Review

Microglial Dysregulation Underlying Neuroinflammatory Pathogenesis in Alzheimer's Disease and Related Dementias

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Review

Microglial Dysregulation Underlying Neuroinflammatory Pathogenesis in Alzheimer's Disease and Related Dementias

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Abstract

Neuroinflammation is considered as one of the core pathogenic factors of neurodegeneration in Alzheimer disease (AD) and related dementias (RD). It is also associated with other two hallmarks of AD dementia, i.e., amyloid beta (Aβ) and neurofibrillary tangles (NFT), and increasingly considered as the third hallmark of AD. Abnormality in microglial pathway plays a crucial role in the neuroinflammation of AD and RD. Microglia dysfunction is linked to many neuroinflammatory signaling pathways towards the progress of developing neurodegeneration resulting to cognitive deficits or dementia. Currently, several therapeutic approaches aim to target inflammatory regulators for AD treatment, and microglia is considered as one of the vital targets. In this article we intend to highlight and discuss various microglia mediated signaling pathways that link to chronic neuroinflammation and cognitive dysfunction/dementia in AD and other diseases. This could help us to understand the degree of microglial association with the disease pathophysiology through analyzing various studies in last few decades including the latest reports. We also aim to highlight the pathways that are more and less conclusively established and determine possible pathways which may help in further exploration and narrowing down or expanding the area of studies that requires further research. AD and RD are one of the most leading causes of death in the world and there is no appropriate drug available for cure or prevention of the disease. Further research is an absolute requirement for better understanding the mechanisms underlying the disease pathophysiology and better planning of basic/therapeutic research and clinical trials. We also provide up-to-date clinical trials that used inflammatory targeting drugs and discuss the failures and promising drug targets.

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Introduction:

Dementia is currently the 7th most leading cause of death globally [1]. Dementia is generally defined by decline in memory, language, problem-solving, spatio-temporal orientation and reasoning abilities etc. [1–6]. The most common cause of dementia is the Alzheimer's disease (AD), because 60% to 80% dementia cases among the elderly people are caused by this disease [2–5]. The remaining 20% to 40% dementia are associated with other neurological diseases which is often termed as AD related dementias (ADRD). ADRD comprises of several neurological diseases that includes Vascular dementia (VD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FD), Lewy body dementia (LBD) and Huntington's disease (HD), Wernicke-Korsakoff Syndrome (WKS), Sickle cell disease (SCD) etc. [5]. Currently 7.2 million Americans with age 65 and older are suffering from AD dementia, which means 1 out of 9 Americans

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(11%) of this age are living with AD [7]. Globally 57 million people had dementia as of 2021 record [1], which is 2 million greater than the previous year 2020 (55 million) [8]. Notably this 2 million increased is happening in just 1 year and records after 2021 is yet to be available. Ultimately, the number is expected to be doubled every 20 years and the fastest growth among elderly people appears to be in world's most populated countries like China, India, and their south Asian and western Pacific neighbours [8]. AD and ADRD directly impact both health and economy. Majority of caregivers for dementia patients are unpaid family members, friends or others; of which 70% is borne by the unpaid family caregivers in various ways including medications and food. If they are paid, the cost is estimated to be about $413.5 billion according to United States' cost of living in 2024 [7]. Globally, treatment cost for over 50 million patients with dementia is estimated to be more than $1 trillion per year, as of 2023 report [9]. Therefore, finding a solution for AD and ADRD is an urgent matter for global health and economy.

Various research over the past few decades have immensely enhanced our knowledge on underlying pathophysiology of AD/ADRD. Several drugs have been developed, and thousands of clinical trials have been carried out. However, a therapeutic measure to intervene, prevent, manage, or cure of the diseases, is yet to be available. Challenges remain due to complex pathogenesis of the disease [10–12] and thereby the need for further research to uncover the unknown pathological mechanisms. Growing evidence from several studies reveal potential involvement of pathological chronic inflammatory mechanisms underlying AD/ADRD development and progression [13–20]. Clinical trials that target inflammatory modulators also indicate promising signs or results [3,5,21]. Among the inflammatory modulators, microglia is one of the most discussed immune cells that may play crucial role in the immune system dysregulation associating with the pathogenesis of dementia or cognitive decline in AD/ADRD [3,5,21–24]. Could microglia dysregulation be judged as central player in the whole or most neuroinflammatory consequences? Are other immune cells and proinflammatory molecules equally important? Are the statements on microglia exaggerating? To what degree the role of microglia is important? This article aims to discuss these points from the available study reports and convey our viewpoints. We will highlight several microglia link immune regulatory pathways that associates with AD/ADRD pathogenesis, including Aβ and Tau link pathways and also point out the negative findings. The outcomes from this literature survey analysis and discussion could reveal ways for better planning in future research as well the extend of belief on the microglia role in disease pathogenesis.

