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Review Article

Epigenetic Regulation of Neuroinflammation in Dementia of Alzheimer's Disease and Other Forms of Dementias

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Received: July 22, 2025; **Published:** August 18, 2025

DOI: 10.31080/ECCMC.2025.08.01047

Abstract

Over the years, research in Alzheimer's disease (AD) continues to advance and enormous progress has been made towards understanding the pathology of AD. However, unavailability of an appropriate drug for treatment of AD raises several questions and scores the lack of thorough understanding of the regulatory mechanisms underlying the disease pathology. It signifies the need for further research to gain deeper understanding of the regulatory mechanisms underlying pathology of AD and uncover the hidden complexity of the disease. While most of the drugs that have been designed and proceeded to clinical trials are focused on clearing the aggregates of amyloid beta and the neurofibrillary tangles, the focus on neuroinflammatory pathways in causing neurodegeneration and dementia in AD is gradually emerging. Other pathological pathways that have profound regulatory functions underlying AD dementia include transportation and metabolism of APOE mediated cholesterol, TREM2 mutation, DNA methylation, histone modification and non-coding RNAs etc. Even though there is progress in this area of research, we believe that further strengthening is necessary highlighting their substantial roles in the pathogenesis of the disease. Over the years, several research have also indicated the involvement of epigenetic mechanisms in the developing memory formation in pathological or physiological conditions of the diseases. This review is particularly focused to highlight the epigenetic regulation of APOE, TREM2, DNA methylation, histone modification and non-coding RNAs that contribute to neuroinflammation leading to dementia of AD and related cognitive impairments.

Keywords: *Alzheimer's Disease; Dementia; Neuroinflammation; TREM2; APOE4; DNA Methylation; Histone Modification; Non-Coding RNAs*

Introduction

Alzheimer's disease (AD) is a well-known progressive neurodegenerative disease that is characterized by increase abnormal accumulation of amyloid plaques and tau tangles in the brain, resulting in declination of reasoning capabilities, loss of memory and confusion etc. It severely deteriorates the normal live of the affected individual and the symptoms worsen with the progression of age. AD and AD related dementias (ADRD) is one of the highest leading causes of death globally and they stand at 7th rank among the leading diseases causing dead to humans [1,2]. Latest reports indicated that 6.9 million Americans with age 65 and older are currently affected by AD's dementia; this shows that millions of Americans living at this age are facing risk of dead prematurely by AD [2-4]. AD or ADRD directly

deteriorates both health and economy globally. The 83% of the caregivers are unpaid family members of the patients, friends and others [5]; if they happened to be paid then the cost is estimated to be $346.6 billion as of 2023 [2]. And total payments for health care, long-term care and hospital services provided to the people of 65 years of age and older with dementia are estimated to be $360 billion as of 2024 [2]. It may be noted that a lifetime cost for providing care of an individual with dementia is estimated to be equal with 392874 USD as of 2022 USD currency value and 70% of it is covered by the unpaid family members. In 2023, more than 11 million family members and other unpaid caregivers provided support to the individuals affected by AD or ADRD [2]. These data provide us a global alarming signal to find appropriate treatment for AD or ADRD at the earliest possibility.

