Review

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

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Review

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

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Abstract: Enormous progress has been made towards understanding the pathophysiology of Alzheimer's disease (AD) over the recent years through the advancement of research in the field of AD research. However, the unavailability of an appropriate drug for treatment raises several questions and scores the lake of thorough understanding the regulatory mechanisms underlying the disease pathophysiology and thereby the needs of further research for deeper understanding and uncover the hidden complexity. Most of the drugs that have been designed and proceed to clinical trials are focused on clearing of the aggregates of amyloid beta and the neurofibrillary tangles that are made of phosphorylated, while the focus on neuroinflammatory pathways is also emerging. Other pathological pathways that have profound regulatory roles underlying AD dementia include APOE mediated cholesterol transportation and metabolism, TREM2 mutation, DNA methylation, histone modification and non-coding RNAs etc. This review is particularly focus on how APOE, TREM2, DNA methylation, histone modification and non-coding RNAs contribute to neuroinflammation and leads to dementia of AD.

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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 decline in reasoning capabilities, loss of memory, confusion, that accompanies with severe deterioration in the normal live of the affected individual; symptom worsens with the progression of age. AD and AD related dementias (ADRD) is one of the most leading causes of death globally and it stands at 7th rank among the leading human diseases causing to dead [1–4]. Latest reports indicated that 6.9 million Americans with age 65 and older are currently affected by AD's dementia, which is 0.2 million higher than the previous year 2022 estimated number (~6.7 millions) that means the Americans of this age are at risk of dead prematurely by AD [5,6]. AD or ADRD directly deteriorates both health and economy globally. Most of the unpaid caregivers that comprises 83% of the caregivers are family members of the patients, friends or others [7]; if they happened to be paid then the cost is estimated to be $346.6 billion as of 2023 [6] which is $7.1 billions more than the previous year 2022 (~$339.5 billion) [3]. 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 [6]. 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; the caregiving includes medications and food as well

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[3,8]. In 2023, more than 11 million family members and other unpaid caregivers provided support to the individuals affected by AD or ADRD [6].

Through the growing development in research in the past few decades, knowledge on underlying pathophysiology 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 fulfilment of other criteria/protocols on the processes of clinical trials [9–11]. This reveals us the need of further research to further uncover the wide rages complexity underlying the disease pathophysiology. Most of the research development, 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 [12]. However, there is growing development towards the neuronal inflammatory pathways underlying the pathogenesis of dementia of AD [13–20]. This review analyses 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 neuroplasticity abnormality leading to cognitive deficits in AD.

Role of TREM2 in the Neuroinflammation Underlying Cognitive Deficit in AD

Growing number of studies increasingly suggest that TREM2 (triggering receptor expressed on myeloid cells 2) plays a potential role towards preventing or slowing down in sporadic AD progression by attenuating neuroinflammation and improving cognitive functions [21–24]. TREM2 is highly expressed on myelin-laden phagocytes in active demyelinating lesions in the postmortem brain of patients with Multiple sclerosis (MS) and the gene expression profile showed macrophages with alteration in phagocytic pathways in the MS patients with TREM2 genetic deficiency [21]. Treatment TREM2 agonistic antibody AL002a in *Trem2*$^{+/-}$ mice, could promote clearance of myelin debris in the cuprizone model of CNS demyelination, enhancing uptake and degradation of myelin, and increased myelin debris removal by microglia [21]. Subsequently, antibody dependent TREM2 activation on microglia increases oligodendrocyte precursors density in areas of demyelination, mature oligodendrocytes formation, enhancing 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; monoclonal Ab-T1 was produced using Balb/C mice immunization with extracellular domain of human TREM2 protein followed by three additional boosts [25]. Monoclonal Ab-T1 targets membrane-bound soluble TREM2 and induce microglial activation and the activated TREM2 enhances uptake of labeled Aβ by macrophages and microglia and promotes TNF-α production as well. Further Ab-T1 also enhances the capability of microglia to phagocytose labeled apoptotic neurons that are thought to be cell debris present around the βA plaque located regions [25]. TREM2 agonistic antibodies such as AL002a (a mouse IgG1 antibody) also showed to have similar roles in 5×FAD mice in that humanized monoclonal IgG1 antibody binds to TREM2 and activates its' signaling pathway leading to reversing Aβ regulatory gene expression, recruitment of microglia to Aβ plaques, decreased Aβ deposition, and improvement in spatial learning and memory [22]. 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 [24].

