Epigenetic Changes Associated with Alzheimer's and Potential Therapeutic Interventions

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The topic of this literature review relates to the importance of epigenetics in the pathology of the most common neurodegenerative disorder: Alzheimer's disease. Recent findings have increasingly implicated epigenetic mechanisms in neurological disorders, and thus an increased understanding of them can better inform methods to combat their progression. The main focus is placed on the three main types of epigenetic changes observed in these disorders, namely relating to DNA methylation, histone methylation and acetylation, and non-coding RNAs. Before discussing the epigenetic changes linked to the aforementioned disorders, this review mentions how different environmental factors impact epigenetics, such as exposure during the prenatal environment, chemical exposure, air pollution, and alcohol and substance use. Subsequently, this literature review compiles and discusses key findings from 33 review articles and primary research papers. Specifically, regarding Alzheimer's disease, key epigenetic changes discussed include increased ANK1 methylation and H3K4me3 levels, TREM2 methylation, and mi-RNAs targeting BACE1 and APP genes. Finally, the paper comments on some of the existing therapeutic strategies targeting epigenetic changes and offers some future directions that may be able to be integrated after some more epigenetic research. All in all, this paper continuously explains the importance of learning about epigenetic mechanisms involved in Alzheimer's, and ways to target them to potentially ease disease pathology.

Introduction

The term "epigenetics" was created in the 1940s by Conrad Waddington (Landgrave-Gómez et al., 2015)[1]. Epigenetic changes are heritable edits that can affect gene expression while maintaining the structure of the DNA sequence (Sharma et al., 2020)[2]. An important difference between the genetic code and the epigenetic code is that epigenetics are much more susceptible to change in response to environmental factors (Sharma et al., 2020)[2].

Epigenetics has three major categories: DNA methylation, histone modifications, and non-coding RNAs. Researchers have often focused on DNA methylation primarily since it plays a major role in various disorders (Sharma et al., 2020)[2]. DNA methylation is the process of adding methyl groups to DNA strands—with the help of enzymes such as DNA methyltransferases—thus inhibiting their genetic expression while unaltering the code (Sharma et al., 2020)[2].

Histone modifications are another type of epigenetic changes. The nucleus contains copious amounts of histone proteins which are used to compact the DNA (Sharma et al., 2020)[2]. Eight histone proteins cluster into an octamer, and a nucleosome is formed when DNA is wrapped around the octamer (Sharma et al., 2020)[2]. Many post-translational modifications are added to the N-terminal tail of histone proteins, including acetylation, methylation, ubiquitination, phosphorylation, etc (Sharma et al., 2020)[2]. Histone methylation tightens the chromatin structure to form heterochromatin, restricting access to the DNA code (Sharma et al., 2020; Gangisetty et al., 2018)[2,3]. Histone acetylation results in euchromatin which loosens the chromatin structure and can result in increased expression of the genetic material in that DNA locus (Sharma et al., 2020; Gangisetty et al., 2018)[2,3]. Much like DNA methylation, enzymes also play a role in modifying the chromatin structure (Sharma et al., 2020)[2]. Histone deacetylases (HDACs) and histone acetyltransferases (HATs) help with acetylation while histone demethylases (HDMs) and histone methyltransferases (HMTs) help with methylation (Sharma et al., 2020)[2].

Non-protein coding RNAs (ncRNAs) are the last main epigenetic change, and can come in two forms: short and long (Sharma et al., 2020)[2]. Their method of controlling gene expression is through stopping translation or helping to disintegrate mRNAs (Gangisetty et al., 2018)[3]. NcRNAs, termed microRNAs (miRNAs) are present throughout the body, but they are particularly bountiful in the brain; this suggests that they could be involved in neurodegenerative diseases (Gangisetty et al., 2018)[3].

Environmental Epigenetics

As mentioned above, environmental factors can influence epigenetic mechanisms. The prenatal stage is where epigenetics

starts to shape through the environmental factors the fetus is exposed to (Ogunjobi et al., 2024)[4]. A developing fetus's DNA methylation patterns may be altered due to the chemicals, stress, and nutrition it receives from its carrier, and affected gene expressions could be modifiers of certain diseases (Ogunjobi et al., 2024)[4]. Chromatin structure, which is the DNA wrapped around histones, may also be impacted by the fetus's environment (Ogunjobi et al., 2024)[4].