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

Our body homeostasis is primarily regulated and maintained by the nervous system and the immune system. Proper communication between the two systems ensures normal functioning of the body. A lack of proper communication between the two systems leads to various disease or disorders such as in AD and related dementias. Neuronal communication is supported by synaptic networks established in an activity-dependent manner to facilitate cognitive functions, such as learning and memory [25]. Immune cells and signaling molecules are necessary for shaping the circuitry system and they control the proper functioning of the nervous system. Disruption in the immune system functioning leads to impairments in neurogenesis and cognition. Neuroinflammation has been considered as a key player in most diseases with nervous system dysregulation and continuously identified as a potential mediator in cognitive deficits. During aging, reduction in dendritic spine density/morphology and loss of synaptic plasticity are occurred which could lead to cognitive impairments and become susceptible to age-related neurodegenerative diseases, such as ADRD [25–27]. Studies have indicated that these alterations have begun since early stage of the disease pathogenesis. Neuroinflammation levels are increased with advancing of age and neurodegeneration which may contribute to accelerating cognitive impairment with the progression of age. Glial activation, increased production of proinflammatory cytokines, abnormal neuronal signaling, magnifying deterioration of the central nervous system microenvironment, occurred during neuroinflammation leading to cognitive impairment and neurodegeneration [28,29]. Not only the

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AD, cognitive decline/dementia is one of the clinical symptoms in several other neurological diseases that associates with neuroinflammation such as VD, DLB, PD, FD, HD, WKS, SCD, ALS etc. [30–35]. Both innate and adaptive immune system disregulation play crucial roles in AD pathogenesis [36–42]. Microglia, astrocytes and oligodendrocytes dysregulations are considered as central contributors to the innate immune system abnormaity in AD. Whereas, B and T lymphocytes primarily contribute to adaptive immune system dysregulation. B and T lymphocytes were detected in the post-mortem brain with AD, cerebrospinal fluid (CSF) of individuals with mild cognitive impairment (MCI) as well as AD patients [37,43–47]; moreover higer frequency of T helper subsets were also present [48,49]. Within the parenchyma of the central nervous system (CNS), microglia constantly monitor synapses and participate in the synaptic pruning process during development (which possibly continues throughout life) [50]. Various research findings in the last several years strongly indicate that malfunction in micorglial signalling contributes a major role in causing neuroinflammation leading to dementia of AD and related dementias. Inflammatory cytokines, such as interleukin-1beta (IL-1β) and tumor necrosis factor (TNF), are released by microglia during neuronal activities and they play a crucial role in regulating the potency of synaptic transmission. Subsequently, a systematic and proper functioning of the immune system is critical for maintaining normal function of nervous system. Therefore, thorough understanding of microglial regulatory function in the immune response in the neurons that alters the normal synaptic transmission, is necessary for understanding the pathological mechanisms underlying AD/ADRD and for therapeutic development.

Microglia activation has been evidenced in various neurodegenerative diseases; and the specific states of activated microglia possess specific functions associating with pathological hallmarks. When pathological protein aggregates, microglia play detrimental roles instead of protection due to excessive uptake of protein aggregates, resulting to microglial phagocytic abnormality, neuroinflammation, and neurodegeneration etc. [51]. Moreover, during unfavorable inflammatory response, infiltration of peripheral immune cells occurred and alters normal microglia shape into pro-inflammatory phenotypes accelerating disease progression [52]. Additionally, impairment of microglia autophagy and extracellular vesicles released from microglia also contribute to pathological progression resulting to neurodegeneration [53]. This reveals, understanding biological mechanisms can assists in finding suitable therapeutic development strategies to enhance microglial phagocytosis and conversion to protective phenotype, reduce/prevent microglial-mediated neuroinflammation and exosome synthesis/secretion, that would ultimately results to stop/prevent cognitive decline in AD and ADRD such as In this review, immune system and neuroplasticity abnormality in which microglia play major roles in affecting the neuronal signaling or neuroplasticity leading to cognitive deficits in AD is narrated based on the available research reports while briefly mentioning about the other diseases with ADRD.

