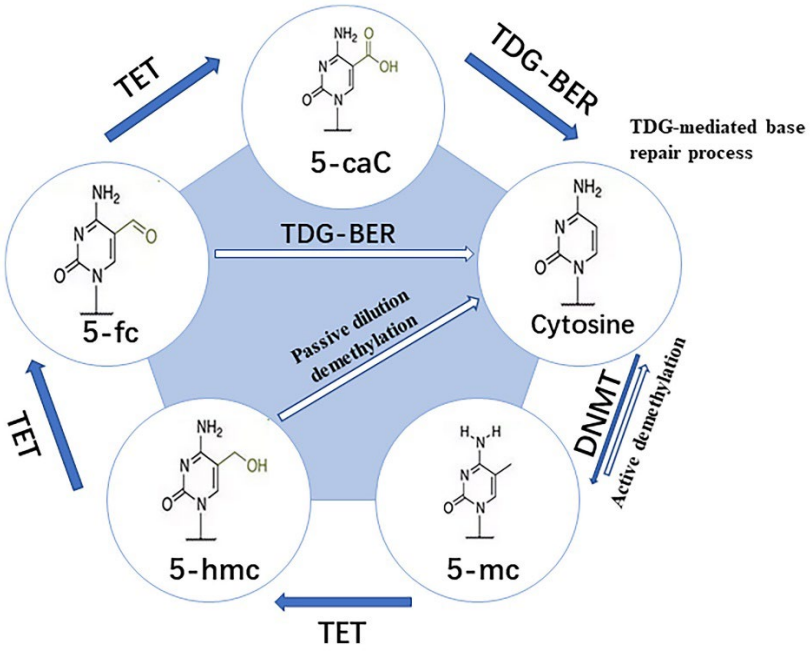

Figure 2. DNA Methylation Pathways. Source: Zhou et al., 2021. Description: This figure shows the different cytosine modifications corresponding to each enzyme responsible for each modification. All the pathways of the dynamic modifications of cytosine that are a common hallmark of DNA methylation are shown above.

DNA methylation is an epigenetic modification regulated by DNA methyltransferase. This process adds methyl groups to DNA molecules, specifically at cytosine bases. This process does not directly alter the DNA sequence but alters

how the genes function and are expressed. The most widespread cytosine modification in the human genome is the formation of 5-methylcytosine (5mC). DNA methylation is found to primarily occur in cytosines, followed by guanine bases and residues (Jang et al., 2017). Thus, methylcytosine (5mC) forms when a methyl group is added to the 5' carbon of cytosine within the CpG dinucleotide (Gao et al., 2022). Furthermore, 5-methylcytosine (5mC) can be oxidized into three distinct chemical modifications that are 5-hydroxymethylcytosine (5-hmC), 5-formylcytosine (5-fC), 5-carboxylcytosine (5-caC), which have been identified as crucial epigenetic control. In a comprehensive review on DNA methylation in Alzheimer's Disease (AD), Tim Beech (2023) believes that 5-hydroxymethylcytosine (5hmC) is the second most common DNA methylation markable modification that plays a massive role in the brain neuronal system and AD neurodegeneration. There have been further advances in studying the biomarkers and mechanisms of AD as recent studies have used mouse models, specifically transgenic mice, to understand the role of 5-hydroxymethylcytosine (5hmC) in neurodegeneration, primarily Alzheimer's disease. In a study conducted by Zhang et al. (2020), they used a mouse model titled 3xTg-AD mouse, which carries three common mutations that are associated with Alzheimer's disease and mimics abnormal tau and beta-amyloid protein levels. These mice were used to compare 5hmC levels in the hippocampal, cortical, and cerebellar neurons with wild mice controls, finding a significantly reduced amount of 5hmC in the hippocampal and cortical neurons of 3xTg-AD mice that were like human AD brains. Furthermore, age-related studies showed that 5hmC levels increased in wild mouse types while remaining constant and sometimes decreased in 3xTg-AD mice. This suggests that the reduction of 5hmC levels plays a huge role in Alzheimer's disease. To back those findings, they used amyloid beta treatments that worked by attaching to and removing beta-amyloid, a protein that accumulates into plaques, from the brain, targeting nerve cells in the brain's hippocampus, which correlates with the study's results that amyloid-beta proteins disrupt 5hmC levels. Altogether, the disruption of 5hmC levels due to changes in amyloid protein production suggests that amyloid proteins and 5hmC levels influence Alzheimer's disease progression by specifically modifying DNA methylation patterns.