The chemical and physical properties of the world can also alter epigenetic changes (Toraño et al., 2016)[5]. Human health decreases with metal exposure—like arsenic, mercury, nickel, lead, and cadmium—partly because it may change the epigenetic code in certain diseases (Toraño et al., 2016)[5]. For example, exposure to arsenic has been shown to produce abnormal DNA methylation and alter histone modifications (Toraño et al., 2016)[5]. Some of this may lead to conditions including cancer, neuropathy, and skin issues (Toraño et al., 2016)[5]. Inhalation of atmospheric toxins may also adjust the methylation of inflammation genes, which leads to lung issues (Toraño et al., 2016)[5]. Additionally, sun exposure can result in skin problems due, to a certain extent, to increased DNA methylation (Toraño et al., 2016)[5].

Unhealthy lifestyle choices are another important factor (Toraño et al., 2016)[5]. Smoking and tobacco consumption can lead to altered DNA methylation in many CpG sites of different body systems and altered histone modifications (Toraño et al., 2016)[5]. Additionally, heavy drinking can inhibit certain miRNA expressions (Toraño et al., 2016)[5]. Moreover, stress levels present in the early stages of life have a correlation with DNA methylation abnormalities (Toraño et al., 2016)[5].

The purpose of this review is to amalgamate some important epigenetic findings on AD in order to both understand AD's pathogenesis and identify potential future treatments targeting these changes.

Alzheimer's Disease

Alzheimer's disease is the most common neurodegenerative disease, and many studies have identified epigenetic mechanisms that possibly contribute to disease. A deeper understanding of the epigenetics of Alzheimer's can be beneficial to the future development of treatments.. Alzheimer's disease (AD) mainly affects the older population. Symptoms include cognitive impairment, dementia, and learning limitations (NIA scientists, 2024). As the disease progresses, patients show signs including unstable mood swings, social isolation, and depression. (NIA scientists, 2024).

There are two main forms of AD: familial AD, which is caused by genetic mutations, and sporadic AD, which results from a complex combination of the interplay between genetics, the environment, and lifestyle choices. It is thought that sporadic AD is potentially caused by abnormal epigenetic changes. The age when AD starts has two categories: Early-onset AD (EOAD) can affect people in their 30s and 40s, while Late-onset AD (LOAD) can impact individuals older than 65 and makes up the majority of AD cases (Sharma et al., 2020)[2].

Two main hallmarks of AD pathogenesis include amyloid plaques and neurofibrillary tangles (NIA scientists, 2024). In AD, amyloid plaques—which reduce cellular function—are created when excessive amounts of beta-amyloid are present and aggregate in the brain (NIA scientists, 2024). Neurofibrillary tangles result from tau proteins forming abnormal clusters that accumulate inside neurons. In healthy neurons, tau proteins will bind to and help stabilize microtubules—which help circulate nutrients and molecules throughout the brain (NIA scientists, 2024). In an Alzheimer's brain, the tau molecules separate from the microtubules due to abnormal chemical changes (NIA scientists, 2024). The separated tau molecules combine to form neurofibrillary tangles inside neurons; this disrupts multiple neuronal functions such as synaptic plasticity, neurogenesis, and transport (NIA scientists, 2024, Cao et al., 2020)[6].

DNA Methylation in Alzheimer's

DNA methylation was first shown to be involved in AD's pathogenesis in 1995 by West et al (West et al., 1995)[7]. They compared a brain with Pick's disease—a dementing disorder—, a brain with AD, and a healthy brain, and found different methylation patterns associated with the AD brain (Dickson, 2006; West et al., 1995)[7,8]. This was the first of many studies to correlate DNA methylation to AD.

