

Review

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Microglial, Astrocytic, Oligodendrocytic, T-Cell and B-Cell Inflammatory Pathways Underlying Cognitive Impairment in Alzheimer's Disease and Related Dementias

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Review

Microglial, Astrocytic, Oligodendrocytic, T-Cell and B-Cell Inflammatory Pathways Underlying Cognitive Impairment in Alzheimer's Disease and Related Dementias

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Abstract: Neuroinflammation is considered one of the major causing factors of neuronal dysfunction leading to dementia associated with Alzheimer disease (AD) or AD related dementias (ADRD). Several published articles have reported potential involvement of microglia, astrocytes, oligodendrocyte, B-cell and T-cell linked with different neuroinflammatory signaling pathways. This article is intended to provide a summary of various published papers in this area and show the neuroinflammatory pathways that associates with the imbalanced level microglia, astrocytes, oligodendrocyte, B-cell and T-cell leading to neuronal dysfunction, dementia or cognitive decline of neurological diseases like AD and ADRD. Several drugs have been designed and tested, yet unable to find an appropriate drug for treatment. Therefore, further attention is essential for deeper understanding the underlying mechanism of these diseases for finding an appropriate drug target and in this review, we provide the importance of cellular neuroinflammatory pathways that induce neuronal dysfunction leading the dementia or cognitive deficits in AD and ADRD.

Keywords: neuroinflammation; microglia; cognitive impairment; Alzheimer's disease and related dementia

Introduction:

Alzheimer disease (AD) is considered as the most common cause of dementia which accounts 60% to 80% cases among the elderly people that accompanies with decline in memory, language, problem-solving, confusion with time/place and poor judgment etc.[1–4]. AD and AD related dementias (ADRD) is one of the most leading causes of death globally. Number of deaths due to AD and ADRD have been reported increased from 0.56 million in 1990 to 1.62 million in 2019[5]. The latest reports mark AD ranking at 7th and 5th leading cause of death globally and in the United States respectively[1,6]. However, the rank will be much higher if the related dementias would be added[7]. Currently 6.7 million Americans with age 65 and older are suffering from AD dementia which means 1 out of 9 Americans (10.8%) of this age are living with AD[8]. AD and ADRD directly impact both health and economy. Majority of caregivers are unpaid family members, friends or others that comprise 83% of caregivers[9], if paid that would cost about \$339.5 billion just for the year 2022[1]. Subsequently, lifetime cost for the care of an individual with dementia is estimated to be \$392874 as of 2022 USD dollar value of which 70% is borne by the unpaid family caregivers in various ways including medications and food[1,10]. Over the past few decades, with the increasing knowledge of

underlying pathophysiology of AD/ADRD, several drugs have been developed, and subsequent clinical trials have been carried out, nonetheless, challenges for a cure or proper treatment remains due to complex pathogenesis of the disease[11–13]. Continuously growing evidence revealed that immunological mechanisms are potentially involved underlying the pathogenesis of AD/ADRD[14–21]. In this review, immune system and neuroplasticity abnormality affecting the neuronal signaling leading to cognitive deficits in AD will be discussed based on the available research reports while briefly mentioning about other diseases with ADRD.

Immune System Involved in the Development of Cognitive Deficit in AD/ADRD

Neuroinflammation has been well documented as a key player in most nervous system dysregulation diseases and continuously identified as a potential mediator of cognitive deficits. Neuroinflammation levels are increased with advancing of age and neurodegeneration, and the influence of age on neuroinflammation may contribute to accelerating cognitive impairment through glial activation, increased production of proinflammatory cytokines, abnormal neuronal signaling, magnifying deterioration of the central nervous system microenvironment etc.[22,23]. Not only the AD, dementia is one of the clinical symptoms in several other neurological diseases that associates with neuroinflammation such as Vascular Dementia, Dementia Lewy Bodies, Parkinson's Disease, Frontotemporal Dementia, Huntington's Disease, Wernicke-Korsakoff Syndrome, Sickle cell disease, Amyotrophic lateral sclerosis etc.[24–29]. Both the innate and adaptive immune system dysregulation have been indicated to have potential role in AD pathogenesis[30–36]. Microglia, astrocytes and oligodendrocytes have been accounted for innate immune system dysregulation in AD. Whereas, the adaptive immune system dysregulation has been proposed from the detection of B and T lymphocytes in the post-mortem AD brain, cerebrospinal fluid (CSF) of mild cognitive impairment (MCI) individuals as well as AD patients[31,37–41], and the presence of higher frequency of T helper subsets⁴².