Microglial Role in Synaptic Processing and Normal Brain Development

Microglia comprises 5%–12% of the total populations of glial cells in the adult rodent brian [44,54] and 0.5%–16% in human brain [54–56], which indicates close proximity of microglia level between rodent and human. The size of microglial cell population remains steady from late postnatal stages until aging and its population size is maintained by spatial and temporal coupling of proliferation and apoptosis. However the turnover of microglia is remarkably fast, that allows the whole population to renew several times during a lifetime as studied revealed in both mice and humans [57]. During innate immuen response, microglia express a wide range of receptors that recognize both exogenous and endogenous central nervous system (CNS) insults [58]. Micorglia also play a crucial role in establishing normal brain development and normal neuronal connectivity and the regulatory processes, such as synaptic pruning ensuring elimination of inappropriate synapses while strengthening the appropriate ones depending on neuronal activity and experience [57,59]. It promotes phagocytic clearance of debris and death cells and as a result provide trophic support insuring tissue repair and maintainance of normal brain homeostasis [60–68]. Microglia phagocitic also results to synapse elimination during early sage but not the late postnatal periods; in this role

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fractalkine receptor CX3CR1 or complement receptor 3 (CR3/CD11b) signalling pathways are involved [62,69]. Earlier studies showed that the motor skill learning was induced by increased dendritic spine formaion in the motor cortex which reveals association of new dendritic spine remodelling rate with the improvement in performance after learning [70,71]. Interestingly, reduction of microglia by removing brain-derived neurotrophic factor in mice showed learning impairments in multiple behavioral assignments such as rotaroad test, fear conditioning and nobel object recognition test; moreover decrease motor learning-dependent synapse formation was also observed [72]. The learining impairement is likely due to binding of BDNF to neuronal TrkB (tropomyosin-related kinase receptor is a a key mediator of synaptic plasticity) increasing TrkB phosphorylation [72]. It has been demonstrated that aged mice (16 months old) lost synapses in the hippocampus (a specific brain region that regulates learning and memory) compared to the younger mice (1 month old) [73]. On the other hand reduced uptake and clearance of Aβ peptide by microglia cause synaptic loss in AD and related neurodegenerative disorders; these events are also typically linked with increased complement system signaling, during early stage of live [73–76]. Microglia thus play a central role in establishing synaptic networks by remodeling synapses and regulates of synaptic plasticity, which involves learning-dependent dendritic spine remodeling and learning-dependent long-term synaptic strengthening long-term potentiation (LTP) [62,69,72,77,78]. It may be noted that LTP is considered to be the foundation of learning and memory [25].

Microglial Imbalance Induce Neuroinflammation and Cognitive Deficit in AD/ADRD

Loss of homeostasis or alterations occurred in the tissues can induce several dynamic processes in microglia converting them into activated state causing changes in their cellular morphology like shortening of the processes and swelling of the soma, surface phenotype changes, expressing secretory mediators and proliferative responses [58,79]. The presence of abnormally elevated amount of activated microglia is crucial in the pathology of AD and several neurodegenerative diseases. In AD, microglial inflammatory response is elevated while their phagocytic clearance role is compromised [58]. This inflammatory state can be induced by increased production of proinflammatory cytokines such as IL-1β and TNF-α and other inflammatory mediators binding patterns such as PAMP or DAMP (danger- or pathogen-associated molecular patterns) binding to PRRs (pattern recognition receptors expressed in microglia and evolutionarily conserved family of innate immune cell receptors); moreover the failure of microgial phagocytic activity is associaed with Aβ deposition and clearance [80–82]. Activated microglia associating with immunoglobulins and complement components, is also closely linked with Aβ deposits in the brain of AD and Down syndrome patients [83,84]. Disruption of microglia activation using DAP12 mutant mouse (KD75) enhances hippocampal LTP [85] whreas greater activation of microglia is associated with the loss of microglial specific fractalkine receptor (Cx3cr1) causing LTP reduction [86]. Again, reduction of LTP could be rescued by the inhibition of IL-1β signaling using Minocycline which is an FDA approved antibiotic drug [87]. On the other hand, loss of Cx3cr1 gene in AD mouse worsens cognitive impairment reveals that role of microglia in AD dimentia to be highly crucial [88]. Additioinally, deletion of the NLRP3 inflammasome which is upstream of IL-1β production rescues LTP that also linked to the reduction of Aβ plaque load in APP/PS1 mice [89]. In the case of hTau-P301S frontotemporal dementia (FTD) mice model, 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-1β production that leads to spatial learning and memory impairments; it may be noted that SIRT1 was reduced in aged FTD mice ranging 13-15 to 20-26 month old [90]. This shows that both SIRT1 and microglia are reduced upon aging, indicating that microglial SIRT1 deficiency has effect on aging accompanied by tau-mediated memory deficits via IL-1β upregulation in mice. Further, selective activation of IL-1β transcription by reducing SIRT1 may be induced via hypomethylation of specific CpG sites on IL-1β proximal promoter [90]. Notably the epigenetic regulation of IL-1β and microglia with the selective hypomethylation of IL-1β is strongly correlated