With the growing development in research in the past few decades, knowledge on regulatory mechanisms underlying pathology of AD has been greatly increased. Several drugs have been developed, and subsequent clinical trials have been carried out. Nonetheless, challenges for a cure or proper treatment of the disease remains, due to complexity of the disease as well as several other shortcomings such as in method designing and the fulfilment of other criteria/protocols that needs to be followed in conducting clinical trials [6,7]. This reveals us the need of further research to further uncover the wide rages of complex regulatory mechanisms or pathways underlying the disease pathology. So far, most of the basic and clinical research, drug development, clinical trials are focused on the abnormal deposition of amyloid plaques and neurofibrillary tau tangles in the brains of AD patients as well as the model organisms based on these symptoms [4,8]. However, there is growing development towards the neuronal inflammatory pathways underlying the pathogenesis of dementia of AD [9,10]. It has been suggested that neuroinflammation may be considered as an indicator for early diagnosis and for disease modifying treatment that could target interferon beta, glatiramer acetate, and teriflunomide [11]. Because patients who have not yet developed clinically definite disease symptoms, have acute inflammatory demyelinating CNS event which is consistent with Multiple sclerosis (MS) patients. And there is a need for strengthening further research on epigenetic pathways that link to neuroinflammation resulting to dementia of AD/ADRD, that can help in expanding therapeutic approaches of the disease. This review aims to display the significant impact of epigenetic regulations walking through several research publications that have provided evidence of TREM2/APOE mutation, DNA methylation, histone modification, non-coding RNAs involvement in the immune system dysfunction and neuroplastic abnormality leading to cognitive deficits in AD/ADRD.

Gene epigenetic network regulatory pathways underlying neuroinflammation and cognitive deficit in AD/ADRD

Several risk genetic variant changes have been discovered in AD, and they are found to have potential roles in the pathogenesis of the disease. TREM2 and APOE genes are among the most highly studied ones, because of their significant roles in AD pathology. The role of these two genes in neuroinflammation and cognition is modulated through multiple routes including glial mediators, cytokines and epigenetic mechanisms.

Role of TREM2

Triggering receptor expressed on myeloid cells 2 which is abbreviated as TREM2, is a transmembrane receptor expressed on the surface of myeloid cells, such as microglia and dendritic cells. Growing number of studies increasingly suggest that TREM2 plays a potential role towards preventing or slowing down the sporadic AD progression by promoting microglial survival, proliferation, and phagocytic activity and attenuating neuroinflammation and improving cognitive functions [12,13]. How does TREM2 attenuates neuroinflammation and helps improve cognitive function? In the brain of MS patients, TREM2 is found to be highly expressed on myelin-laden phagocytes in the active demyelinating lesions [12] and the genes encoding inflammatory cytokines such as IL-6 and IL-17, interferon-gamma (IFNγ), are also high in MS lesions [14]. It may be noted that not only TREM2, IL-6 and IL-17, IFNγ are also expressed in microglia in central nervous system (CNS) [15]. Like in AD, inflammation, demyelination and neurodegeneration also occurred in the central nervous system (CNS) of MS [16] and cognitive dysfunction is one of the symptom of MS [17]. In the mouse model of AD [18] and MS [12], deficiency in TREM2 gene expression showed defects in macrophages/microglial phagocytic pathways. These studies reveal the path of TREM2 in regulating

neuroinflammation, neuronal circuitry system, neurodegeneration and cognitive dysfunction in these diseases. Several more studies on mice and humans have established the connections of TREM2 network extensively. In a chimeric mouse model of AD, TREM2 deletion decreases microglial survival and impairs phagocytosis of key microglial substrates such as APOE (apolipoprotein E), inhibits SDF-1α/CXCR4-mediated chemotaxis, culminating in an impaired response to Aβ plaques [18]. Treatment with TREM2 agonistic antibody on AL002a in *Trem2*$^{+/-}$ mice, could promote clearance of myelin debris in CNS, enhancing uptake and degradation of myelin, and increased myelin debris removal by microglia [12]. Subsequently, antibody dependent TREM2 activation in microglia, increases, oligodendrocyte precursors density in areas of demyelination, maturation of oligodendrocytes formation, remyelination and axonal integrity. Study on 5×FAD mice model for amyloid deposition, monoclonal antibody Ab-T1 which is reactive against the extracellular domain of TREM2, could attenuate neuroinflammation and improve cognitive function [19]. Monoclonal Ab-T1 targets membrane-bound soluble TREM2 and induces microglial activation; the activated TREM2 enhances uptake of labeled Aβ by macrophages and microglia and promotes TNF-α production. Further Ab-T1 also enhances the capability of microglia to phagocytose labeled apoptotic neurons that are thought to be cell debris present around the Aβ plaque located regions [19]. TREM2 agonistic antibodies such as AL002a (a mouse IgG1 antibody) also showed similar roles in 5×FAD mice in that humanized monoclonal IgG1 antibody binds to TREM2 and activates its' signaling pathway, reversing Aβ regulatory gene expression, increase recruitment of microglia to Aβ plaques, decreased Aβ deposition, and improvement in spatial learning and memory [13]. Additionally anti-human TREM2 agonistic monoclonal antibody AL002c administration on 5×FAD mice expressing either the common variant (CV) or the R47H variant of TREM2 induction of proliferation in both CV- and R47H-transgenic mice and prolonged administration of AL002c reduced filamentous plaques and neurite dystrophy, impacted behavior, and tempered microglial inflammatory response [20]. These extensive studies establish the neuroprotective pathway of TREM2 via helping in reducing inflammation and increase cognitive function.