A subsequent study attempted to assess the role of potential environmentally-influenced epigenetic changes in Alzheimer's by studying 23 sets of twins, where one twin suffers from Alzheimer's and the other twin is the healthy control (Konki et al., 2019)[9]. In this case, the participants of the study were either monozygotic or dizygotic twins, meaning that they share either 100% or 50% of their DNA (Konki et al., 2019)[9]. In addition, they studied 12 fresh frozen post-mortem brains, with 6 having AD and 6 being a control (Konki et al., 2019)[9]. Therefore, this experimental method allows the investigation of the effect of differing environmental factors on AD pathogenesis, helping to verify the role of the environment on epigenetics in Alzheimer's disease. (Konki et al., 2019)[9]. When analyzing the peripheral blood DNA methylation, the study found the twins differed in 11 genomic areas, most of which regarded neuronal functions (Konki et al., 2019)[9]. One of the genes that were differentially methylated was the ADARB2 gene, particularly in the anterior hippocampus (Konki et al., 2019)[9]. While the ADARB2 gene's function hasn't been completely understood, it is involved in neural mechanisms (Konki et al., 2019)[9]. However, other studies have shown that mutations to this gene display AD symptoms in the hosts (Konki et al., 2019)[9]. For example, when the ADARB2 gene in mice didn't have the exon 3, the

mice's hippocampus-dependent memory formation, learning, and synaptic function were diminished (Konki et al., 2019)[9]. Additionally, an ADARB2 variant was demonstrated to increase cognitive decline by helping contribute to mild cognitive impairment turning into AD (Konki et al., 2019)[9]. Konki et.al's study then further investigated the ADARB2 DNA methylation differences in 62 Finnish and Swedish twins and discovered that a multitude of environmental factors alter the expression of the gene (Konki et al., 2019)[9]. Some of them align with the factors involved in AD pathogenesis, including smoking, age, gender, and APOE genotype (Konki et al., 2019)[9].

While Konki et al. learned that ADARB2 is not able to serve as a biomarker for AD, based on the evidence, it may be shown to contribute to AD pathogenesis or symptoms (Konki et al., 2019)[9]. There are some limitations to this study. For starters, these researchers' subjects were not ethnically diverse, suggesting that their findings may not apply to every race. They also had a relatively small sample size, so further studies with more subjects will help corroborate this theory.

However, while ADARB2 likely has no potential as a biomarker, some studies discovered that the TREM2 gene and the brain-derived neurotrophic factor (BDNF) gene, which promotes survival and growth of neurons, may be able to serve as them (Sharma et al., 2020)[2]. The TREM2 gene helps the microglial cells remove unwanted waste from the brain and helps clear amyloid plaques (GE 2010; U.S. National Library of Medicine, 2010)[10,11]. The BDNF gene promotes survival and growth of neurons (Bathina et.al, 2015)[12]. Methylation in the promoter area of BDNF was found to help turn amnestic mild cognitive impairment into AD (Sharma et al., 2020)[2]. Similarly, when a study examined TREM2 methylation in AD patients' hippocampus and compared it to healthy patients, they noted an increase in the AD brains (Celarain et al., 2016)[13]. When analyzing the TREM2 mRNA levels, their AD brain samples had a higher frequency of them compared to the control brains. While the samples had disparate ages and were predominantly male, these researchers used a logistic regression to account for these variables. They also put all the samples through an RNA quality threshold to ensure more accurate results. Since TREM2 helps the brain respond to misfolded proteins and cellular damage, its aberrant methylation can contribute towards the buildup of the hallmarks of AD pathology. On the other hand, elevated TREM2 methylation may happen to try to maintain homeostasis and help fight AD. If this is the case, a future therapeutic strategy may be to enhance the methylation's function and help it clear waste.

Furthermore, studies associated DNA methylation of the ANK1 gene in the brain's cortex with AD pathology (Smith et al., 2019)[14]. Specifically, a study by Smith et al. investigated the role of ANK1 DNA methylation in 8 CpG sites present in many neurodegenerative disease, including AD, Vascular dementia, Dementia with Lewy bodies, Huntington's disease, and PD (Smith et al., 2019)[14]. They used postmortem brains from 6 different UK banks to observe their findings, and they had a relatively larger sample size than some of the other studies. While they did not find any significant changes of the methylation levels in Huntington's disease or in PD, they found DNA hypermethylation in AD, Vascular Dementia, and Dementia with Lewy Bodies in the entorhinal cortex of the brain (Smith et al., 2019)[14]. Since all of these neurological conditions are related to AD pathology, this study enhanced the idea that ANK1 DNA methylation is possibly an important epigenetic factor in AD, and it may have implications of being a potential biomarker (Smith et al., 2019)[14].