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in aging humans and patients with dementia [89–93]. On the other hand, temporal lobe astrocytes were elevated with IL-1, S-100, and glial fibrillary acidic protein, which reveals that the astrogliosis in Alzheimer disease may be promoted by elevation of interleukin 1 [83]. It has also been reported that aberrant inflammatory responses is associated with aging brains in human [94,95]. Moreover, basal level of proinflammatory cytokines are specifically elevated with aging [96], while those of anti-inflammatory cytokines are reduced [97]. Interestingly, genetic deletion of pro-inflammatory nuclear factor-jB signaling in the hypothalamic microglia could restore impairments in hippocampal dependent learning and memory in normally aging animals [98]. Moreover, in APP/PS1 mice, microglia-specific deletion of the gene encoding PGE2 receptor EP2 restores microglial chemotaxis and Aβ clearance, while suppressing toxic inflammation and rescuing psynaptic insults and memory deficits [99]. This suggessts that epigenetic mechanisms which affects communication and pro-inflammatory activation of microglia contributes to cognitive deficits in aging and neurodegenerative diseases such as AD/ADRD. More number of pro-inflammatory cytokines have been identified to play a role in AD brain such as IL-1α, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IFN-α, which are produced in neurons or microglia [100–103]. At this juncture, it may be noted that proinflammatory cytokines are recruited from the circulation by endothelial cells, inflammatory cells, and the blood–brain barrier (BBB) when biochemical or mechanical damages occur [104,105].

Microglial Inflammatory Signalling Through TREM2, CD33 and APOE4 Mutations Leading to Cognitive Deficit

Many studies reported that declination of synaptic function in AD patients could be the result of increased inflammation in the brain. There has been positive effects on synaptic plasticity when inflammation was targeted through genetic manipulation in AD models [106]. And studies on humans continue to support microglial inflammatory pathogenesis in AD as well. Genetic mutations identified to be risk factor by genome-wide-association studies in microglia regulatory genes such as TREM2 (triggering receptor expressed on myeloid cells 2) and CD33, were found to have to sporadic AD [107,108]. It may be noted that TREM2 is a lipid/lipoprotein binding receptor expressed on the surface of microglia and some other myeloid cells including macrophages, dendritic cells, osteoclasts [109–111]. Therefore, role of TREM2 in regulating innate immune response is a critical one. A heterozygous rare variant rs75932628 of TREM2 gene that change Arginine to Histidine (R47H) in the protein product was found to be associated with a significant increased risk of AD [112]. The rare missense mutation rs75932628-T was predicted to cause R47H indicated to have cause risk to early- as well as late-onset AD [113,114]. Notably, rs75932628-T have also been implicated to increase risk in PD, FD, and ALS [115–119]. It has been suggested that the risks could be resulted from the loss of TREM2 function caused by the mutation. Because the homozygous loss-of-function mutations in TREM2 gene was linked to autosomal recessive form of early-onset dementia, moreover the R47H substitution could also lead to an increased predisposition to AD through the deregulation of inflammatory processes resulting to dementia [120]. On the other hand, rs3865444-C of CD33 gene in AD susceptibility locus was associated with greater expression of CD33 in the surface of monocytes of young and older human individuals; and moreover with the diminished internalization of Aβ42 peptide, accumulation of neuritic/fibrillar amyloid pathology, increased numbers of activated human microglia etc. [121]. Meanwhile, bioinformatic analysis indicated that microglia-specific TYRO protein tyrosine kinase binding protein (TYROBP) signaling may the most dysregulated pathway in sporadic AD [122]. TREM/TYROBP signaling along with CD33 also activate phagocytosis while suppressing Toll-like receptor-mediated inflammation (TLRs) [123,124].