Role of APOE in the Neuroinflammation Underlying Cognitive Deficit in AD/ADRD

The role of APOE (apolipoprotein E) in ADRD has been also well documented. APOE is associated with lipoproteins in the plasma which functions in systemic lipid metabolism; in the CNS,

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APOE involves in maintaining, growth and repair of neurons acting as a primary cholesterol carrier [26]. APOE is associated with AD associated neurofibrillary tangles, Aβ plaque and with late onset familial AD; the level of APOE4 is much higher than APOE2 and APOE3 in elderly patients [26]. 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 [27]. 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 [28]. Moreover, promoter region of APOE, but not APP, was found to be hypermethylated in the prefrontal cortex region of postmortem brain AD patients [29].

APOE has been further studied for gene-specific DNA methylation differences associated with AD pathogenesis. The AD-associated gene, *APOE* is differentially methylated in AD patients [30]. The three common alleles of APOE, E2 (Arg158Cys), E3 (Cys112Arg) and E4 (Cys112) [31,32], are defined by two SNPs (rs429358, and rs7412) located in coding region exon 4, overlaps with a well-defined CpG island (CGI) [33]. The two SNPs not only change protein codons but also the quantity of CpG dinucleotides, which is the primary sites for DNA methylation [34–36]. 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 patients [30]. This suggests that in the brain of AD patients, APOE CGI could differentially methylated in a tissue and APOE genotype specific manner, further reveals possible epigenetic alteration contributing to neural cell dysfunction in AD brain. Subsequently, TREM2 mRNA expression level was increased in peripheral leukocytes, while decreased in TREM DNA methylation, in AD patients [37]. Moreover, TREM2 mRNA expression was negatively correlated with the methylation rate of specific CpG sites in TREM2 intron 1 [37]. It may be noted that, epigenetic alterations have been well in various neurological disorders with cognitive disfunctions, including psychiatric disorders [38], autism [39], Parkinson's disease [40,41] etc.

DNA Methylation Role in the Neuroinflammation Underlying Cognitive Deficit in AD

In the area of epigenetic regulation in the course and development of AD, role of DNA methylation and hydroxymethylation, histone posttranslational modifications, and non-coding RNA regulation (microRNAs) are widely examined [42]. DNA methylation in the frontal cortex of AD patients and middle-aged controls, showed hypomethylation in the IL1β promoter region during early stages of AD and returned to the level of middle-aged controls in later stages, whereas IL6 methylation decreased with AD progression [43]. While the report of DNA methylation peripheral blood is inconclusive, promising evidence strongly uphold the deregulation of DNA methylation in the peripheral blood in the pathology of AD cannot be ruled out. Elevation of DNA methylation in the promoter region of brain-derived neurotrophic factor BDNF was observed in peripheral blood of AD patients when compared with level of gender- and age-matched controls [43,44]. Moreover, the percent methylation of certain CpG sites within the BDNF promotor was negatively correlated with neuropsychological test scores, suggesting that BDNF promoter methylation is associated with cognitive deficit manifestations of AD [44]. Notably, DNA 5-hydroxymethylcytosine (5hmC) modification associates with gene transcription in tissue specific manner and used for locating for dynamic DNA methylation regions, during mammalian development as well as in human diseases [45]. In AD, 5hmC level in the entorhinal cortex and cerebellum was significantly lowered compared with age-matched controls [46]. Further, 5hmC within the hippocampus of AD brain was higher than that of cerebellum [47]. However, another study showed 20.2% reduction in 5hmC immunoreactivity in the hippocampus of AD patients when compared with non-demented [46]. Interestingly, TREM2 expression level has a positive correlation with TREM2 5hmC enrichment in exon 2, in the hippocampus of AD, further indicates 5hmC role in TREM2 gene expression, thereby its role in brain tissue repair [48]. Similar observation was found in monozygotic twins discordant for AD; showing

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31.4% lower level of 5hmC immunoreactivity in the CA1 hippocampus of AD twin compared with the non-demented twin [49]. 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 [49]. APOE CGI is also highly methylated in human postmortem brain and the methylation is altered in frontal lobe of AD brain [50], but not cerebellar tissue [51], and the alteration in tissue specific manner is associated with APOE genotype [30]. Noting ApoE is primarily produced in astrocytes in the brain, indicates strong possibility of epigenetic APOE regulation in glia in risk of AD. 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; the presence of 5hmC at a lower level was also found in heart, kidney, liver, muscle, and lung [52]. Other neurological disorders with cognitive deficits such as Rett syndrome, autism spectrum disorder and Huntington's disease also showed alteration of global 5hmC [53–55].

