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Review Article

Epigenetic Modification in Alzheimer Disease

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ABSTRACT

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by progressive cognitive decline and memory loss, imposing a significant burden on affected individuals and their families. Despite the recent promising progress in therapeutic approaches, more needs to be done to understand the intricate molecular mechanisms underlying the development and progression of AD. Alzheimer's disease is characterized by the formation and deposit abnormal peptides such as amyloid plaques and neurofibrillary tangles in the Brain. There are currently no validated biomarkers which can be used to accurately diagnose Alzheimer's disease (AD) or to distinguish it from other dementia-causing neuropathologies.As of right now, there are no verified biomarkers that can be used to reliably diagnose Alzheimer's disease (AD) or differentiate it from other neuropathologies that cause dementia. Epigenetic changes have become recognised as significant players in the pathophysiology of AD in the hunt for novel, more trustworthy biomarkers and effective treatment alternatives. Numerous studies have indicated that histone posttranslational modifications, non-coding RNA regulation (with a focus on microRNAs), DNA methylation and hydroxymethylation, and these processes are crucial for the progression and development and accumulation of aberrant peptides in the brain, such as amyloid plaques and neurofibrillary tangles, is what defines Alzheimer's disease. Treatment plans intended to stop these deposits from forming have not proved effective. As of right now, the condition has no viable remedies. Treatments targeted at reversing these alterations by interfering with DNA methylation, histone acetylation, and microRNA expression may represent potential avenues of research in the future, given the multitude of epigenetic changes found in Alzheimer's disease.Extensive research has suggested an important role of DNA methylation and hydroxymethylation, histone posttranslational modifications, and non-coding RNA regulation in the course and development of AD

INTRODUCTION

Significant changes have occurred in the field of epigenetics since the early 1940s, when British

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embryologist Conrad Waddington originally introduced the Epigenetic concept [1]. However, there is still much to learn about the roles that epigenetic pathways play in various disease processes. Epigenetic changes have been linked to the genesis of a number of human diseases, including Alzheimer's disease (AD). The main areas of research for epigenetic changes linked to AD pathogenesis are posttranslational modifications of histones, regulation of non-coding RNA, and DNA methylation and hydroxymethylation (Figure 1). Furthermore, epigenetic mechanisms—specifically, DNA methylation and non-coding RNAs—control the expression of mitochondrial genes, just as they do with nuclear DNA. Consequently, studies investigating possible links between AD and mitochondrial epigenetics, or mitoepigenetics

Epigenetic modifications are a key factor in Alzheimer's disease (AD) and are linked to the disease's progression and neuropathology:

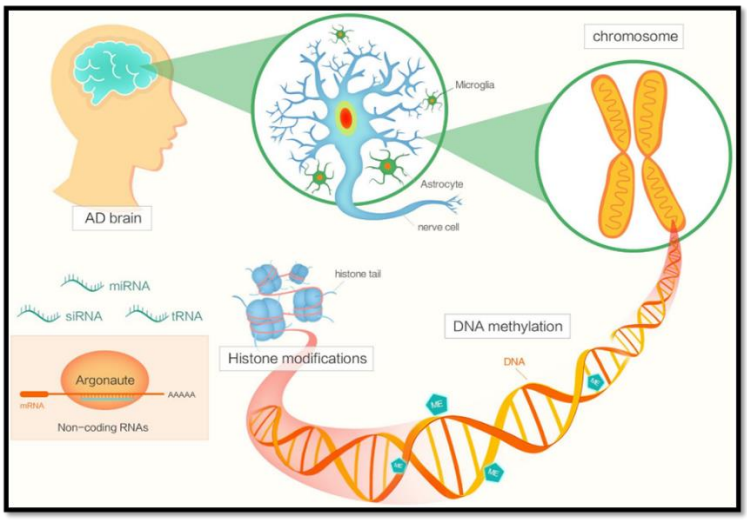

Fig.1.1.The Epigenetics of Alzheimer Disease

3.1 DNA Methylation

A critical epigenetic modification that regulates transcription and cellular processes in the brain. DNA methylation patterns in the brains of people with AD are different from those of people without AD.

3.2 Histone Modification

Histones are proteins that DNA wraps around to form chromatin. Histone modifications, such as acetylation, methylation, and phosphorylation, are involved in the pathologic mechanisms of AD.