Histone Modifications

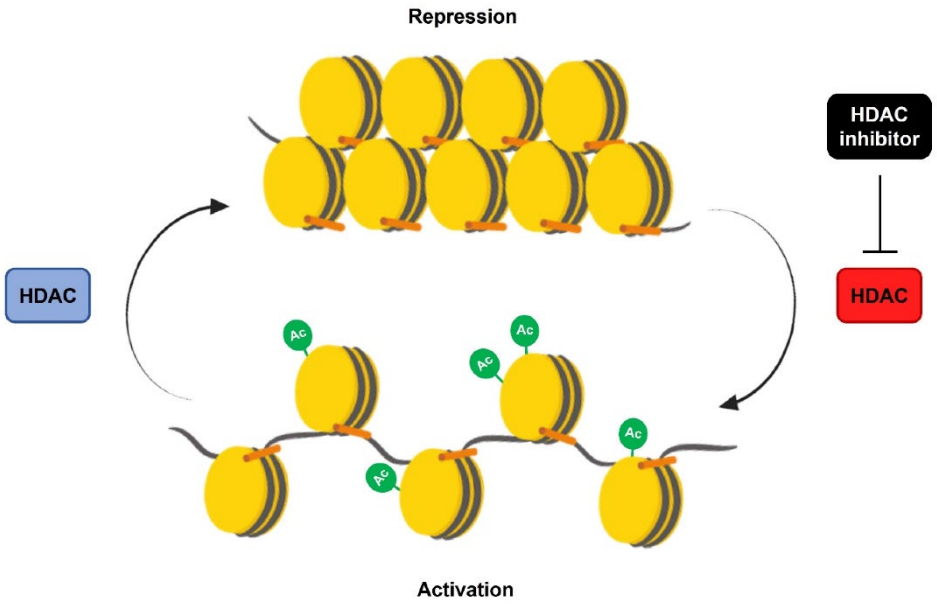

Figure 3. Histone Modifications. Source: Santana et al., 2023. Description: This figure represents the role of histone modifications in the repression and activation of the histones. HDACs promote the loss of histone acetylation by the removal of acetyl groups, which results in gene expression through the alteration of the chromatin structure.

Similar to DNA methylation, histone modifications play a huge role in gene expression and gene regulation. Specific histone modifications such as histone acetylation and methylation change the structure of chromatin and affect transcriptional activity by regulating gene expression (Dong et Weng, 2013). Histones are very important proteins wrapped up in DNA strands that form the nucleosomes, the basic building blocks of chromatins (Santana et al., 2023). Specifically, histone modification has major and widespread sites for post-translational modifications, such as methylation, acetylation, phosphorylation, ubiquitylation, and SUMOylation (Santana et al., 2023). Focusing on histone acetylation, many studies have identified these modifications as having a major impact and role in memory functions and gene expression. From within a huge collection of histone acetylation marks, the acetylation at the 16th lysine residue of the histone H4 protein, also referred to as H4K16ac has been identified as a key modification that affects chromatin structure, gene expression, and other DNA-related structures such as transcription and damage repair (Nativio et al., 2018). In their study, Nativio et al. (2018) used chromatin immunoprecipitation sequencing, a technique for mapping genome-wide DNA binding sites of transcription factors and other proteins, to profile genome-wide H4K16ac modifications in postmortem brain tissue from AD patients, cognitively normal older people, and younger control experiments. That study showed that while normal aging is common with increased acetylation of H4K16ac, AD patients reflect more depletion or losses of H4K16ac modifications. Altogether, it is evident that Alzheimer's disease is attributed to disrupting normal aging processes related to histone modifications. Similarly, the epigenome-wide study by Klein et al. (2019) shows a significant alteration in histone acetylation that is key to tau pathology in the aging and AD human brain. The methodology used by Klein et al. (2019) consisted of using advanced epigenome techniques to map acetylation patterns, similar to the technology used by Nativio et al. (2018). From that, they provided insights into how tau proteins and the accumulation of such proteins affect histone modifications, specifically histone acetylation (Klein et al., 2019). Their focus on how H3K9ac modifications are altered due to tau pathology in AD shows that tau pathology is heavily lined with histone acetylation across large genome-wide locations (Klein et al., 2019). It was evident that major effects were located and observed in euchromatic type A and heterochromatic type B compartments of the chromatin structure (Klein et al., 2019). This suggests that the alteration in chromatin structure, specifically in nuclear lamina organizations, has a role in the tau-induced epigenetic changes related to AD progression. Altogether, both the studies by Nativio et al. (2018) and Klein et al. (2019) highlight the roles of specific histone acetylation, such as H4K16ac and H3K9ac, that contribute to AD pathology and progression.