Microglial Path in the Neuroinflammation Underlying Cognitive Deficit in AD/ADRD

Microglia comprises of 5%–12% of the total populations of glial cells in the adult rodent brain [38,43] and 0.5%–16% in human brain[43,44], indicating close proximity of its level between rodent and human. In the brain, the size of microglial cell population remains steady from late postnatal stages until aging which is maintained by spatial and temporal coupling of proliferation and apoptosis; however the turnover of microglia is remarkably fast allowing renewal of the whole population several times during a lifetime as studied in mice and humans [45]. Microglia initiate an immune response as it express a wide range of receptors that recognize both exogenous and endogenous central nervous system (CNS) insults[46]. Microglia play a crucial role in establishing normal brain development and normal neuronal connectivity and regulatory process such as synaptic pruning ensuring elimination of inappropriate synapses while strengthening the appropriate ones depending on neuronal activity and experience [45,47] and promote phagocytic clearance of cell debris and death cells and provide trophic support insuring tissue repair and maintain normal brain homeostasis[48–56]. However loss of homeostasis or tissue change conditions induce several dynamic processes in microglia and convert them into an activated state accompanied by changes in cellular morphology like shortening of the processes and swelling of the soma, surface phenotype, secretory mediators, and proliferative responses[46,57]. The presence of imbalance amount of activated microglia is crucial for AD and several neurodegenerative diseases. In AD microglial inflammatory activity has been found increased while its' functions in phagocytic clearance are compromised[46]. This compromise of microglial phagocytosis may be due to enhance production proinflammatory cytokines such as IL-1 β and TNF- α and other inflammatory mediators through binding of PAMP or DAMP (danger- or pathogen-associated molecular patterns) binding to