In a case control study, lower level of DNA methylation at TREM2 intron 1 was caused by higher TREM2 mRNA expression in the peripheral leukocytes of AD subjects, suggesting to be a biomarker for AD [21]. This reveals positive effect of TREM2 upregulation in CNS while possessing negative a role in the periphery. In another recent study, a newly identified transcription factor named as Yin Yang 1 (YY1) was found to be required for *TREM2* expression [22]. YY1 is an evolutionarily conserved transcription factor which binds closely to the transcription start site of *TREM2* and this binding is necessary for YY1-mediated TREM2 expression. Treatment with inflammation eliciting agent (LPS) which can target microglia, significantly lowers TREM2 and YY1 level in BV2 cells and AD model mice brain [22]. These findings further indicate the epigenetic participation in mediating TREM2 function.

Role of APOE

APOE is a glycoprotein that functions in lipoprotein metabolism, cellular lipid transport and immunoregulation, and it is highly expressed in monocyte-derived macrophages (MDM), Kupfer cells and microglia [23]. In CNS, APOE involves in maintaining growth, repair of neurons and act as a primary cholesterol carrier, by redistributing the lipids that follows deafferentation and neurodegeneration [24]. APOE is also associated with lipoproteins in systemic lipid metabolism in the liver and other organs modulating catabolism of triglyceride-rich lipoprotein particles [24]. In AD, APOE is associated with neurofibrillary tangles and Aβ in senile plaques; among the three polymorphisms, the level of APOE4 is found to be much higher than APOE2 and APOE3 in sporadic AD patients [24]. Further, APOE4 gene is associated with the late onset of familial and sporadic forms of AD [25], and it increases the risk of AD about 5 times higher (from 20% to 90%) [25]. Family based studies evidenced that the onset age decreased from 84 to 68 years with increased level of APOE4 alleles and homozygosity for APOE4 is virtually sufficient to cause AD by the age 80 [25]. This reveals that APOE4 gene dose is a major risk factor for late onset AD. Subsequently, when human APOE isoforms were expressed in APP expressing mice lacking murine ApoE gene; delay in onset of plaque deposition and reduction in plaque burden with varying isoform-specificity (E2>E3>E4) and gene dose-dependent manner was observed [26]. It is suggested that individuals with homozygous for the APOE4 allele has eight times higher risk likely to

develop AD compared with the individuals without the APOE4 allele [25]. Moreover, promoter region of APOE, but not APP, was found to be hypermethylated in the prefrontal cortex region of postmortem brain AD patients [27].

Subsequently, in the gene-specific DNA methylation studies, APOE gene was found to be differentially methylated in AD patients [28]. The three common alleles, APOE2 (Arg158Cys), APOE3 (Cys112Arg) and APOE4 (Cys112) [29,30], are categorically labelled based on two SNPs (rs429358, and rs7412) located in coding region exon 4, that overlaps with a well-defined CpG island (CGI) [31]. The two SNPs not only change protein codons but also the quantity of CpG dinucleotides, which is the primary sites for DNA methylation [32]. APOE CGI has transcriptional enhancer activity with APOE4 allele as well as cell type specificity, moreover APOE4 allele alters the DNA methylation landscape of the APOE CGI which leads increased risk in AD [28]. This suggests that APOE CGI could be differentially methylated in a tissue within the brain of AD patients, in a manner specific to APOE genotype and thereby reveals possible epigenetic alteration contributing to neural cell dysfunction in the CNS of AD patients.