Anti-inflammatory role of TREM2 functions through IL-4 pathway in the brain [125]. Lack of TREM2 also cause impaired clearance of apoptotic neurons and inflammation which may be responsible for the brain degeneration as observed in patients with polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy/Nasu-Hakola disease [111]. This phenomenon was found in dementia associated with bone cystic lesions [126]. TREM2 levels were elevated in the

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microglia of AD patients, particularly in microglia with plaques and neurofibrillary changes, and TREM2 levels correlated with the neurodegeneration markers. In post-mortem temporal cortical samples from AD and normal cases, TREM2 protein was positively correlated with increased phosphorylated tau and active caspase 3, and loss of the presynaptic protein SNAP25 [115]. Moreover, high immunoreactivity of TREM2 protein with microglia was also associated with amyloid plaques in neuritic pathology-enriched areas of the brain [115].

Further, amyloid pathology also links to many other proteins such as human ApoE apolipoprotein isoforms ApoE2, ApoE3, and ApoE4 which differentially stimulate APP transcription affecting Aβ 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 Aβ synthesis; ApoE3 is neutral while ApoE2 plays a protective role [127]. Genetic and proteomics studies in human patients, demonstrated significant association of APOE4 level with Aβ, as well as high avidity binding of APOE4 to Aβ, with late-onset familial AD [128]. These findings also indicate a possible role of APOE4 to suppress TREM2 function in the amyloid pathology of the disease. Infect, single-nucleus RNA sequencing using human postmortem brain tissue showed different APOE and TREM2 genotypes association with the neuropathology. APOE and TREM2 risk variants were identified in microglia subpopulations with depleted CD163-positive amyloid-responsive microglia (ARM) [129]. Besides AD, a co-inheritance of APOE4 was also observed with 2-fold increased risk of dementia in SCD patients [31].

Microglial Inflammatory Signaling Through Complement System Leading to Cognitive Impairment

Role of microglia promoting synaptic dysfunction during both aging and AD through complement signaling is supported by a series of studies. Oligomeric Aβ causes microglia to release high C1q level marking elimination of synapses by microglia through classical complement cascade occurred during early stage of AD, before the plaque deposition became evident [130]. 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 manner when exposed to soluble Aβ oligomers, revealing synaptic dysfunction in aging and AD through microglial elevation of complement signaling [130]. In the unfixed brain taken from AD patient with dementia, plaques with amyloid core surrounded by a corona of degenerating neurites were found, which contain complement factors Clq, C3b, C3c, C3d and C4 [131]. GWAS on TREM2, CR1, APOJ/Clusterin and CD33, and integrated network studies with TYR-OBP in humans also support the microglia and complement related pathways in late onset AD [113,122,132,133].

During inflammation, microglia also act as antigen presenting cells (APCs) [134], microglia interaction with the complement system [135], can affect antigen presentation and further influence regulation in adaptive immune response and vice versa. HLA-DR (human leukocyte antigen D related) is a subtype of the MHCII (histocompatibility complex class II) responsible for presenting foreign antigen to T-lymphocytes, and it has crucial role in inflammation [84,136]. HLA-DR-positive reactive microglia were found in gray matter throughout the cortex of postmortem brains of AD patients, where the senile plaque formation occurred, while hippocampal HLA-DR-positive cells were also positively correlated with the numbers of plaques [84]. Not only the HLA-DR, HLA-A,B,C (MHCI) positive reactive microglia were also present in postmortem AD brain tissues, however number of HLA-DR positive cells was higher than HLA-A,B,C positive ones, in addition to the separate population from glial fibrillary acidic-protein-positive astrocytes [137]. Interestingly, neurotoxic reactive astrocytes were induced by activated microglia A1s (reactive astrocyte type 1) in AD, HD, PD, ALS, MS [138], indicating immune cells complementing one another in neuroinflammation of these diseases.

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Aβ and Tau Pathology Link to Microglia and Cognitive Impairment in AD and ADRD

Accumulation of Aβ aggregates, hyperphosphorylated tau accumulation and the neurofibrillary tangles (NFT) composed by microtubule-associated protein tau (MAPT), are the hallmark findings of AD pathogenesis. Abnormal accumulation of these proteins led to neuronal cell death and synapse loss which is parallel to the onset of cognitive abnormality symptoms [139]. This may be due to macroglia by inducing chronic neuroinflammation, promoting amyloid plaque formation and spreading, intensifying neuronal damage [140]. Following amyloid plaque accumulation, microglia cluster around amyloid plaques and acclimatize and results to activated morphology with distinct transcriptional signature, converting them disease-associated microglia or microglial neurodegenerative phenotype or activated response microglia [140].