Non Coding RNA's

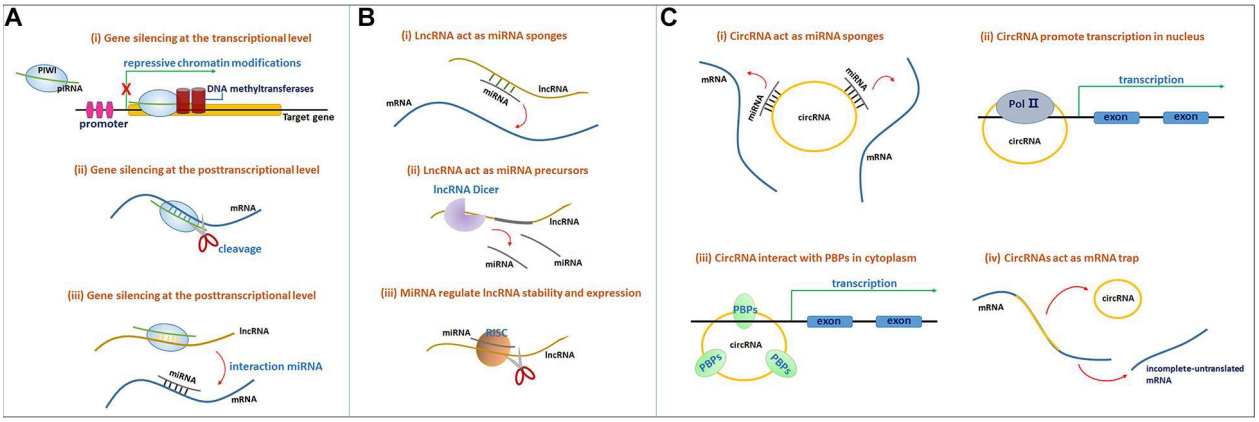

Figure 4. Non-Coding RNA Molecular Mechanisms. Source: Zhang et al., 2021. Description: The figure above represents the different molecular mechanisms of specific RNA strands. The image depicts the different interactions of RNA strands and their subsequent gene suppression or adverse outcomes.