Histone Modification Dysregulation in the Neuroinflammation Underlying Cognitive Deficit in AD and Related Dementias

Number of studies reported in 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. [56–58]. 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 and its role on gene expression is affected by the position and degree of methylation. Further, 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 in contextual fear conditioning, 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, increased histone acetylation by histone deacetylase inhibitors trichostatin A (TCA) or sodium butyrate enhance LTP at Schaffer-collateral synapses in area CA1, indicates histone-associated heterochromatin undergoes changes in structure during the formation of long-term memory [62]. And reduced the late phase of hippocampal LTP due to a deficiency of HAT activity [63]. Since LTP is participates in cellular mechanism of memory formation, these reports indicate potential involvement of histone acetylation and deacetylation in hippocampal synaptic plasticity and in memory formation cannot be ruled out. Subsequently, upon fear conditioning test histone acetylation was increased in the BDNF promoter region in the hippocampus and the prefrontal cortex, [64,65]; it indicates role of histone modification in neuroinflammation and fear memory consolidation. TSA also involve in in reducing senile plaques and improving memory and learning behaviors in APP/PS1 mice, suggesting it's 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]. In human AD patients, loss or gain of some histone marks has been found through large-scale epigenome studies, demonstrating involvement of the complex dynamics of histone modifications in AD [68–71]. Total histone H3 level increased in in the frontal cortex of AD patients compared to age-matched controls, was associated with an increase in global DNA methylation [72]. Histone modification of H3K4me3 level, a gene activation-related histone mark was increased in the prefrontal cortex of both AD patients and a mouse model of tauopathy, along with the family of histone methyl transferases (HMTs) that catalyze this modification [73].

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Those 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, contributing to understanding the role of histone methylation in AD tau pathology [73]. The H3K4me3 level in CK-p25 mouse model of AD, also had increased in the peak enrichment of the mark in regions associated with immune response pathways, while decreased in regions associated with synaptic and learning functions; similar patterns were also observed in the hippocampus of AD patients [74]. 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 on the memory impairment [75]. HDAC6 inhibition resulted in a significant reduction in tau protein aggregation and clearance, and improved mitochondrial damage induced by Aβ [76,77].

Other histone modifications such as histone posttranslational modifications (hPTMs) ubiquitylation, SUMOylation, histone phosphorylation are also found in AD. Phosphorylation of serine (S) 47 of histone H4 (H4S47p) was increased in cells expressing an APP isoform and in Aβ-treated neurons, which correlates with mild cognitive impairment (MCI); the increased level is h8gher in the AD brain samples, demonstrating APP and/or Aβ-mediated dysregulation in histone phosphorylation of the disease [78]. The levels of H2B ubiquitylation at Lys-120 (H2BK120ub) was found increased in the frontal cortex of AD patients [79]. The 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 [79,80]. 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 studies using mice [81]. Interestingly HDAC1 SUMOylation rescued learning and memory impairment, while reducing amyloid plaques and neuronal death in the hippocampus of APP/PS1 mice [82].

Non-Coding RNA Involvement in the Neuroinflammation Underlying Cognitive Deficit in AD/ADRD

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 pathophysiology of AD [83]. ncRNAs involve in the pathophysiological processes of cell proliferation and apoptosis, oxidative stress, Aβ aggregation, tau phosphorylation, neuroinflammation and autophagy; and in in the key signaling pathways associated with AD pathology [84]. Increased levels of miR-206 in the hippocampal tissue, cerebrospinal fluid miR-206 decreases the expression BDNF by targeting the 30 - UTR of the BDNF mRNA and inhibits its expression in APP/PS1 transgenic mice [85]. The role of BDNF in neuroprotection against apoptosis and promoting neuron survival, the formation of new synapses, and plasticity has been well documented [85–87] and the BDNF level is reduced in the affected individuals with different neurodegenerative diseases [88,89] and thereby the role of miR-206 in disease pathogenesis affecting BDNF. Further miR-613 also targets the 30-UTR of the BDNF mRNA and inhibits BDNF expression; the increased miR-613 level was observed in the serum and cerebral spinal fluid (CSF) of patients with mild MCI and dementia of the AD type; as well as hippocampus of APP/PS1 transgenic mice [90]. Moreover, the increased expression of miR-613 accompanied a significant decrease in the levels of the BDNF mRNA and protein. On the other hand, lncRNAs are RNA sequences having more than 200 nucleotides that are not transcribed but can regulate genes at the transcriptional, post-transcriptional, and translational levels [83]. They may function as miRNA sponges, preventing miRNAs from completing their regulatory function [84] and can be detected in tissues and fluids such as blood and urine [91]. Long non-coding RNAs function as miRNA sponges. LncRNAs can adsorb targets in miRNAs through binding to their own miRNA reaction elements, that suppresses the targeting of mRNAs by miRNA and the degradation caused by miRNAs [92]. Sponging miRNAs is one of the common posttranscriptional regulatory mechanisms of lncRNAs [84]. 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 [93].