PRRs (pattern recognition receptors expressed in microglia which is evolutionarily conserved family of innate immune cell receptors) and the failure of microglial phagocytic activity is associated with β -amyloid ($A\beta$) deposition and clearance in AD[58–60]. In AD as well as Down syndrome patients, activated microglia along with immunoglobulins and complement components are also closely associated with $A\beta$ deposits in the brain[61,62]. Further, microglia phagocytosis also involves synapse elimination during early but not late postnatal periods through fractalkine receptor CX3CR1 or complement receptor 3 (CR3/CD11b) signalling pathways[50,63]. Earlier studies also showed that the motor skill learning was induced by increased dendritic spine formation in the motor cortex revealing that the degree of new dendritic spine remodelling is associated with improvement in performance after learning[64,65]. Interestingly, reduction of microglia by removing brain-derived neurotrophic factor (BDNF) in mice showed deficits learning in multiple assignments such as rotarod test, fear conditioning test and novel object recognition test associates, as well as decrease motor learning-dependent synapse formation[66]. This may be due to binding of BDNF to neuronal TrkB (tropomyosin-related kinase receptor is a key mediator of synaptic plasticity) increasing TrkB phosphorylation[66]. Thus microglia play a central role in establishing synaptic networks by remodeling synapses and thereby regulates of synaptic plasticity with learning-dependent dendritic spine remodeling and learning-dependent long-term synaptic strengthening long-term potentiation (LTP)[50,63,66–68]. It may be noted that LTP is considered to be the foundation of learning and memory[69]. Disruption of microglia activation using DAP12 mutant mouse (KD75) enhances hippocampal LTP [70] whereas greater activation of microglia with the loss of microglial specific fractalkine receptor (Cx3cr1) causes LTP reduction [71] and reduction in LTP could be rescued by inhibition of IL-1 β signaling with the use of Minocycline, an FDA approved antibiotic drug[72]. On the other hand, loss of Cx3cr1 gene in AD mouse mouse worsens cognitive impairments revealing role of microglia in AD dementia[73]. Additionally, deletion of the NLRP3 inflammasome – which is upstream of IL-1 β production also rescues LTP that accompanies with the reduction of Ab plaque load in an APP/ PS1 AD mice[74]. Further, in hTau-P301S frontotemporal dementia (FTD) mice with deletion of microglial Sirtuin 1 (SIRT1, a member of the sirtuin family which plays a potential role in key cellular processes, including senescence/aging and inflammation) increases IL-1 β production and leads to spatial learning and memory impairments, whereas SIRT1 was reduced in aged FTD mice, from 13-15 month of age to 20-26 month old groups[75]. This shows that both SIRT1 and microglia are reduced upon aging, in which microglial SIRT1 deficiency has effect on aging accompanied by tau-mediated memory deficits via IL-1 β upregulation in mice. Further, selective activation of IL-1 β transcription by reduction of SIRT1 may be signalled via hypomethylation of specific CpG sites on IL-1 β proximal promoter[75]. Notably the epigenetic regulation of IL-1 β and microglia with the selective hypomethylation of IL-1 β is strongly correlated in aging humans and patients with dementia[74–78]. Moreover, temporal lobe astrocytes were elevated with IL-1, S-100, and glial fibrillary acidic protein and thereby the astrogliosis in Alzheimer disease may be promoted by elevation of interleukin 1[61]. It is also known that aberrant inflammatory responses is associated with aging brains in human[79,80]. Specifically, basal levels of proinflammatory cytokines are elevated with aging (Sierra et al., 2007), while those of anti-inflammatory cytokines are reduced (Ye and Johnson, 1999). Additionally, genetic deletion of pro-inflammatory nuclear factor- κ B signaling in the hypothalamic microglia of aged brain could restore impairments in hippocampal dependent learning and memory in normally aging animals[81]. Moreover, in APP/PS1 mouse model for AD, microglia-specific deletion of the gene encoding the PGE2 receptor EP2 restores microglial chemotaxis and $A\beta$ clearance, suppresses toxic inflammation, and rescues synaptic insults and memory deficits[82]. This suggests that epigenetic mechanisms which affects communication and pro-inflammatory activation of microglia contributes to cognitive deficits in aging and neurodegenerative diseases such as AD. More number of pro-inflammatory cytokines have been identified to play a role in AD brain such as IL-1 α , IL-6, TNF- α , granulocyte-macrophage colony-stimulating factor (GM-CSF), and IFN- α , which are produced in neurons or microglia[83–86]. The

proinflammatory cytokines are recruited from the circulation by endothelial cells, inflammatory cells, and the blood–brain barrier (BBB) when biochemical or mechanical damages occur[87,88].

Several studies have shown that inflammation is increased in AD patients and as a result synaptic function will be declined[89]. There have been positive effects on synaptic plasticity in AD models when inflammation was targeted through genetic manipulation. And several reports in human studies continue to support microglial inflammatory pathogenesis in AD. Several genome wide association studies in humans demonstrated that mutations in microglia regulatory genes such as TREM2 (triggering receptor expressed on myeloid cells 2, a lipid/lipoprotein binding receptor) and CD33 lead to sporadic AD. It may be noted that TREM2 is an innate immune receptor which is expressed on the surface of microglia and some other myeloid cells including macrophages, dendritic cells, osteoclasts[90–92]. A heterozygous rare variant rs75932628 of TREM2 gene that encodes Arginine to histidine (R47H) in the TREM2 protein was found to be associated with a significant increase in the risk of AD[93]. And a rare missense mutation (rs75932628-T) TREM2 gene, was predicted to be involved in the R47H substitution of TREM2 in AD[94]. It may be noted that rs75932628-T have been found to increase risk for Parkinson's disease, frontotemporal dementia, and amyotrophic lateral sclerosis[95–99]. It has been suggested that the risks could be resulted from the loss of TREM2 function caused by the mutation. Noting that homozygous loss-of-function mutations in TREM2 gene, have been associated with an autosomal recessive form of early-onset dementia [100] and the anti-inflammatory role of TREM2 through IL-4 pathway in the brain[101], the R47H substitution may lead to an increased predisposition to AD through the deregulation of inflammatory processes resulting dementia. In CD33 AD susceptibility locus, the risk allele rs3865444-C was associated with greater cell surface expression of CD33 in the monocytes of young and older human individuals as well as with the diminished internalization of A β 42 peptide, accumulation of neuritic amyloid pathology and fibrillar amyloid, and increased numbers of activated human microglia[102]. Meanwhile, bioinformatic analysis observed that microglia-specific TYRO protein tyrosine kinase binding protein (TYROBP) signaling to be the most dysregulated pathway in sporadic AD[103]. TREM/TYROBP signaling along with CD33 was also activate phagocytosis while suppressing Toll-like receptor-mediated inflammation[104,105]. Lack of TREM2 was also cause impaired clearance of apoptotic neurons and inflammation which may be responsible for the brain degeneration observed in patients with polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy/Nasu-Hakola disease [92] that has dementia associated with bone cystic lesions[106]. On the other hand, Human ApoE apolipoprotein isoforms ApoE2, ApoE3, and ApoE4 differentially stimulate APP transcription affecting A β secretion. ApoE4 showed to be potential genetic risk factor for AD, through MAP-kinase signaling pathway increasing cFos phosphorylation and APP-gene transcription, that leads to increased APP and A β synthesis, while ApoE3 is neutral, and ApoE2 plays a protective role[107]. Genetic and proteomics studies with human AD patients demonstrated highly significant association of APOE4 level as well as high avidity binding of APOE4 to A β , with late-onset familial AD[108]. A co-inheritance of APOE4 was observed to have 2-fold increased risk of dementia in SCD patients[25].