Furthermore, microRNA modifications play an especially important and crucial role in Alzheimer's disease progression and pathology. MicroRNAs are produced in the microRNA precursor genes (mir-gene) through miRNA genes (Ranganathan et al., 2014). They are small, non-coding RNAs that affect post-translational gene regulation and play huge roles in gene expression (Bushati et Cohen, 2007). In fact, many non-coding RNAs engage in neuron functionality in addition to neurodegenerative processes such as reduction in the neurons, glial cells, and many other processes (Tecalco-Cruz et al., 2020). In one study, microRNA-132 (miR-132) is reduced significantly in AD mouse models. The study conducted by Walgrave et al. (2023) used AD mouse models by adding and removing microRNA-132 (miR-132) utilizing single-cell transcriptomics, proteomics, and various databases to prove its implications on Alzheimer's disease. In their controlled experiment, they noticed microRNA-132 (miR-132) modifications affecting microglial homeostasis in the mouse hippocampus and any associated diseases. Most importantly, Walgrave et al. (2023) highlighted that microRNA-132 (miR-132) is severely reduced in Alzheimer's brain and reported the coincidental neuronal functions and other aspects of miR-132 with Alzheimer's disease. Similarly, another group of researchers utilized mice models in a controlled experiment to identify induced tau proteins and cognitive deficits in Alzheimer's disease due to microRNA-125b elevations (Banzhaf-Strathmann et al., 2014). Their methodology focused on overexpressing miR125b in neurons to analyze the impact on tau proteins and cognitive losses by injecting miR-125b into the hippocampus of mice. Their results provided further breakthroughs on microRNA influence on AD by identifying that an increase or overexpression of microRNA-125b increases tau hyperphosphorylation. Tau hyperphosphorylation, a very common occurrence in AD pathology, is a process where tau proteins are abnormally phosphorylated, thus leading to neuronal and synaptic losses (Rawat et al., 2022). In addition, Banzhaf-Strathmann et al. (2014) identified that increasing microRNA-125b in the hippocampus of AD mouse models also affects cognitive skills and functions such as memory. They summarized that this cognitive impairment of the AD mice is an additional effect of previously identified downregulations of increased tau phosphorylation. Altogether, it is evident that microRNA modifications have a strong influence on AD pathology and potentially can be used as a therapeutic approach for treating AD.

Moreover, many researchers have researched and discussed the influence of long non-coding RNA modifications on Alzheimer's disease. Generally, long non-coding RNAs control gene expression both locally and distally while also regulating enhancer-promoter interactions (Vance et al., 2014). In Alzheimer's disease, long non-coding RNAs have contributed to AD pathology by aggravating amyloid protein production, tau hyperphosphorylation, and many other functional processes (Lan et al., 2022). Similar to microRNA modifications, long non-coding RNA modifications have specific and multiple modifications that influence Alzheimer's disease. For example, a study by Wang et al. (2020) investigated the role of long non-coding RNA WT1-AS in Alzheimer's disease by using an AD mouse model to assess its impact on major functions that correlate with AD pathology. As set out, the researchers identified that the overexpression and increase in WT1-AS decreased oxidation stress injury (OSI) and neuronal apoptosis in the AD mouse models. This effect adversely promotes oxidation stress, an imbalance of chemicals in a person's body that eventually leads to cell damage and cell death in neurons. Additionally, WT1-AS overexpression results in WT1 reductions which is a protein that controls microRNA-375 (Wang et al., 2020). The researchers also highlighted that reducing microRNA-375 due to overexpression of WT1-AS negatively impacts neuronal cells and their survival by targeting SIX4, a protein that contributes to oxidation stress injury and neuronal apoptosis. Adjacent to that study, researchers Ma et al. (2019) studied the effect of long non-coding RNA MALAT1 on Alzheimer's disease. Their methodology used AD models in rat embryos and changed long non-coding RNA MALAT1 levels to identify neuron death, growth, and apoptosis. From the study, Ma et al. (2019) identified that long non-coding RNA MALAT1 changes neuroinflammatory responses that affect signaling pathways and cytokines. These changes in neuroinflammatory responses clearly correlate to the progression of AD. In addition, their research concluded that reducing the levels of MALAT1 leads to the impairment or damage of neurons and hinders their growth. Finally, it was evident that MALAT1 inversely influences microRNA-125b, which affects neuronal apoptosis, overgrowth, and inflammation. Thus, increased microRNA-125b due to increased MALAT1 results in enhanced apoptosis, inflammation, and worsened neuronal functions (Ma et al., 2019). Altogether, many studies focusing on specific long non-coding RNA strands

have shown promising connections to Alzheimer's disease, prompting an enhanced look for potential therapeutic treatments targeting those modifications.