Histone Modifications in Alzheimer's

Histone methylation and acetylation

Many studies that have involved transgenic mice as test subjects have found promising correlations between histone modifications and AD (Sharma et al., 2020)[2]. Some of them have shown elevated H4K12ac in the early AD stages, H4K12ac with patients experiencing amnestic mild cognitive impairment, H3K27me3, and H3K4me3 (Sharma et al., 2020)[2]. One study examined the prefrontal cortex (PFC)–responsible for controlling memory and decision-making – of AD patient postmortem tissues and AD mouse models (Cao et al., 2020)[6]. To determine the abnormal histone levels in AD brains, the researchers immunostained three AD brains and three control brains, examining 10 to 12 brain slices each. All brains were relatively age or sex matched. They observed the increase of H3K4me3 in AD patients, which may explain why AD patients experience memory loss and impaired cognitive functions (Cao et al., 2020)[6]. However, repressive H3K27me3 and enhancer H3K4me levels in the PFC had only a little change associated with them (Cao et al., 2020)[6]. To further corroborate their theory, they also examined PS19 transgenic tau mice, which mimic the tau tangles formed in AD human brain, and wild-type mice (Cao et al., 2020)[6]. After immunostaining the mice' brains, the researchers learned that their results aligned with the human brains' patterns (Cao et al., 2020)[6]. They then looked for the source behind this H3K4me3 elevation and found that the SET1/MLL family of HMTs, which are responsible for encoding H2K4me3, were higher in the AD human and mice brains compared to the healthy brains (Cao et al., 2020)[6].

Within the study by Cao et al, there is some data that implicates H3K4me3 as a causal mechanism for Alzheimer's (Cao et al., 2020)[6]. For instance, they looked at how AD symptoms improved after inhibiting the H3K4me3 levels (Cao et al., 2020)[6]. They administered WDR5-0103—an inhibitor for the SET1/MLL HMTs—on the mouse subjects, with 10 to 13 for each variable (Cao et al., 2020)[6]. WDR5-0103 doesn't inhibit other HMTs when it's concentration is up to 100 μM, reduc-

ing some unnecessary variables in the experiment (Cao et al., 2020)[6]. After three days of treatment, the researchers performed behavior tests on the mice, assessing recognition memory and spatial memory (Cao et al., 2020)[6]. The AD mice without the inhibitors had reduced memory in most of the tests, but all the AD mice with different doses of the inhibitor gave better results (Cao et al., 2020)[6]. To see if WDR5-0103's therapeutic potential works for AD patients, they performed similar experiments on 5xFAD mice, a different AD mouse model that carries 5 familial mutations on the human amyloid precursor protein (Cao et al., 2020)[6]. They used 6 mice per group and each one's age was relatively 5 to 6 months (Cao et al., 2020)[6]. The H3Kme3 levels were still elevated in the AD mice, and the memory behaviors aligned with their previous results (Cao et al., 2020)[6]. By using whole-cell patch-clamp electrophysiology, they also learned that WDR5-0103 improved some synaptic functions (Cao et al., 2020)[6]. WDR5-0103 may be a potential therapeutic with more research, since H3Kme3 seems to be a cause of Alzheimer's (Cao et al., 2020)[6].

However, it must be noted that the study by Cao et al. has some limitations. Firstly, while the mouse models used are supposed to mimic human AD, they may not fully capture the intricacy of the disease, which could lead to erroneous results. They also could have benefitted from giving the inhibitor for a longer amount of time before performing the tests. For the future, they could also have a larger sample size for more accurate results as well. In a different study, the researchers looked at the entorhinal cortex of AD patients and controls to observe lysine H3K27 acetylation patterns (Marzi et al. 2018)[15]. Some of the 4,162 differently acetylated areas they found were associated with AD-related genes—such as APP, PSEN1, PSEN2, and MAPT (Marzi et al. 2018)[15].