It has been demonstrated that aging mice (16 months old) lost synapses in the hippocampus compared to the younger mice (1 month old), which is a specific brain region that regulates learning and memory[109]. And reduced microglial A β peptide uptake and clearance that cause synaptic loss in AD and related neurodegenerative disorders is also typically link with increased complement system signaling in the early state[109–112]. On the other hand, in human APP transgenic mouse model of AD (Tg2576) when complement C3 was deleted there is concomitant loss of C1q with increasing synaptic density and prevents age-associated synaptic loss while rescuing LTP[113]. The complement protein C1q is the first component of the classical complement pathway that binds to fibrillar A β with have been shown to activate complement [114,115] and in human AD brain, the activation of C1q and with or without the activation of proinflammatory events has been shown to be associated with fibrillar A β plaques and activated microglia in AD brain with dementia [116] as well as in hippocampal LTP observed in mice[117].

The role of microglia promoting synaptic dysfunction during both aging and AD through complement signaling is supported by a series of studies. Oligomeric A β causes microglia to release increased C1q level that marks elimination synapses by microglia through classical complement cascade occurred in early stage of AD before overt plaque deposition[117]. Inhibition of C1q, C3, or the microglial complement receptor CR3 reduces the number of phagocytic microglia, as well as the extent of early synapse loss, whereas microglia in adult brains engulf synaptic material in a CR3-dependent process when exposed to soluble A β oligomers, revealing synaptic dysfunction in aging and AD through microglial elevation of complement signaling[117].

In human, GWAS on TREM2, CR1, APOJ/Clusterin and CD33, and integrated network studies with TYR-OBP also support the microglia and complement-related pathways in late onset AD[93,94,103,118–123]. TREM2 levels were elevated in the microglia of AD patients, particularly in microglia associated with plaques and neurofibrillary changes, and TREM2 levels correlated with markers of neurodegeneration. In post-mortem temporal cortical samples from AD and normal cases, TREM2 protein was found to have positive correlation with increased phosphorylated tau and active caspase 3, and loss of the presynaptic protein SNAP25; moreover, high immunoreactivity of TREM2 protein with microglia associated with amyloid plaques and in neuritic pathology-enriched areas in the brain[95]. In the unfixed brain taken from AD patient with dementia, plaques with amyloid core surrounded by a corona of degenerating neurites were found and the plaques contain the complement factors Clq, C3b, C3c, C3d and C4.[124]. On the other hand, HLA-DR-positive (human leukocyte antigen D related) reactive microglia were found in gray matter throughout the cortex of postmortem brains of patients AD patients with senile dementia and concentrated particularly in the brain areas where senile plaque formation occurred; positive correlation between the hippocampal HLA-DR-positive cells and numbers of plaques were also found[62]. HLA-DR is class II cell surface glycoprotein of the human histocompatibility complex (MHC) which usually expressed on the surface of cells that are simultaneously presenting foreign antigen to T-lymphocytes. Another study also found HLA-A,B,C (MHC class I) and HLA-DR (MHC class II) positive reactive microglia present in postmortem AD brain tissues, however higher number was found with HLA-DR, and HLA-A,B,C positive cells were shown to be a separate population from glial fibrillary acidic-protein-positive astrocytes[125]. Interestingly, neurotoxic reactive astrocytes are also found to be induced by activated microglia A1s (reactive astrocyte type 1) are AD, Huntington's (HD), Parkinson's Disease (PD), Amyotrophic lateral sclerosis (ALS), and Multiple Sclerosis.[126].