Epigenetic mechanisms underlying neuroinflammation and cognitive deficit in AD/ADRD

Epigenetic changes are heredity in nature and it leads to changes in phenotypes that are independent of altered DNA sequences [33]. Under pathological or physiological conditions, epigenetic mechanisms play important roles in learning and memory in psychiatric disorders, neurodegenerative diseases including AD [34,35]. Epigenetic mechanisms control different events in the neuronal processing including the expression of number of genes after mitosis, learning, memory and cognitive processes [35]. Epigenetic regulation in the development of AD, include the role of DNA methylation, hydroxy-methylation, histone posttranslational modifications, and non-coding RNA regulation (microRNAs).

Role of DNA methylation

DNA methyltransferases (DNMTs) have been found to play a significant role in dynamic DNA methylation and transcriptional modulation in the genome, which associates with memory, learning, and cognition [36]. DNMTs are the key enzymes in DNA methylation process and it specifically transfers the methyl group from the methyl donor S-adenosylmethionine (SAM) to the 5-position of cytosine generating 5-methylcytosine [37]. In the late onset AD patients, DNMT1 expression and DNA methylation were elevated and positively correlated with APOE4; this suggests that global DNA methylation could serve as a reliable marker for AD [38]. Subsequently, neuronal distribution of nAChRs in the frontal cortex of AD patients was decreased when compared to age-matched and middle aged controls [39]. It may be noted that choline is a major donor for histone and DNA methylation which is important in normal brain development and it helps in the structural and functional integrity of membranes and regulates cholinergic neurotransmission via the synthesis of acetylcholine and thereby the function of nAChRs [40]. Neuroinflammatory response genes such as IL-1β and IL-6, showed a peak expression level during the first stages of the AD disease and reduced to the control levels at later stages of the disease [41]. It may be noted that IL-1β and IL-6 genes are also modulated by DNA methylation in different chronic and degenerative diseases [41]. On the other hand, deregulation of DNA methylation in the peripheral blood cannot be ruled out in the pathology of AD. DNA methylation in the promoter region of brain-derived neurotrophic factor (BDNF) was found to be elevated in peripheral blood of AD patients when compared with level of gender- and age-matched controls [41,42]. Moreover, the percentage of DNA methylation in certain CpG sites within the BDNF promotor region was negatively correlated with neuropsychological test scores, suggesting that BDNF promoter methylation is associated with cognitive deficit manifestations of AD [42]. Notably, DNA 5-hydroxymethylcytosine (5hmC) modification associates with gene transcription in tissue specific manner and it is used for locating for dynamic DNA methylation regions, during mammalian development as well as in human diseases [43]. In AD, 5hmC level in the entorhinal cortex and cerebellum was significantly lowered compared with age-matched controls [44]. Further, 5hmC within the hippocampus of AD brain was higher than that of cerebellum [45]. However, another study showed 20.2% reduction in 5hmC immunoreactivity in the hippocampus of AD patients when compared with non-demented [44]. Further studies can provide a more conclusive report on this.