Histone phosphorylation

Histone phosphorylation is another modification that may impact AD. For example, hyperphosphorylation of Ser 47 of Histone H4 may help AD pathogenesis develop (De Plano et al., 2024)[16]. Another study discovered the elevation of H3 phosphorylation in the AD frontal cortex (De Plano et al., 2024)[16]. They learned this by using 10 AD and age-matched control postmortem human brains each (Rao et al., 2012)[17]. They then extracted genomic DNA from the frontal cortex of these brains (Rao et al., 2012)[17]. This abnormal epigenetic function may cause apoptosis and a degradation of synaptic proteins (Rao et al., 2012)[17]. This causal mechanism implies that treatments reducing H3 phosphorylation levels may improve cognitive functions and slow the degradation progress (Rao et al., 2012)[17]. Addressing some of the limitations of this study can help enhance its findings (Rao et al., 2012)[17]. For instance, the sample size of 10 brains per variable is somewhat small; expanding it in variety and size would further support the results. Additionally, applying an H3 phosphorylation inhibitor to mice with similar symptoms would test for therapeutic potential. With these additional measures, this could be a plausible theory.

Non-coding RNAs in Alzheimer's disease

In addition to DNA methylation and histone modifications, non-coding RNAs—specifically miRNAs—have been studied in AD pathology. There are some notable ones that have therapeutic potential, since they directly correlate to AD hallmarks.

For instance, when analyzing the relationship between miR-29c levels and Beta-site Amyloid Precursor Protein Cleaving Enzyme 1 (BACE1) levels, which produces amyloid beta proteins, one set of researchers found that miR-29c levels were low in the AD subjects compared to the controls (Lei et al., 2015)[18]. With further experiments, they realized that miR-29c inhibits BACE1 expression by attaching to the 3'UTR of BACE1 (Lei et al., 2015)[18]. Therefore, if miR-29c levels are reduced, then BACE1 expression would increase, which further enhances its link with AD pathogenesis (Lei et al., 2015)[18]. Additional research on this is necessary, since this study used 31 AD and 29 control postmortem brains which were all obtained from two hospitals in Tijan, China (Lei et al., 2015)[18]. This doesn't suggest a lot of diversity in the subjects, which may impact the extrapolation of the findings to additional populations (Lei et al., 2015)[18]. Additionally, for the cell cultures, these researchers emulated miR-29c, which may not completely represent the actual miRNA (Lei et al., 2015)[18]. For future research, expanding the diversity and size of the samples, and using naturally enhanced miR-29c samples may be of use.

Another study to find a link between BACE1 and a non-coding RNA—miR-186 was that of Kim et al. (Kim et al., 2016)[19]. Since many older patients have AD, the scientific world has been trying to form connections between age-related epigenetics and AD (Kim et al., 2016)[19]. The researchers discovered that age reduces miR-186 levels which then increases the amount of BACE1 generating amyloid beta (Kim et al., 2016)[19]. First, they observed around 100 mRNA levels in mice brains ranging from 2 months to 13 months old (Kim et al., 2016)[19]. They noticed that as the age increased, miR-186 levels decreased in the mouse cortices (Kim et al., 2016)[19]. Then, they computationally searched for genes affected by miR-186. They realized that miR-186 is prevalent in neurons, much like BACE1 (Kim et al., 2016)[19]. According to the computational data, miR-186 binds to the 3'UTR of BACE1 to decrease its levels, which would explain the correlation between AD and miR-186 (Kim et al., 2016)[19].

To confirm this with their own experiments, Kim et al. performed a luciferase assay by combining a luciferase reporter construct with the 3'UTR of mouse BACE1 mRNA (Kim et al., 2016)[19]. They then implemented it in both a control and miR-186 inside mouse Neuro-2a neuronal cells (Kim et al., 2016)[19].

The miR-186 had a less pronounced luciferase than the control, meaning that it reduced BACE1 expression more (Kim et al., 2016)[19]. Then, the researchers mutated the 3'UTR fragments and compared them with the controls (Kim et al., 2016)[19]. The miR-186 had no effect on the mutated fragments, proving that miR-186 targets BACE1 through that site (Kim et al., 2016)[19]. Once they overexpressed the miR-186, the BACE1 protein and mRNA levels decreased (Kim et al., 2016)[19]. The overexpression also lowered amyloid beta levels in APP-mutated cells (Kim et al., 2016)[19]. Once they inhibited endogenous miR-186 by using anti-miR-186, the BACE1 protein levels rose (Kim et al., 2016)[19]. Taken together, this data proves that miR-186 may be a casualty factor for amyloid beta protein, making it a candidate for a future therapeutic drug, specifically one that enhances the amount of miR-186 in the cortices. In the future, to expand the research, the study could include human brains to ensure that the findings correlate.