Neuronal communication is supported by synaptic networks established in an activity-dependent manner to facilitate cognitive functions, such as learning and memory[69]. During aging, reduction in dendritic spine density and morphology as well as the loss of synaptic plasticity could lead to cognitive impairments and susceptibility to age-related neurodegenerative diseases, such as AD and indicate that the process began during early stage of the disease pathogenesis[69,127,128]. Moreover, in APP transgenic mice A β causes dendritic spine changes by destabilizing microtubules and spine loss can be recovered by microtubule polymerization while the hippocampal spine loss closely resembles the progressive changes of spine morphology from mushroom-shaped to stubby[128].

Along with A β and microglia, Tau (tubulin associated unit) protein, encoded by a single gene called MAPT is also another potential contributor to the dementia of AD. Tau found abundantly in the neurons of CNS, with maximum availability in cerebral cortex, and lesser amount in astrocytes as well as oligodendrocytes, and it primarily maintains stability of microtubules in axons[129,130]. Tau also has multiple roles in axonal development, exon elongation, exonal transport, iron homeostasis regulation, myelination, nuclear architecture, and neurogenesis[131,132]. In different neurodegenerative conditions, intraneuronal hyperphosphorylated tau is found to be aggregated which known as tauopathies, and it appears to be a leading cause of dementia in AD, in which the condition is known to be secondary tauopathy[31]. Tau promotes assembly of microtubules in the neurons by binding to tubulin, however in the brain of AD patient tau can dissociate from microtubules[133]. In the condition of aberrant hyperphosphorylation of Tau, reduces the binding

capacity of Tau, causing microtubule instability and leads to various tauopathies[134]. The major part of abnormal neurofilament tau/neuroinflammatory tangles (NFT) is composed of hyperphosphorylated tau, and in various neurodegenerative stages, it creates a coupled helical filament (PHF) by twisting around each other that can accumulate in the neural perikarial cytoplasm, axons, and dendrites, causing deregulation and loss of cytoskeletal microtubules and tubulin associated proteins[135]. NFTs also spread from the transentorhinal cortex to the hippocampal formation and neocortex[136]. Increased oxidative stress causes accumulation of tau and A β at synapse sites continually and it results to the loss of dendritic spines, presynaptic terminals, and axonal dystrophy[135,137]. In fact, various studies have been carried out to block tau hyperphosphorylation using different types of drugs. Interestingly glycogen synthase kinase 3 (GSK3b) inhibitor, saracatinib, has been found potentially effective showing memory enhancement in transgenic mice and the drug is currently undergoing phase II trial[138,139]. In the cerebrospinal fluid (CSF) taken from temporal and frontal autopsy brain tissue of AD patients showed that increase NFT level with cognitive dysfunction[140]. Further, CSF levels of released tau and A β [1–42] has been proposed as promising biomarkers for early AD detection[141].

Astrocyte's Role in the Neuroinflammation Underlying Cognitive Deficit in AD/ADRD