3.3 MicroRNA's(miRNA).

Some miRNAs are downregulated in early AD, including miR-23b-3p, miR-125b-5p, miR146a-5p, miR-137, miR-181c, miR-9

3.4 Oxidative Stress:-

Increased aerobic metabolism in neurons in the adult brain can lead to oxidative Stress, which may induce Epigenetic changes. Increased aerobic metabolism in neurons in the adult brain can lead to oxid Epigenetic modifications are chemically reversible, so treatments that reverse these modifications are a promising therapeutic strategy for AD. Some potential therapeutic targets include histone deacetylases (HDACs).

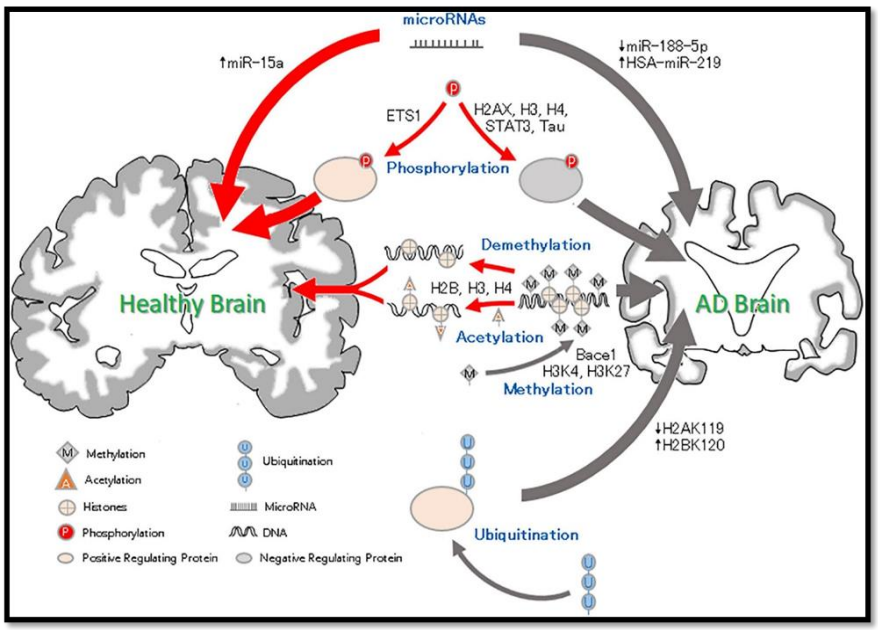

Fig.1.2

When dementia occurs, Alzheimer's disease (AD) is the most common cause. It typically affects individuals over 60 and manifests as a gradual loss of memory and cognitive function, language impairments, ideamotor apraxia—the inability to convert ideas into actions—impaired judgement and planning, apathy, depression, and, in later stages, psychosis with paranoid delusions. The presence of aberrant peptide deposits in the brain is a characteristic of AD. The most recognisable lesions are neurotic extracellular plaques of the amyloid β (Aβ) peptide, which is made up of 33–40 amino acids and is produced when the transmembrane protein known as amyloid precursor protein, or APP, is broken down by protease. The numerous deformed neuronal extensions found in these neuritic plaques are referred to as dystrophic neurites. At their core, activated microglial cells are seen.

According to certain data, amyloid deposits may be harmful and may even result in the death or malfunction of individual neurones. The α-, β-, and γ-secretase enzymes in the normal brain break down APP into functional pieces. An increase in β- and γ-secretase in comparison to α-secretase can occasionally result in the build-up of peptides with 40 and 42 amino acids, which are referred to as amyloid β40 (Aβ40) and amyloid β42 (Aβ42). It seems that the Aβ42 peptide has more neurotoxic qualities. Small clumps of two to twelve peptides, known as Aβ oligomers, seem to be particularly harmful (1). Another type of plaque is diffuse plaque, which does not have a dense centre of dystrophic and amyloid neurites. They are not linked to either neuronal death or cognitive impairment, in contrast to neuritic plaques.