Results

With the identification of many epigenetic modifications concerning Alzheimer's disease, researchers have shifted their focus to epigenetic treatment targeting Alzheimer's disease modifications. There are three main epigenetic treatments: DNA methylation inhibitors, histone deacetylase (HDAC) inhibitors, and non-coding RNA-based therapies.

Potential Epigenetic Therapies

Firstly, researchers have identified DNA methylation inhibitors as potential targets for reversing any neurological-level damage that occurred due to epigenetic modification in Alzheimer's disease patients. As discussed, many DNA methylation modifications have severely affected neuronal and cognitive functions in Alzheimer's disease patients, providing a baseline or target for potential therapies to reverse these deficits. As highlighted in a study, there are many DNA methylation inhibitor therapies, such as epigallocatechin gallate, epigallocatechin 3-gallate, tea catechin, and catechin derivatives, that have proved to be effective in Alzheimer's disease subjects (Kaur et al., 2022). More specifically, epigallocatechin gallate, a phenolic compound in green tea that targets DNA hypermethylation. Therefore, specific phytochemicals such as epigallocatechin gallate have been shown to improve amyloid fibril transformation and highlight the potential of fixing neuronal problems associated with Alzheimer's disease pathology (Payne et al., 2022). Similarly, tea catechin is a DNMT inhibitor that can increase antioxidant activity and inhibit inflammation and oxidation stress while lowering amyloid beta production (Afzal et al., 2022). Finally, epigallocatechin 3-gallate can prevent protein misfolding and cell death in amyloid beta-treated neurons (Kaur et al., 2022). Altogether, all these treatments can help treat Alzheimer's disease by focusing on specific DNA methylation modifications through DNA methyltransferase inhibitors.

Another epigenetic therapy shown to alleviate AD pathology is histone deacetylase inhibitors. The histone deacetylase inhibitor works by removing the additional acetyl group added through the histone modification from the histone, resulting in a better chromatin structure and subsequent gene repression from the modification. Histone deacetylase inhibitors, primarily used as anti-cancer drugs, play an important role in epigenetic functions such as apoptosis and cell death reversal (Kim et Bae, 2011). Furthermore, HDAC enzymes involve biological processes such as development, differentiation, and cell death (Kim et Bae, 2011). Breakthrough research by Zhang et al. (2024) focused on the impact of histone deacetylase inhibitors sodium valproate (VPA) and WT161. Their study used cellular and AD mouse models to assess these inhibitors' impact on histone deacetylase expression, amyloid beta expression, and various cognitive functions. They even used techniques such as western blotting, immunohistochemistry, and other behavioral tests. VPA and WT161 inhibitors reduce the expression of HDAC1 and HDAC6, which are linked with the production of amyloid precursor protein and its following secretases (Zhang et al., 2024). Altogether, the researchers concluded that VPA and WT161 can effectively reduce amyloid beta depositions and improve cognitive functions in both cellular and mouse models. Furthermore, another study conducted by Janczura et al. (2018) utilized the HDAC3 inhibitor RGFP-977 on an in vivo AD mouse model to assess the effects of this inhibitor on Alzheimer's disease-related pathology and cognitive functions. Their study demonstrated reduced amyloid and tau phosphorylation accumulation, eliminating some Alzheimer's disease-related pathologies. Their treatment method also improved cognitive functions in the mice, indicating that this is a very promising treatment for Alzheimer's disease. Altogether, Janczura et al. (2018) and Zhang et al. (2024) provide a therapeutic target for Alzheimer's disease through controlled experiments supporting that HDAC inhibitors can reverse or slow down neurodegenerative processes in AD.