Interestingly, TREM2 expression level has a positive correlation with TREM2 5hmC enrichment in exon 2, in the hippocampus region of AD brain, indicates 5hmC role in TREM2 gene expression, and thereby its role in brain tissue repair [46]. Similar observation was found in monozygotic twins discordant for AD; showing 31.4% lower level of 5hmC immunoreactivity in the CA1 hippocampus of AD twin compared with the non-demented twin [47]. Furthermore, in mid-frontal gyrus and mid-temporal gyrus of AD brains, 5hmC level was relatively lower in astrocytes and microglia while elevated in neurons [47]. APOE CGI is also highly methylated in human postmortem brain and the methylation is altered in frontal lobe of AD brain [48], but not cerebellar tissue [49]. Moreover, the alteration of DNA methylation in tissue specific manner is associated with APOE genotype [28]. Noting that APOE is primarily produced in astrocytes in CNS, there is strong possibility of epigenetic APOE regulation leading to the risk of AD through glia. It may be noted that 5hmC is most abundant in CNS with a highest level found in cerebral cortex, followed by the brainstem, spinal cord, and cerebellum; moreover the presence of 5hmC at a lower level was also found in heart, kidney, liver, muscle, and lung [50]. Other neurological disorders with cognitive deficits such as Rett syndrome, autism spectrum disorder and Huntington's disease also showed alteration of global 5hmC [51-53]. On the other hand, TREM2 mRNA expression level was increased in peripheral leukocytes, while decreased in TREM2 DNA methylation in AD patients [21]. Subsequently, TREM2 mRNA expression was negatively correlated with the methylation rate of specific CpG sites in TREM2 intron 1 [21]. It may be noted that, epigenetic alterations have been well documented in various neurological disorders with cognitive disfunctions, including psychiatric disorders [54], autism [55], Parkinson's disease [56] etc.

Role of histone modification

Number of studies reported that histone modifications play a crucial role in diverse biological processes such as in neuroinflammation and neuron development in aging, AD, PD, ALS, and attention deficit/hyperactivity disorder (ADHD) etc. [57,58]. In relation to inflammation associated disorders, histone methylations are closely linked with chromatin remodeling and gene transcription [59]. Histone methylation is primarily regulated by histone methyltransferase and histone demethylase in lysine and serine sites; its role on gene expression is affected by the position and degree of methylation. Increased in chromatin modifications (increased histone-tail acetylation) by inhibitors of histone deacetylases induced sprouting of dendrites (an increased number of synapses) and reinstated learning behavior and access to long-term memories [60]. This reveals that dysregulation in histone acetylation has crucial roles in neurodegenerative diseases associated with learning and memory deficits, as well as long-term memories deficits with dementia. Chromatin regulation contributing to synaptic plasticity can drive adaptive behaviors through dynamic and precise regulation of transcription output in neurons [61]. In mice, acetylation of histone H3 in CA1 region of hippocampus involve in regulating contextual fear, that happen through activation of N-methyl-D-aspartic acid (NMDA) receptors and ERK, which is a biochemical event present in long term memory [62]. Moreover, treatment with histone deacetylase inhibitors trichostatin A (TCA) or sodium butyrate enhances histone H3 acetylation and strengthen Schaffer-collateral synapses and LTP in CA1 area of hippocampus; this indicates changes in histone-associated heterochromatin in structure during the formation of long-term memory [62]. Deficiency of HAT activity results in reduction of late phase of hippocampal LTP [63]. These reports indicate potential involvement of histone acetylation and deacetylation in hippocampal synaptic plasticity and thereby reveals the participation of LTP in cellular mechanism of long-term memory formation. Subsequently, upon fear conditioning test, histone acetylation was found increased in the BDNF promoter region in the hippocampus and the prefrontal cortex [64,65]; this indicates the role of histone modification in neuroinflammation and fear memory consolidation. TSA also involve in reducing senile plaques and improving memory and learning behaviors in APP/PS1 mice, suggesting its' possible role towards inhibiting Aβ production or enhancing Aβ clearance [66]. One the other hand, either increased or decreased histone methylation-modifying enzymes can enhance impairment of memory and cognitive functions, in addition to memory functions in the transcriptional regulation and chromatin modification pathways [67]. Large-scale epigenome studies with AD patients observed loss or gain of some histone, demonstrating involvement of the complex dynamics of histone modifications in AD [68]. Total histone H3 level increased in in the frontal cortex of AD patients compared to age-