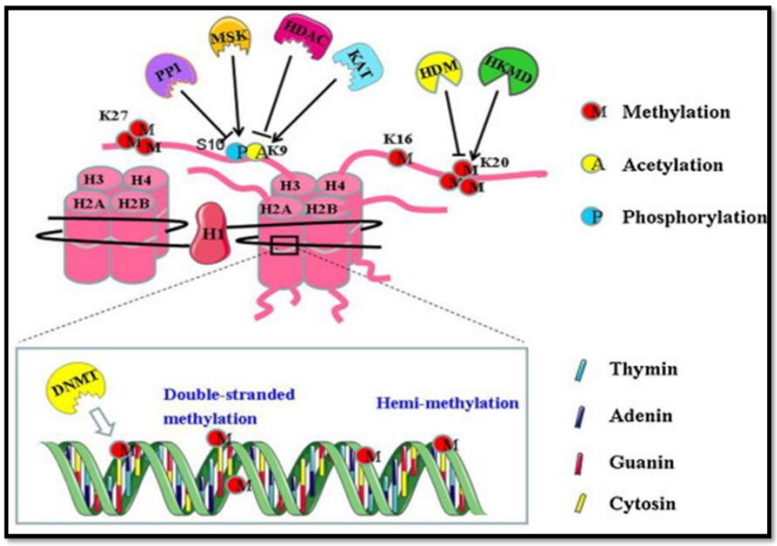

Fig.1.3.Epigenetic mechanism in Alzheimer Disease

Any heritable modifications that influence the expression of a gene or genes without changing the actual DNA sequence are referred to as epigenetics. As a result, unlike genetic code, epigenetic information is unique to a single cell or tissue and can alter in response to various environmental stimuli, ageing, or illness [2]. The primary distinction between genetic variants, which are typically unaffected by environmental stimuli, and epigenetics is that the former involves the reaction produced to environmental influences [3]. DNA methylation, histone modification, and noncoding RNA molecules are the three main epigenetic mechanisms that control the interaction between genes and environmental stimuli. These systems also impact the regulation of gene expression.

1.DNA Methylation:

The main focus of epigenetics is the study of chromatin structural alterations that alter phenotype without altering genotype. DNA methylation, which involves adding a methyl group to DNA, is the most researched epigenetic biological phenomena that regulates genetic expression. The technique modifies DNA activity, gene expression, and gene function without changing the DNA sequence. The most extensively studied process of epigenetics is DNA methylation, which has been linked to a number of illnesses, including depression, Parkinsonism, and AD [4-7]. The process of adding a methyl residue to the DNA chain with the aid of an enzyme called a DNA methyltransferase is known as DNA methylation. The cytosine residue is the most often and commonly methylated site by this enzyme, resulting in the synthesis of 5-methylcytosine (5-mC) in CpG dinucleotide clusters [8-11]. The expression of a gene is suppressed when any of the CpG islands—sites of the CpG clusters—that are situated on the promoter region of that gene experience methylation [12]. Additionally, methylation of the centromeric regions, sometimes referred to as repetitive repeats, contains CpG dinucleotides, which stabilise the chromosome and stop translocation occurrences [13].

Global DNA Methylation:

DNA methylation in different brain regions of a sample population with and without AD has been examined by a number of research teams. A thorough review of the literature reveals conflicting findings regarding whether AD brains have changed global DNA methylation. According to preliminary observations, postmortem AD brains had lower levels of global DNA methylation in the hippocampus and entorhinal cortex [14,15]. Others, however, have noted that

AD is associated with an overall rise in DNA methylation [16-17]. Other research, however, has not discovered any differences between AD and controls [18,19]. These publications' discrepancies appear to go beyond the precise brain regions where the measurements were made or the techniques employed to quantify DNA methylation. For instance, Bradley-Whitman and colleagues and Chouliaras and colleagues presented conflicting findings about the methylation status of neurones in AD patients' hippocampal regions. In AD, DNA methylation was found to have significantly decreased in the former study and significantly increased in the latter . To address these discrepancies, more research is required, and maybe the many teams looking at DNA methylation in AD could standardise their methods.Another unsolved question is the connection between alterations in DNA methylation and AD neuropathology. According to reports, the middle frontal and middle temporal gyrus of AD brains had noticeably greater 5 hmC levels than those of age-matched controls. Additionally, the scientists noted that NFTs and high 5 hmC levels were positively correlated [20]. These findings are supported by the finding that increased tau pathology was associated with 17 differentially methylation locations in AD patients' blood [21]. Others, however, have noted that tangle-positive neurones exhibit lower levels of global DNA methylation . In AD and age-matched control cases, Chouliaras and associates assessed the hippocampus's 5-mC and 5-hmC levels.