Glial cell such as, astrocytes also function in clearing pathological deposits A β through phagocytosis and degradation in the CNS[142]. Astrocytes constitutes the largest population of glial cells in the brain [143]. Apart from the traditionally view being known only as structural elements supporting brain structure, astrocytes have many more important functions in the CNS for normal development, including developmental synapse formation and pruning through both secreted factors and direct contact with the synapse[143–145], and actively modulate synaptic glutamate levels, scavenge free radicals, produce neurotrophic factors, and regulate the blood brain barrier[143,146,147]. Astrocytes contact neuronal somata, dendrites, spines, and presynaptic terminal, possibly through Ca²⁺ signaling[148]. In adult, hippocampal astrocytes play an important role in promoting neurogenesis as observed in adult neural stem cells[149]. Removal of astrocytes in mice, caused dramatic decrease in glutamate transporter expression, which can result degeneration of granular neurons (since excitotoxic effects of glutamate causes a similar phenotype); this evidence that astrocytes are important for the survival of neurons in the adult brain[150]. These series of studies reveal a crucial role of deregulation of astrocytes in ADRD. In fact, studies have indicated reactive astrocytes could worsen inflammatory processes that can lead to neurodegeneration[151,152]. Astrocytes affected by inflammatory conditions produce pro-inflammatory cytokines, IL-1 β and TNF- α , while increased production of reactive oxygen species (ROS)[153]. Astrocytes vulnerability upon injuries such as trauma, infection, misfolded protein accumulation, and excitotoxicity has been reported in neurodegenerative disease such as AD, AD, HD and ALS etc.[154]. In AD patients' reactive astrocytes cluster around amyloid plaques are significantly high in the brain [155]. Several lines of studies evidence that astrocytes also participate in eliminating amyloid plaques and neurons containing A β and thereby enhance phagocytosis by microglia [156–158]. Apolipoprotein E (ApoE) promotes amyloid formation in the brain and the deposition of A β peptides is also affected by the expression of astrocyte specific APOE in AD mice[156]. It is suspected that degradation and clearance of deposited A β by astrocytes through ApoE signaling might be impaired in AD[156]. Additionally complement pathway is activated in AD mice in such a way that central complement factor C3 secreted from astrocytes interacts with microglial C3a receptor (C3aR) to mediate A β accumulation and neuroinflammation[157]. A β also acts as an upstream activator of astroglial nuclear factor kappa B (NF- κ B) which leads to the release of complement C3, that acts on the neuronal C3a receptor (C3aR) influencing dendritic morphology and cognitive function[159]. Hyperactivation of astroglial NF- κ B worsens A β pathology and neuroinflammation in amyloid precursor protein (APP) transgenic mice and results C3 elevation, whereas treatment of APP mice with the C3aR antagonist (C3aRA)

ameliorates A β plaque and microgliosis[157]. It shows existence of complement-dependent intercellular cross talk with A β , astroglial NF- κ B in AD pathogenesis, as overproduction of A β in the neurons activates astroglial NF- κ B to elicit extracellular release of C3. The C3 in turn interacts with neuronal and microglial C3aR to alter cognitive function and impair A β phagocytosis in AD[157]. The combined treatment of FDA approved drug Adu and focused ultrasound, but not individually in 5 $\times$ FAD mice, significantly lessen cognitive deficit and decreased amyloid plaques level in the hippocampus and moreover activation of microglia and the number of astrocytes associated with amyloid plaques were also increased[160]. Subsequently, study on APP knock-in mouse (AppSAA) with three mutations (Austrian, Swedish, and Arctic) in the APP gene, also revealed alterations in lipid metabolism and disease-associated transcriptomic signature in the microglia with high amount of intracellular A β , vascular amyloid deposits, accumulation of parenchymal amyloid plaques, alteration of astroglial and microglial functions, and increased CSF markers of neurodegeneration etc.[161]. In AD and Down syndrome patients, interleukin 1 (IL-1), an immune response-generated cytokine was found stimulating astrocyte proliferation and reactivity (astrogliosis); up to 30 times as many glial cells was present in the brain[61]. Moreover, upregulation of astrocytic GABA and MAOB was also found in the postmortem brains AD patients[162].