matched controls, was also associated with an increased in global DNA methylation [69]. Histone modification of H3K4me3 (a gene activation related histone) was also increased in the prefrontal cortex of both AD patients and a mouse model of tauopathy, along with the family of histone methyl transferases (HMTs) which catalyze this modification [70]. These changes were associated with memory-related impairments and synaptic functions, and tau hyperphosphorylation, which can be recovered by selective inhibition of H3K4me3 HMTs in mice [70]. And the association of this to immune system is supported by observation of increased H3K4me3 level in CK-p25 AD mice, in the marked regions associated with immune response pathways, while decreased in the regions associated with synaptic and learning functions; similar patterns were also observed in the hippocampus of AD patients [71]. Additionally, HDAC6 expression in the cerebral cortex and hippocampus was increased by 52% and 91% respectively in AD patients, while genetic depletion of HDAC6 in APP/PS1 mice showed marked ameliorative effect in memory impairment [72]. HDAC6 inhibition resulted in a significant reduction in tau protein aggregation and clearance, and improved mitochondrial damage induced by Aβ [73]. These series of findings largely evidence and expand our knowledge in understanding the role of histone modification mechanisms leading to neuroinflammation, synaptic functions and learning and memory in AD pathology.

Other histone modifications such as histone posttranslational modifications (hPTMs) ubiquitylation, SUMOylation, histone phosphorylation are also found in AD. Phosphorylation of serine 47 of histone H4 (H4S47p) was increased in cells expressing an APP isoform and in Aβ treated neurons, which was correlated with mild cognitive impairment (MCI). The increased level was higher in the AD brain samples, demonstrating APP and/or Aβ mediated dysregulation in histone phosphorylation of the disease [74]. The levels of H2B ubiquitylation at Lys-120 (H2BK120ub) was found increased in the frontal cortex of AD patients [75]. Further, ubiquitin-proteasome system is also found to be responsible for the normal degradation of proteins, which seemed impaired in AD that associates with Aβ accumulation and paired helical filaments of hyperphosphorylated tau [76]. SUMOylation of histone deacetylases1 (HDAC1) occurred in Lys-444 and Lys-476 and regulate its biological activities, revealing role of SUMOylation in AD to be indirect as shown by *invitro* and *invivo* studies using mice [77]. Interestingly HDAC1 SUMOylation rescued learning and memory impairment, while reducing amyloid plaques and neuronal death in the hippocampus of APP/PS1 mice [78].

Role of non-coding RNA

Recent studies using peripheral blood from AD patients revealed that, non-coding (nc) RNAs, microRNAs and long noncoding (lnc) RNAs, have potential role in the pathology of AD [79]. ncRNAs involve in the pathophysiological processes of cell proliferation and apoptosis, oxidative stress, Aβ aggregation, tau phosphorylation, neuroinflammation and autophagy; and in the key signaling pathways associated with AD pathology [80]. Increased levels of miR-206 in the hippocampus and cerebrospinal fluid was associated with decreased expression of BDNF by targeting at the 30 - UTR of the BDNF mRNA in APP/PS1 transgenic mice [81]. BDNF has potential role in neuroprotection against apoptosis, and it promotes neuron survival, formation of new synapses, and neural plasticity [82,83]. It has been found that BDNF level was reduced in the affected individuals with different neurodegenerative diseases [84,85]. Collectively these studies reveal that ncRNA miR-206 involves in the pathogenesis of AD by decreasing the level of BDNF. Similarly, another ncRNA miR-613 also targets the 30-UTR of BDNF mRNA and inhibits BDNF expression. Moreover, increased miR-613 level was observed in the serum and cerebral spinal fluid (CSF) of patients with mild MCI and dementia of AD type, as well as in the hippocampus of APP/PS1 transgenic mice [86]. The increased expression of miR-613 was also associated with a significant decreased level of BDNF mRNA and protein.