Tau is found abundantly in the neurons of CNS, with maximum level in cerebral cortex, and it primarily maintains stability of microtubules in axons [141,142]. In APP transgenic mice Aβ causes dendritic spine changes by destabilizing microtubules. The loss of spines can be recovered by microtubule polymerization while the hippocampal spine loss closely resembles the progressive changes of spine morphology from mushroom-shaped to stubby [27]. Tau also has multiple roles in axonal development, exon elongation, exonal transport, iron homeostasis regulation, myelination, nuclear architecture, and neurogenesis [143,144]. In different neurodegenerative conditions, aggregated intraneuronal hyperphosphorylated tau was found, which is often 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 [37]. Tau promotes assembly of microtubules in the neurons by binding to tubulin, however in the brain of AD patients tau can dissociate from microtubules [145]. In the condition of aberrant hyperphosphorylation of Tau, the binding capacity of Tau reduces, causing microtubule instability that leads to various tauopathies [146]. The abnormal neurofilament tau/neuroinflammatory NFT is largely composed of hyperphosphorylated tau, which creates paired helical filament (PHF) by twisting around each other and accumulate in the neural perikarial cytoplasm, axons, and dendrites, causing deregulation, loss of cytoskeletal microtubules and tubulin associated proteins [147]. NFTs also spread from the trans entorhinal cortex to the hippocampal formation and neocortex [148]. Increased oxidative stress causes accumulation of tau and Aβ at synapse sites continually deading to the loss of dendritic spines, presynaptic terminals, and axonal dystrophy [147,149]. In fact, various studies have been carried out to block tau hyperphosphorylation using different types of drugs. Interestingly glycogen synthase kinase 3 (GSK3b) inhibiter, baricitinib, has been found potentially effective showing memory enhancement in transgenic mice and the drug is currently undergoing phase II trial [150,151]. In the cerebrospinal fluid (CSF) taken from temporal and frontal autopsy brain tissue of AD patients showed increased NFT level with cognitive dysfunction [152]. Moreover, CSF released tau and Aβ42 has been proposed to be promising biomarkers for early AD detection [153].

Table 1. List of proteins/genes involved in the signaling pathway leading to neuroinflammation.

Protein/gene name	Physiological and/or pathological functions in neuroinflammation
APOE2, APOE3, APOE4	They are isoforms of APOE which mediate lipid transport in the brain and periphery. In the neuroinflammatory condition, APOE2 has protective role, APOE3 has neutral function, while APOE4 is high-risk factor of neuroinflammation by increasing APP and Aβ synthesis through MAP-kinase signaling pathway [127,154].

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Aβ40, Aβ42	Both are byproducts of cleavage of APP, which induce heme synthesis by the mitochondria and increase iron uptake, enhance abnormal phosphorylation of tau protein and in subsequent aggregation into NFTs; Aβ40 lowers intraneuronal regulatory heme while Aβ42 enhances intraneuronal regulatory heme and aggregates to form amyloid plaques in the brain, considered as biomarker for AD [155,156].
BDNF	Binds to neuronal TrkB, involve in synapse formation and regulates learning and memory, reduces neuroinflammation by inhibiting pro-inflammatory pathways and cytokines [72,157].
C1q, C3, CR3, C3b, C3c, C3d, C4, CD33, CR1	Complement cascade involved in immune response. Neuroinflammatory response of this cascade accompanied with greater number of phagocytic microglia and early synapse loss, [130] and plaque accumulation [131,158,159].
CX3CR1	Chemokine receptor that binds to CX3CL1 is primarily expressed in microglia. [160] CX3CL1-CX3CR1 signaling participates in the removal of damaged neurons and neurogenesis. [161] Under pathological condition, CX3CL1-CX3CR1 signaling promote microglia activation as well as production of proinflammatory cytokines resulting to neuroinflammation [162].
DAMP/PAMP	DAMP (from damaged host cells) /PAMP (from microorganisms) binds to PRRs expressed in microglia and participates in innate immune response [163]. Abnormality in the DAMP/PAPP-PRRs binding process or signaling can lead to failure of microgial phagocytic activity and promote the release of proinflammatory cytokines such as IL-1 and IL-6 and subsequently increase Aβ deposition and clearance in the brian [80–82].
EP2	Protects neurons from NMDA receptor-mediated excitotoxicity and OGD induced-anoxia in neurons and hippocampal region [164]. Inflammatory action of EP2 induces microglia and astrocytic