Histone Modification in AD:

A nucleosome is created in chromatin when DNA is encircled by histone proteins. Histones regulate nucleosome location, chromatin architecture, and transcription factors' and other DNA-binding proteins' access to DNA. Chromatin structures that are tightly or loosely packed around histones are referred to as heterochromatin and euchromatin, respectively. In general, euchromatic regions have more transcriptional activity than heterochromatic ones. On the other hand, posttranslational modifications (PTMs) of the histones' amino-terminal tails control how they bind with DNA, which in turn controls how genes are expressed. Histone tails can be methylated, acetylated, ubiquitylated, SUMOylated, glycosylated, and ADP-ribosylated in a physiological manner [22].

Acetylation:

Acetylation is a famous illustration of histone PTM. Histone acetyltransferases (HATs) are a family of enzymes that can acetylate the amino-terminal lysines of one or more core histones. Since the acetyl groups that HATs add can be eliminated by histone deacetylases (HDACs), this reaction is reversible. In general, acetyl groups at the amino terminus of histones "open" the chromatin by reducing the contact between histones and DNA. To put it another way, cells can control gene expression by varying the activity of HATs and HDACs, which in turn affects how easily DNA-binding proteins like transcription factors can reach the DNA [23].

Memory functions and synaptic plasticity are altered in AD due to dysregulation of histone acetylation [24,25] (Table 2). In light of this, Santana and associates found that AD patients had mild hypoacetylation of the hippocampus and hyperacetylation of the cerebellum. Cytoskeletal disarray and the activation of Rho GTPase-mediated processes were linked to these alterations [26]. Similar outcomes were shown in mice; for instance, Arancio et al. Found that learning-induced acetylation of H4 in the APP/PS1 mice's hippocampal regions was reduced by 50% [27]. Others have verified the beneficial effects of HDAC inhibitors on AD-like pathologies in a number of animal models of AD (e.g., [28-32). However, the majority of HDAC inhibitors are not effective in treating AD, which limits their use.

Histone Methylation/Demethylation

Histone methylation/demethylation is a reversible process involving the addition or Removal of methyl groups to the N-terminal region of lysine or arginine residues. Histone methyltransferases (HMTs) and histone demethylases (HDMs), respectively, mediate the process. Gene expression is altered by changes in chromatin structure, which are linked to changes in histone methylation. Interestingly, lysine residues can experience mono-, di-, and tri-methylation, but arginine residues can only experience mono-methylation. Numerous physiological and pathological processes have been connected to these alterations, which either activate or repress gene expression. Mice with impaired working memory, for instance, lack the Jmjd2B gene in neurones, a histone demethylase specific for H3K9me3 [89].Histone methylation alterations and AD have been the subject of much study, which has been discussed elsewhere, for example [90]. Histone methylation status alterations in AD have been documented by several labs . For instance, in the frontal cortex of AD brains, Anderson and Turko discovered a 25 and 35% decrease in H2B-methylation at residues K108 and R55, respectively . Despite the study's small sample size of AD brains, the findings were compelling. Persico and associates verified that AD patients had increased H3K27me3 and decreased H3K4me3 signals in comparison to healthy people . Numerous theories have been put up to connect the pathophysiology of AD to the documented alterations in histone methylation. Tau aggregation neurodegeneration have been linked to direct methylation of the MAPT gene [33].

Epigenetic Therapies in Alzheimer Disease :

Acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and the glutamate NMDA receptor antagonist memantine, which are medications specifically designed to treat memory impairments, are the currently approved treatments for AD, as was previously mentioned. NMDA receptor antagonists stop abnormal stimulation, and acetylcholinesterase inhibitors raise the neurotransmitter acetylcholine levels, which are reduced in AD brains (34). These medications do not slow the disease's course, but they do produce a noticeable and temporary improvement in cognitive and functional abilities. However, observational research indicates that the combination of these therapies lengthens the period of time before patients require residential admission (35). Consequently, there is a lot of interest in investigating novel therapies for the illness. Anti-amyloid treatments are the primary focus of AD research (36). New anti-amyloid antibodies like aducanumab and BAN2401 have given this field of study new hope despite the severe side effects of active immunotherapy and the persistent failures of passive immunotherapy. This is because preliminary clinical trials have demonstrated that these antibodies can lower the amyloid load (37). Other therapies that support Aβ clearance or stop plaque formation have been developed under the amyloid cascade hypothesis. Nevertheless, not only have none of the therapies in this field of study been proven to be successful, but several of them have even made clinical conditions worse (38, 39)

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