Subsequently, lncRNAs are RNA sequences having more than 200 nucleotides. Like the rest of ncRNAs, they are not transcribed but can regulate genes at the transcriptional, post-transcriptional, and translational levels [79]. They may function as miRNA sponges, preventing miRNAs from completing their regulatory function [80]. They can be detected in tissues and fluids such as blood and urine [87]. lncRNAs function as miRNA sponges and they can adsorb targets in miRNAs through binding to their own miRNA reaction elements and suppresses the degradation of mRNAs caused by miRNAs [88]. Sponging miRNAs is one of the common posttranscriptional regulatory mechanisms of lncRNAs [80]. Notably 51A RNA was upregulated in the plasma of AD patients and was negatively correlated with the

Mini-Mental State Examination (MMSE) score in AD patients [89]. However, the finding could not be conclusive as no significant difference was found between AD patients and controls in some other studies [80,90]. Interestingly, lncRNA 51A was often upregulated in cerebral cortices of AD and the expression causes a splicing shift of sortilin-related receptor 1 (SOLR1) from the canonical long protein variant A to an alternatively spliced protein form. This resulted in decreased synthesis of SORL1 variant A leading to impaired processing of APP and increased Aβ formation [91]. SORL1 has been suggested to play a role in regulating endosomal traffic and recycling of neurons in human [91]. Subsequently, lncRNAs BACE-AS1, NEAT1, GAS5, were upregulated in the plasma of AD patients while lncRNA MALAT1 was downregulated [91]. lncMALAT1 also has a potential neuroprotective and anti-inflammatory role in different neurological diseases [91]. Overexpression of lncMALAT1 inhibited neurons from apoptosis and promoted neurite outgrowth, while reducing IL-6 and TNF-α levels [92]. lncMALAT1 also targets miR-125 and reversely regulates miR-125b expression. This further indicates neuroprotective role of lncMALAT1 associating with miR-125. Because the miR-125b promotes AD development and progression by promoting neuronal cell apoptosis and tau phosphorylation, the reverse effect to miR-125b expression is protective against AD development and progression [92].

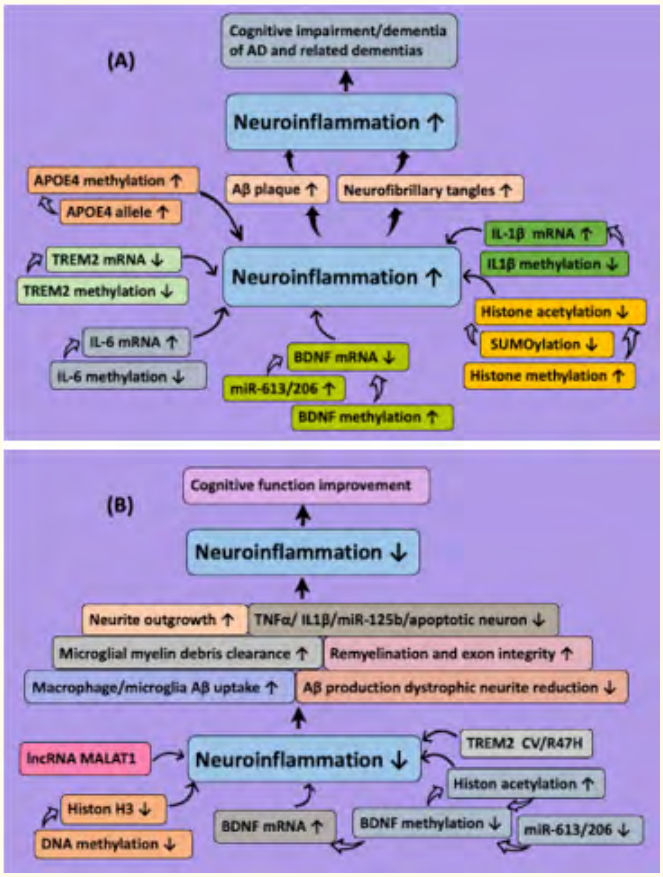

Figure: *Possible epigenetic regulatory pathway underlying neuroinflammation in AD and related dementia*

(A) Gene-epigenetic mechanisms leading to neuroinflammation and dementia. (B) Possible gene-epigenetic deregulation of neuroinflammation and cognitive function improvement. The arrow sign '↑' within the box indicates upregulation, whereas arrow sign '↓' indicates downregulation.