Finally, non-coding microRNA and long non-coding RNA-based therapies have been identified as possible therapies for Alzheimer's disease. As discussed earlier, the overexpression or deregulation of specific non-coding

RNAs contributes to Alzheimer's disease pathology and impairment of cognitive functions. Similarly, the overexpression or deregulation of specific non-coding RNAs can reverse Alzheimer's disease, therefore reversing any damage that occurred by those non-coding RNAs. For example, a study by Faghihi et al. (2008) demonstrated a practical approach by targeting BACE-1 antisense transcript (BACE1-AS) in Alzheimer's disease mouse models and cellular models. This non-coding RNA leads to an increase in the production of amyloid beta proteins, thus promoting Alzheimer's disease pathology. Elevated BACE1-AS levels even contribute to the progression of AD by contributing to a harmful feed-forward loop. Therefore, Faghihi et al. (2008) discussed the potential epigenetic therapy of reducing BACE1-AS levels in Alzheimer's patients to lower the production of amyloid beta proteins. Another example of a possible therapeutic approach is evident in the study discussed earlier by Ma et al. (2019) on how long non-coding RNA MALAT1 plays a role in Alzheimer's disease. As mentioned, the reduction of MALAT1 in Alzheimer's disease patients leads to the impairment or damage of neurons and hinders their growth. In addition, it was specified that the overexpression of MALAT1 can reduce neuroinflammation and promote neurite outgrowth, an important mechanism that could protect neurons in Alzheimer's patients. Therefore. targeting MALAT1, specifically reducing it, can positively affect gene expression post-transcriptionally and promote neuronal growth. Thus, a specific approach is offered as epigenetic therapy for Alzheimer's disease.

Conclusion

In conclusion, the three main epigenetics – DNA methylation inhibitors, histone deacetylase (HDAC) inhibitors, and non-coding RNA-based therapies – have been identified as potential therapies for reversing any epigenetic modifications in Alzheimer's disease patients. First, many DNA methylation inhibitors have been shown to reverse any damage done by DNA methylation and hypermethylation modifications, showing potential in the therapeutic sector for neurodegenerative disease. Next, many researchers have focused on the use of histone deacetylase (HDAC) inhibitors in reversing histone modifications found in Alzheimer's disease patients related to cognitive deficits and neuronal impairment. This breakthrough research has shed light on the impact of epigenetic therapies in treating Alzheimer's disease progression. Finally, non-coding RNA-based therapies have shown potential as a therapeutic approach in AD mouse models, relieving some of the significant symptoms and pathologies related to Alzheimer's disease. While there have been a substantial number of studies relating epigenetic modifications and their subsequent therapies to Alzheimer's disease, most of these studies are in pre-clinical trials with no indication of whether this will be taken to further steps. Therefore, additional research and enhancement in this subject matter are critical in moving from pre-clinical trials to human clinical trials. In addition, more advocation for the role of epigenetics in Alzheimer's disease and its potential as a therapeutic approach in some cases will help accelerate the discovery of more therapies and involvement in clinical trials. Altogether, epigenetic modifications that serve as a biomarker for Alzheimer's disease also have a very high potential as a therapy for Alzheimer's disease, eliminating any damage or loss resulting from the modification highlighted above.

Limitations

This paper utilizes a wide range of credible sources and studies to prove that epigenetic therapies are potential treatment options for reversing some damage done by epigenetic modifications. Multiple existing credible studies discuss and present successful results in identifying specific epigenetic mechanisms and modifications in Alzheimer's disease mouse models. Multiple studies show how specific epigenetic inhibitors have a positive impact on downregulating Alzheimer's progression and pathology. However, certain limitations are still inbuilt and unavoidable. For instance, implementing successful pre-clinical trials into human clinical trials will be challenging as success in Alzheimer's disease mouse models will not directly translate into a successful human trial. Furthermore, as there is a wide variety of symptoms and modifications in Alzheimer's patients worldwide, many factors may influence the results of human

clinical trials, such as environmental, demographic, and experimental factors. Finally, there could be potential challenges targeting specific regions of the brain to alleviate the damage done by epigenetic modifications in the human genome. Altogether, while this field is a rapidly growing field of research, there are some limitations that prevent the progression of these pre-clinical trials to human clinical trials. With further advancements and in-depth research, the use of epigenetic therapies in Alzheimer's disease patients shows a lot of promise and potential.

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