Oligodendrocyte's Role in the Neuroinflammation Underlying Cognitive Deficit in AD/ADRD

Clinical studies have shown the relationship between depression and dementia, or cognitive decline and moreover cross-sectional studies and meta-analyses have repeatedly shown an association between late-life depression (LLD) and dementia, particularly AD and vascular dementia[163,164]. LLD is linked with vascular change and white matter degeneration in the brain, gray matter change and the link between LLD and mild cognitive impairment suggests that depression can lead to persistent cognitive impairment[163]. White matter changes are also associated with the age and severity of dementia in AD patients[164]. White matter is largely composed of glial cell oligodendrocytes[165]. White matter changes have been correlated with AD, vascular dementia, dementia with Lewy bodies, and psychiatric disorders with the focus on oligodendrocytes and myelin[166,167]. Oligodendrocytes which has a crucial role in the formation and maintenance of myelin [168] has also possible roles in the disease process, because myelin disruption can lead to the degeneration and death of neurons, disrupt in transmitting signals, and result in cognitive impairment, memory loss, and other neurological deficits associated with AD[166,169]. In the autopsy tissue sections from AD and Lewy body dementia patients, reduction of nuclear diameter of neurons and oligodendrocytes in the CA4 region of hippocampus was observed[169]. Damage in oligodendrocytes using demyelinating agent, impaired learning in PS1 mutant knockin mice with more vulnerable to death by glutamate and amyloid beta-peptide and showed abnormality in calcium signaling responsible for their death[166]. Subsequently, TNF α was found to promotes proliferation of oligodendrocyte progenitors and remyelination [170] indicating that damage on oligodendrocytes would contribute to neuroinflammation leading to neurodegeneration and cognitive impairments. On the other hand, astrocytes, and oligodendrocytes in grey and white matter regions of the brain metabolize fatty acids [171] and impaired lipid metabolism has a crucial role in AD[172]. White matter lesions with astrocytic, microglial and oligodendrocyte precursor cell responses are also often identified by T2-weighted magnetic resonance images (MRI) in the aging brain[173]. Further study on APPPS1 mice showed defects in myelin integrity and myelin amount associated with chronic plaque deposition and decreased oligodendrocytes[174]. Chronic amyloid plaque deposition and decreased oligodendrocyte number in the cortex of post postmortem AD brain was also found.[174]. In vitro studies also observed that A β peptides are toxic to oligodendrocytes because A β 1-40, a truncated fragment, A β 25-35 induced death of oligodendrocytes in a dose-dependent manner[175].

Role of T Cell, B Cell, Neutrophils in the Neuroinflammation Underlying Cognitive Deficit in AD/ADRD

Adaptive immune system is comprised of T cells, B cells, antigen-presenting cells (APCs) like macrophages, dendritic cells, and antibodies[176]. The presence of T cells brain of AD and PD patients indicates possible interaction between the cerebral innate immune system and the peripheral adaptive immune system, and T cell infiltration into the brain promoting crosstalk between T cells and microglia, resulting in the acceleration of neuroinflammation has been proposed[176]. Chronic inflammatory conditions present in periphery could lead to increase the risk of late-onset AD, possibly by inducing neuroinflammation[15], accompanied by alterations in peripheral blood cell populations with increased numbers of neutrophils and decreased numbers of T cells and B cells[177]. A decrease in peripheral T cells suggests possibility of a proportion or subpopulation of T cells may be migrating into the brain[24]. Several subtypes of CD4⁺ T cells, are also determined by the secreted cytokines (IFN- γ , Lymphotoxin, TGF β , TNF α , FGF, CCL15, CCL17, TNFRSF4, ICOS, IL-4, IL-13, IL-4, IL-5, IL-6, IL-9, IL-10, IL-17, IL-17F, IL-21, IL-22, IL-25) involved in various immunological processes, such as B cell maturation and macrophage activation etc.[24,178]. Antigen presenting cells (APCs), such as dendritic cells, B cells and macrophages, can activate CD4⁺ T cells via MHCII [24] and MHCII expressing microglia and astrocytes can directly activate CD4⁺ T cells[179]. Additionally, increased response of Neutrophils leading to raise inflammatory cytokine levels, have also been implicated in AD pathogenesis[180]. It may be noted that preclinical, and human post-mortem studies in AD have consistently demonstrated the presence of T cells in brain parenchyma[181–184].