Moreover, additional abnormal changes in miRNAs were shown to enhance BACE1 levels in the brain, including mi-339-5p and miR-195—which are both reduced in AD patients (Long et al., 2014; Zhu et al., 2012)[20,21].

APP has also been found to be subject to miRNA regulation (Long et al., 2019). The amyloid precursor protein (APP) 5'-UTR is impacted by miR-346, and it augments APP levels in the CNS specifically (Long et al., 2019)[22]. However, as AD progresses, both the miR-346 levels and the APP levels reduce (Long et al., 2019)[22]. Other miRNAs that control APP include miR-101, miR-153, and miR-298 (Long et al., 2019)[22].

Therapeutic strategies

As the human population ages, the complex pathogenesis of Alzheimer's disease must be unraveled. A major recent focus of the field of neurodegeneration has become to understand the epigenetic changes that are linked to disease pathogenesis and whether they may have a causative role. A better understanding of disease-associated epigenetics can inform the design of potent new therapeutics that can target disease pathology in the millions of individuals suffering from AD. While many studies, particularly in recent years, have dived deeper into understanding how epigenetic mechanisms impact AD pathogenesis, there is still much to be discovered about this topic.

Some therapeutic strategies already exist. For example, by including DNA methyl donors, such as folate, in AD patients' diets, their cognition improves slightly (Sharma et al., 2020)[2]. By analyzing numerous data sets on folate levels and AD, one study discovered that AD patients are more likely to have folate deficiencies, which is a risk factor (Zhang et al., 2021)[23]. This may be because folate controls some enzymes that manage amyloid proteins and neuritic plaques, both of which are hallmarks of Alzheimer's (Zhang et al., 2021)[23]. To track this, a study observed trends in 579 elderly people's dietary journals (Corrada et al., 2005)[24]. After a mean follow-up of around 9 years, 57 of those volunteers were diagnosed with AD (Corrada et al., 2005)[24]. This study noted that the subjects with higher folate ingestion had a decreased AD risk (Corrada et al., 2005)[24].

HDAC inhibitors are a developing method of reducing AD symptoms; HDAC inhibitors are drugs that target enzymes encoding histone modifications (Santana et al. 2023)[25]. It has been promising when tested in animals, and with further research, it may help humans (Santana et al. 2023)[25]. A group of researchers decided to compare the behaviors of AD mice, AD mice exposed to inhibitors, and wild-type mice (Zhang et al., 2024)[26]. The nesting latency of the AD mice was much longer than both the mice with inhibitors and the controls, who had relatively the same time (Zhang et al., 2024)[26]. The quality of the AD mice' nests were also reduced (Zhang et al., 2024)[26]. There is potential that cognitive functions in humans could also improve with HDAC inhibitors.

Anti-miRNAs are another therapy that has been developed; they imitate miRNAs and have effectively reduced expression for an upregulated target, such as BACE1 (Sharma et al., 2020)[2]. However, they are difficult to integrate into current treatments since researchers are having trouble targeting them to a specific cell.

Currently, there are therapies being developed that target epigenetics. The ORY-2001 is one of them (Vafidemstat 2020)[27]. It inhibits lysine-specific histone demethylase 1 (LSD1). LSD1 is an enzyme that epigenetically changes histones by taking out methyl groups; it is often associated with neurological conditions and Alzheimer's (Vafidemstat 2020)[27]. This inhibition helps keep neurons alive and improves cognitive function and memory (Vafidemstat 2020)[27]. Phase 1 of the trial happened in 2017; its goal was to use small doses in 88 non-AD volunteers to test its safety on the general human population (Vafidemstat 2020)[27]. Doses from 0.6 and 4 mg didn't produce overly harmful effects (Vafidemstat 2020)[27]. The number of platelets in the body dropped after 5 days of a 2.5 mg/day dose (Vafidemstat 2020)[27]. However, it went back to normal after a week, suggesting that the drug is not too detrimental (Vafidemstat 2020)[27]. Phase 2a of the trial took place in 2018; it tested the safety and initial efficacy of the drug with mile to moderate AD patients (Vafidemstat 2020)[27]. For test subjects, 117 patients with amyloid pathologies in the cerebrospinal fluid (CSF) were used. For the first six months, some people received 0.6 or 1.2 mg of the drug daily and others received a placebo daily (Vafidemstat 2020)[27]. For the following six months, everyone received the actual drug dose (Vafidemstat 2020)[27]. Four identical studies were happening in the United States as well (Vafidemstat 2020)[27]. Compared to the placebo group, the drug was safe and did not drop platelet levels anymore (Vafidemstat 2020)[27]. While the people who took the drug showed no changes in AD pathology or cognition, it reduced inflammation in the brain compared to the control group (Vafidemstat 2020)[27]. A different study with