Conclusion

AD is the most common cause of dementia that accounts for 60 to 80% cases of all known dementias. It surpasses other types of dementias such as cerebrovascular dementia, frontotemporal dementia, Lewy body dementia, hippocampal sclerosis dementia, and mixed [2]. In 2021, AD and other forms of dementia have claimed 1.8 million lives [1]. According to WHO 2023 report, more than 55 million people are living with Alzheimer's and other dementias worldwide [93]. However, no medication or therapy has been found to prevent or cure of AD/ADRD until now. Therefore, one of the top priorities in human diseases research around the globe needs to be given to AD research. Currently, finding an appropriate treatment for AD and ADRD is highly challenging as 99% of the clinical trials have failed and only 1% was found to be promising which is approved by United States's FDA. However, even that 1% also works only to moderately slow down the disease progression. This reveals that the current knowledge on disease pathology is insufficient in finding an appropriate drug for treating AD/ADRD.

In the past several years, finding drugs that target on aggregates of amyloid plaque and neurofibrillary tangles in brain of the AD patients, has been given great emphasis. However, there are several other penitential regulatory pathways which play major roles in the progression of the disease, but they have not been given enough attention for drug targets. These potential drug targets link to neuroinflammatory response regulated by epigenetic mechanisms which includes DNA methylation, histone modification and non-coding RNAs etc. These regulations are connected through different inflammatory mediators such as IL-1β, microglia that link to cognitive deficits in dementia and ADRD. Emerging progress on developments and clinical trials targeting immune pathways also showed promising sings [94]. Moreover, in addition to deposition of extracellular Aβ plaques and intracellular neurofibrillary tangles, neuroinflammation has been identified as the third core characteristic which is crucial in AD pathogenesis [95]. To our knowledge, this review has covered most of the up-to-date information from various studies on the role of gene-epigenetic mechanisms underlying neuroinflammation and cognitive impairments in AD and related dementias. These studies reveal that epigenetic mechanisms could be potential targets for developing appropriate drugs and treatment for dementia in AD and related diseases. Epigenetic regulation in the pathogenesis of AD/ADRD by DNA methylation, histone modification and non-coding RNAs and the two well-known regulatory genes APOE and TREM2 in AD dementia, are well documented to be potential biomarkers. Epigenetic mechanism such as DNA methylation revealed to be a global promising marker for detection/early detection in neurodegeneration and learning and memory impairment in neurodegenerative diseases. Additionally, mTOR pathway [96], miR-34a/miR-545 [97], lncRNA-BACE1-AS [98], and circular RNA ciRS-7 [99], have also been suggested to be potential biomarkers for early detection of AD.

Regulatory mechanisms underlying the pathology of cognitive deficit or dementia in AD or ADRD is highly complex, and it needs to be studied further from various approaches that would enable to design appropriate drugs for treatment. As of now the current available data is insufficient as stated by various experts in finding an appropriate drugs for treating AD dementia and ADRD, further research to find molecular targets, biomarkers, and diagnostic techniques for early detection, better methodologies, better study designs fulfilling the criteria of clinical trials with the FDA approval standard, is required. Meanwhile, current approaches for drug designing and clinical trials have not thoroughly examined several potential drug targets that includes the epigenetic mechanisms. Given the potential roles of epigenetic regulations in AD or ADRD, it is necessary to extend attention in research on epigenetics and clinical trials in this area.

Conflict of Interests

Authors declare no conflict of interest.

Funding Support

None.

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