Modest involvement of T cell infiltration, microglial proliferation and activation, accumulation of misfolded self-antigens and progressive neuronal dysfunction, and neural death due to neuro-inflammatory response is common in various neurodegenerative diseases with cognitive disfunction such as AD, PD, ALS, MS, and prion-induced neurodegenerative disease etc.[185,186]. Pharmacological inhibition of microglial proliferation by activating colony-stimulating factor 1 receptor (CSF1R) with GW2580, reduces T cell infiltration in AD APP/PS1, and results improvement in memory and open field tasks and in preventing synaptic degeneration[187]. Increased T cell infiltration has been observed in brains of AD patients [188] and T cells present in the affected hippocampal region are near microglia[181], while the peripheral T cells demonstrated increased reactivity to A β in AD patients[189]. However, the phenotype of peripheral T cells in transgenic AD mice has a regulatory or suppressive role [190] and lower response of CD4⁺ T cells following re-stimulation in AD transgenic mice suggests T cell tolerance to the antigen[191]. Microglia are suggested to be immune suppressive toward T cells, while peripheral immune infiltrates are causing T cell infiltration, activation, pathogenesis, and injury resolution in MS and autoimmune encephalomyelitis (EAE)[192]. In AD cases with mild/moderate dementia had increased gene expression of the inflammatory molecule major histocompatibility complex (MHC) II in the hippocampus, and MHC II protein levels were also increased which was inversely correlated with cognitive ability and decreased in T cell numbers in the hippocampus and the cortex; moreover, transition into AD dementia correlates with increased MHC II(+) microglia-mediated immunity with a parallel decrease in T cell number[193]. Amelioration of AD in Rag2-deficient APP/PS1 mice is primarily linked to the loss of pathogenic T cells as well B cells[194]. Rag deficiency increases AD progression due to loss of nonspecific immunoglobulin that activates microglial phagocytosis and subsequent clearance of A β plaques[195]. While immunoglobulins that target A β may interfere with plaque formation and disease progression, B cells may contribute furthermore than just producing immunoglobulins[196]. The contribution of B cells in AD has been shown in three transgenic mice models for AD, APP/PS, 3 $\times$ TgAD (APP/PS/TAU) and 5 $\times$ FAD (APP-K670N/M671L+I716V+V717I with PS1-M146L+L286V)[196]. Accumulation of activated B cells in circulation, and infiltration of B cells into the brain parenchyma leading to immunoglobulin deposits around A β plaques, is associated with AD[196]. Even when the AD-fostering transgenes were expressed, the loss of B cells alone was found to be sufficient to reduce A β plaque burden associated with microglia reversing behavioral

and memory deficits and restores TGF β + microglia[196]. Moreover, since therapeutic depletion of B cells at the onset of the disease retards AD progression in mice, suggests that therapeutic target of B cells may also benefit for the treatment of AD patients[196]. However, B cells are a heterogenous population of cells, and their function and subset accumulation are regulated by the inflammatory milieu [196] and lesser studies had been done both in mice and human, further studies are required for a more conclusive roles of B cells in ADRD.

Discussion and Conclusion

AD or ADRD is one of the most critical health issues that remain to be resolve that brings one of most deaths caused by diseases and drastically affects the global economy. The regulatory mechanisms underlying the pathology of cognitive deficit in AD or ADRD is highly complex, and it needs to be examined from several angles to uncover different regulatory pathways that would enable to design appropriate medicine for treatment or cure the cognitive deficit symptoms of the diseases. Enormous efforts with thoughtfully designed vast studies have been carried out and as a result dysregulation of several molecular and cellular signaling pathways have been identified that play potential roles in causing mild/moderate cognitive deficits and dementia of AD/ADRD. Discovering of these pathways has directed to designing and producing drugs for treatment to reduce or recover memory lost occurred to the affected individuals. However, an appropriate drug to treat AD/ADRD is yet to be available. This reveals the insufficiency of the available data and the need to take up greater challenges in finding suitable medicine for the treatment, and thereby the need for a deeper understanding of the underlying mechanisms of cognitive impairments of the diseases. Emerging research on inflammatory pathways that link to immune cells such as microglia, astrocytes as well as oligodendrocytes is highly promising. As there are multiple pathways in neurodegeneration leading to cognitive deficits in ADRD, designing drugs for multiple target sites is needed, to prevent or stop progression or retrieve to normalcy of ADRD. The above several lines of enormous studies and several more that have not been covered in this review, has strongly indicated that, to bring better understanding of ADRD, it's treatment or cure requires understanding of histopathologic changes in neurodegenerative diseases as it could highlight key aspects of the degenerative process leading to dementia.

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