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	inflammatory response and Aβ deposition, and pro-inflammatory effectors such as COX-2, iNOS, NOX [99,164].
GSK3b	Primarily localized in the developing CNS and involves in different developmental events in the immature brain such as neurogenesis, neuronal migration, differentiation and survival [165]. Under unfavorable conditions led GSK3b become a mediator for neuroinflammation [166].
TNF-α, IL-1β, IL-1, IL-6, GM-CSF, IFN-α	Circulating proinflammatory cytokines are produced to orchestrate immune responses to injury and infection as they play crucial activating innate immune response. Under normal condition, roles in tissue repair, metabolic regulation, B-cell differentiation, host defense from infection/pathogens [167–170]. Their sustain activation leads to acute or chronic inflammation and neurodegeneration [100–103,171,172].
IL-4	Anti-inflammatory role in the brain and protects from neuroinflammation [125]
MHCI	Expressed in all nucleated cells and enables antigen presentation to CD8+ T cells for adaptive immune response. MHCI+ microglia in high under neurodegenerative condition [173].
MHCII	Particularly expressed in antigen presenting cells such as dendritic cells, B cells, and microglia and enable to present antigen to CD8+ T cells for adaptive immune response CD4+ T cells. Homeostatic level of MHCII+ microglia and CD4+ T cells are low; however, the level is upregulated during chronic neurodegeneration [173].
NLRP3	Regulates innate immune responses by activating caspase-1, IL-1β and IL-18, with is necessary for host defense against pathogen intrusions including numerous bacterial, viral, and fungal infections. However, excessive or altered regulation of NLRP3 inflammasome activity involves in the pathogenesis of several inflammatory, autoimmune, and degenerative diseases [174,175].

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SIRT1	Anti-inflammatory role in the brain and protects from neuroinflammation [90,176].
SNAP25	One of the key regulators involve in the formation of soluble SNARE complexes that are central to hormonal secretion and synaptic transmission plays, also plays a substantial role in bridging central neurological systems with peripheral metabolic homeostasis [177]. Alteration in SNAP-25 expression could damage intracellular trafficking and degradation pathways, resulting to accumulation of tau and amyloid-beta, leading to neuroinflammation [178].
TLRs	Main components of innate immune system essential for the recognition of conserved structural motifs on wide range of pathogens and some endogenous molecules and has substantial roles in nondevelopment [179,180]. During neuroinflammation, activation of TLRs play a key role in the production of proinflammatory cytokines (IL-1β, IL-6, TNF-α, and IFN-γ), chemokines, prostaglandins and ROS, by microglia and astrocytes [179].
TREM2	Anti-inflammatory role in the brain and protects from neuroinflammation and neurodegeneration [125]
TYROBP	Anti-inflammatory role in the brain and responsible for maintaining a stable neural micro-environment to prevent neuron death (TYROBP is mainly found in the neurons as well as immune cells) [181]. TYROBP-TREM2 signaling is considered to play a crucial role in stabilizing neuroinflammation [122,181].

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Table 2. FDA approved drugs for improving cognitive decline or dementia in AD, their mode of action and side effects.

Generic name (brand name)	Mode of action	Side effects
Lecanemab (Leqembi)	Reduces soluble Aβ protofibrils and amyloid markers (Aβ42 and Aβ42/Aβ40 ratio) of early AD resulting to moderately less decline of cognitive impairement [3,182].	Amyloid-related imaging abnormalities and headache. [183]
Donanemab (Kisunla)	Removes Aβ plaques aggregates and slows progression clinical of the disease [184,185].	Amyloid-related imaging abnormalities and headache. [183]
Benzgalantamine (Zunveyl)	Inhibits acetylcholinesterase in reversible manner and increases acetylcholine availability at the synapses and enhance cholinergic transmission and reduce mild to moderate dementia [186].	Nausea, vomiting, diarrhea, dizziness, headache and appetite loss. [183]
Donepezil (Aricept)	Inhibits acetylcholinesterase in reversible manner and increase acetylcholine availability at the synapses and enhance cholinergic transmission and reduce mild to moderate dementia [186].	Nausea, vomiting, appetite loss, muscle cramps and increased frequency of bowel movements. [183]
Galantamine (Razadyne)	Inhibits acetylcholinesterase in reversible manner and increase acetylcholine availability at the synapses and enhance cholinergic transmission and reduce mild to moderate dementia [187]	Nausea, vomiting, appetite loss and increased frequency of bowel movements. [183]
Rivastigmine (Exelon)	Inhibits acetylcholinesterase in reversible manner and increase acetylcholine availability at the synapses and enhance	Nausea, vomiting, appetite loss and increased frequency of bowel movements. [183]