12 AD people showed improvement on aggression levels after consuming 1.2 mg of the drug daily for 6 months (Vafidemstat 2020)[27]. While the drug has not shown that it can help cure AD by removing tau tangles or amyloid plaques, it has potential to alleviate some symptoms of the disease, which can still help the global AD population.

While some clinical trials are currently in place to further the therapeutic scope of epigenetics, there are some challenges in development. One challenge concerns targeting the drug to a particular cell or blood barrier (Dai et al., 2024)[28]. Since both enzymes and non-coding RNAs associated with epigenetics are spread in different parts of the body according to function, it is difficult to locate and achieve the desirable placement (Dai et al., 2024)[28]. Similarly, the current HDAC inhibitors tend to prevent the functions of a wide range of enzymes (Dai et al., 2024)[28]. This broad range leads to unintentional side effects—such as nausea, vomiting, fatigue, cardiac issues, hypoxia, etc (Dai et al., 2024; Subramanian et al., 2010)[28,29].

Another hurdle is the insufficient characterization of epigenetic mechanisms, which is a requirement in developing a safe, effective drug (Dai et al., 2024)[28]. For example, TREM2 has been examined for its therapeutic potential (Morgan & Mielke, 2021)[30]. Some studies argue that elevating it in the brain helps improve cognitive functions (Morgan & Mielke, 2021)[30]. Namely, one study discovered that increased TREM2 led to fewer amyloid plaques in AD mouse models in vivo (Lee et al., 2018)[31]. They used Bacterial Artificial Chromosome (BAC)-mediated transgenesis to provide the mouse genome with some human TREM2 gene segments, which increased TREM2 levels in the mice (Lee et al., 2018)[31]. They then deleted some key coding exons of certain genes to ensure that TREM2 was the only gene being overexpressed (Lee et al., 2018)[31]. This elevation changed microglial responses and improved disease symptoms in most of the AD mouse models (Lee et al., 2018)[31]. To make their discovery, they crossed BAC-TREM2 mice with APP and PSEN1-mutated mice (Lee et al., 2018)[31]. Using immunostaining, they looked at the amyloid plaque levels, noting that amyloid plaque levels in the bred mice were greatly lower (Lee et al., 2018)[31]. Since APP levels remained constant in all mice, the TREM2 was likely the cause of this shift (Lee et al., 2018)[31]. Based on the findings, this study supports the idea of elevating TREM2 levels to improve AD (Lee et al., 2018)[31]. However, another study opposed the idea by claiming that lowering TREM2 levels diminishes neuroinflammation and brain damage (Leyns et al., 2017)[32]. They bred both mice with TREM2 and mice without TREM2 with PS19 tau-transgenic mice to form two types of mice (Leyns et al., 2017)[32]. PS19 mice undergo neurodegeneration and tau tangles due to the P301S mutation that causes frontotemporal dementia (Leyns et al., 2017)[32]. This study only used male PS19 mice because their effects are more pronounced (Leyns et al., 2017)[32]. After extracting and dissecting the mice brains, the researchers discovered that the bred mice without the TREM2 levels had less brain atrophy and lower synaptic degeneration in the hippocampus region (Leyns et al., 2017)[32]. Based on these two studies, it is possible that TREM2 lowers amyloid plaques but negatively responds with tau tangles (Leyns et al., 2017)[32]. These contradictory findings show that a complete understanding of TREM2 is needed before creating a drug for it, since it affects different AD pathologies in diverse ways, and having less than satisfactory knowledge could be detrimental to the patient.