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However, no significant difference was also found between AD patients and controls in some other studies [84,94]. lncRNA 51A is also found to be upregulated often in cerebral cortices of AD and its expression causes a splicing shift of sortilin-related receptor 1 (SOLR1) from the canonical long protein variant A to an alternatively spliced protein form, resulting in decreased synthesis of SORL1 variant A, and leading to impaired processing of APP and increased Aβ formation [95,96]. SORL1 has been suggested to play a role in regulating endosomal traffic and recycling of neurons in human [96]. Subsequently, lncRNAs BACE-AS1, NEAT1, GAS5, were upregulated in the plasma of AD patients while lncRNA MALAT1 was downregulated [96]. lncMALAT1 also has a potential neuroprotective and anti-inflammatory role in different neurological diseases [96,97]. overexpression of lncMALAT1 inhibited neurons from apoptosis and promoted neurite outgrowth, while reducing IL-6 and TNF-α levels [97]. lncMALAT1 also targets miR-125 and reversely regulated miR-125b expression, further indicates its neuroprotective role associating with miR-125; because 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 [97].

Discussion and Conclusion

AD is characterized by the onset of cognitive impairment leading to dementia and premature death of the affected individual. AD and ADRD stands at 7th position among the leading cause of death globally. AD is the most common cause of dementia that accounts for 60 to 80 % cases of dementias, and it surpasses other types of dementias such as cerebrovascular dementia, frontotemporal dementia, Lewy body dementia, hippocampal schelerosis dementia, and mixed, etc. [6]. Officially 119399 AD death certificates were recorded in 2021 [6]. The greatest challenge remains is that there is no proven way to prevent Alzheimer's disease, and there is currently no cure. According to World Health Organization report in 2023, more than 55 million people are living with Alzheimer's and other dementias worldwide [98]. In 2021, Alzheimer’s disease and other forms of dementia have claimed to death 1.8 million lives [2]. And in 2019, the cost for care for dementia was estimated to be USD 1.3 trillion globally of which around 50% of the costs were attributable to informal carers by family members and close friends [98]. As devastating effect of dementia enormously impacts not only the affected individuals but also families, communities and health care systems, and deteriorates the global economy, it should be a top priority for research centers around the globe to find ways to prevent, slow down the disease progression, better manage and cure for Alzheimer's and other dementias. On the other hand, finding an appropriate treatment for AD and ADRD is highly challenging as 99% of the clinical trials are failing and the 1% successfully approved drug by United States’s FDA only works to moderately to slow down the disease progression. To counter this, much deeper research is required to uncover the complex pathology of the disease and proper method designing and the fulfilment of other criteria/protocols for clinical trials.

In addition to targeting of amyloid plaque and neurofibrillary tangles aggregation in the brain of AD patients, there are several regulatory pathways that are thought to play major roles in the progression of the disease; that include neuroinflammatory response, APOE mediated cholesterol transportation and metabolism, TREM2 pathway, DNA methylation, histone modification and non-coding RNAs etc. [70,84,99–103]. And all these are connected through different inflammatory mediators such IL-1β, microglia that link to cognitive deficits in AD dementia and ADRD [6,100]. Emerging progress on developments and clinical trials targeting immune pathways also showed promising sings [104]. 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 [105]. Regulatory mechanisms underlying the pathology of cognitive deficit or dementia in AD or ADRD is highly complex, and it needs to be studied from various approaches that would enable to design appropriate drugs for treatment. As the current available data is insufficient in the search for appropriate drugs for treating AD dementia and ADRD, further research to find molecular targets, biomarkers, and diagnostic techniques for

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early detection, better methodologies, better study designs fulfilling the criteria of clinical trials with the FDA approval standard, is required.

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