In addition to this, converting molecular probes—molecules used to study and interact with target enzymes—into therapies needs many in vivo studies to confirm its eligibility, which is another obstacle (Dai et al., 2024)[28]. This requires a lot of time, resources, and willing scientists. Moreover, humans could start to develop resistance to these epigenetic agents, which is already evident against the epigenetic drugs targeting cancer (Dai et al., 2024)[28].

Future Directions

A future therapeutic focus could be identifying the individual patterns associated with the patient's disease and creating personalized medicine targeting epigenetic changes. Or rather, identifying the epigenetic patterns of patients living in the same cities, or areas with similar environmental conditions, can help create different medications better tailored to people's exposure.

Another future direction could be focusing on using non-coding RNAs and DNA methylation patterns as biomarkers for the disease to detect it earlier. Using DNA methylation patterns as a biomarker has been considered because it is not invasive and can be looked at by taking blood samples. (Song et al., 2023)[33]. If possible, identifying epigenetic patterns associated with these diseases that are close to universal in most people with the disease could serve as useful biomarkers.

There are some limitations associated with the experimental studies. For instance, some results of the experimental studies have been found to conflict with each other due to the differing methylation patterns and differing environmental exposures in patients. Bias is another factor that is difficult to eliminate when dealing with human subjects. For example, in Corrada et al.'s study of analyzing dietary journals, they mentioned that some people may not have properly logged all of their food intakes, which would invalidate the findings.

Converting preclinical trials into having human subjects is also a difficult factor to consider. In the nesting latency experiment, they gave some mice two types of inhibitors: VPA and WT161 (Zhang et al., 2024)[26]. VPA has been tested in clinical trials before, so there is more information on how safe it is for humans (Zhang et al., 2024)[26]. However, WT161 is recently developed, and it is going to require cost and time to determine whether it is safe for humans, since this study only tested it on

mice (Zhang et al., 2024)[26]. This will hinder the development of the treatment.

Conclusion

The importance of epigenetics has been recently highlighted, with researchers focusing on understanding the impact of epigenetic changes in the pathogenesis of different diseases and developing treatments to target them. Some of the main epigenetic changes occurring in AD that have been discussed in this review are increased ANK1 methylation levels, increased H3K4me3 levels, TREM2 methylation, and miRNAs targeting BACE1 and APP genes. Also, the paper discussed how environmental impacts, such as the embryonic environment and chemical exposures, can affect epigenetics. Finally, the paper provides a summary of established therapeutic strategies and future directions to improve them.

AD and other neurodegenerative diseases are heavily influenced by epigenetic mechanisms—such as DNA methylation, histone modifications, and noncoding RNAs, Thorough characterization of the mechanisms by which specific altered epigenetic modifications lead to AD pathogenesis can better inform treatments that target the causes of AD, which may be the path to curing AD completely. The epigenetic modifications characterized and therapies developed may be applied to other types of diseases as well, further revolutionizing the world of medicine. More clinical trials and research are required to make this a possibility.

Methodology

We reviewed and compiled information from primary and secondary sources on topics of environmental impact on epigenetics and Alzheimer's Disease. We have searched key terms such as "epigenetic changes + neurodegenerative diseases", "DNA methylation + Alzheimer's", and "Environmental Factors influencing epigenetics", mainly using the databases Google Scholar and PubMed, and focusing on recent research to ensure that we are getting informed on the latest advancements. We applied a date filter from 2016-2024 to find most of the articles present. When reviewing secondary sources, we also looked at the bibliography to identify the primary research to gain additional information and make our own inferences. We determined the relevance of the articles by proofreading the abstract, results, conclusions, and methods sections, and we assessed their credibility by critical evaluation of the findings presented in the paper, as well as looking at the impact factor of the authors, the paper, and the Journal. We focused on including mostly in-vitro and human models, while also only including English-language articles. Then we collated all the information used from each separate source in our personal notes and subsequently performed a secondary literature analysis.

Due to research-based constraints, research in additional databases is not currently feasible for this paper. We addressed several limitations of each study in the paper, to give the reader a thorough understanding of the findings. However, in the future, expanding the databases could provide a more detailed and broader scope of this topic.

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