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	cholinergic transmission and reduce mild to moderate dementia [188,189].	
Memantine (Namenda)	Uncompetitive NMDA receptor antagonist, reduces glutamatergic overstimulation, lowers neuronal damage and reduce moderate to severe dementia. [190]	Headache, constipation, confusion and dizziness. [183]
Memantine plus Donepezil (Namzaric)	Memantine blocks or antagonizes NMDA receptor by mimicking glutamine while Donepezil inhibits choline esterase and the combined effect results to lower moderate to severe dementia at greater degree.	Nausea, vomiting, appetite loss, increased frequency of bowel movements, headache, constipation, confusion and dizziness. [183]

Aβ: Amyloid beta; NMDA: N-methyl-D-aspartate. Further details of clinical trial status of these drugs are available at www.ClinicalTrials.gov or www.fda.gov. Amyloid-related imaging abnormalities (ARIA) represents a common side effect such as temporary swellings in brain areas that resolves over time, small bleeding spots in or on the swelling brain surface [191,192]. ARIA may not cause symptoms but can be serious; however, may sometime show symptoms like headache, dizziness, nausea, confusion and vision changes etc [192].

Conclusions

AD and ADRD are one of the most critical health issues that remain to be resolved. These diseases cause one of the most human deaths and drastically affects the global economy. The regulatory mechanisms underlying the pathology of cognitive deficit in AD or ADRD is highly complex, which needs to be examined from several angles. A thorough and clear understanding of the pathophysiological mechanisms can provide proper direction in finding specific therapeutic targets and enable the professionals to design appropriate medicine for treatment of the cognitive deficits caused by these diseases. Various well-designed studies have been carried out and as a result dysregulation of several molecular and cellular signaling pathways that link to mild/moderate cognitive deficits and dementia of AD/ADRD, have been identified. Discovering of these pathways has allowed development of drugs to improve memory in affected individuals. However, an appropriate drug for proper treatment of AD/ADRD is yet to be available. It may be noted that out of thousands of clinical trials, only about 1% revealed to be promising [193,194]. The number of failures in clinical trials is enormous. Various factors may be accountable of this failure including insufficiency of available data, lack of understanding the disease mechanism and faults occurred during drug development or clinical trial processes. Many experts in the field have argued with various reasons such as unavailability of adequate evidence that can justify the clinical trials, using

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inappropriately designed clinical trial methods, developed drugs failing to meet the rational drug development principles specifically prepared for AD/ADRD therapeutic development, and low efficiency of the drugs [195]. There are examples worth mentioning to justify these arguments. Two drugs, bapineuzumab and solanezumab were made proceed to phase III trials despite the fact that phase II trial did not produce convincing results, and ultimately led to the failure [196–198]. Besides, recurrence of human error due to lack of learning or ignorance from past failures, is an avoidable error that could have been stopped from happening again; and be free from repeatedly facing the same challenges, negative outcomes, and weakening the confidence [199]. Additionally, delayed intervention in symptomatic dementia, can also hinder the success of clinical traials [200]. To overcome these challenges, both clinical and basic research with more intelligent and holistic approaches are necessary.

In the recent years, emerging research findings on inflammatory pathways that link to immune cells such as microglia, astrocytes as well as oligodendrocytes, are highly promising with therapeutic significance. Since, there are multiple pathways in neurodegeneration leading to cognitive deficits in AD or ADRD, designing drugs for multiple target sites is expected to yield better results. Vast number of studies that have been cited in review and several more that have not been covered, strongly indicate that, understanding the histopathologic changes in neurodegenerative diseases can provide a clearer knowledge on the pathogenesis of AD/ADRD and better approaches for therapeutic development. Because understanding the histopathologic changes highlights key aspects of the degenerative process leading to dementia and thereby the primary roles of immune cells in the disease condition. Inflammation was previously believed to be occurred because of protein aggregations in the brain, however accumulating evidence demonstrate that immune signaling dysregulation may not just be a consequence of protein aggregation but rather it began at the earliest stages of the disease process leading to the building up of the protein aggregates [201]. And the role of microglia in synaptic loss has been demonstrated to occur in the early stage of disease progression [130]. Therefore, designing drugs for clinical trials that targets the regulatory pathways of inflammation that involved microglia will be a promising approach for the treatment of AD and other forms of dementias.

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Abbreviations

AD: Alzheimer's disease; ADRD: Alzheimer's disease related dementias; ALS: Amyotrophic lateral sclerosis; APOE2: Apolipoprotein E2; APOE3: Apolipoprotein E3; APOE4: Apolipoprotein E4; APOJ: Apolipoprotein J; BDNF: Brain-derived neurotrophic factor; C1q: Complement Component 1q; C3: Complement component 3; C3b: Complement Component 3b; C3c: Complement Component 3c; C3d: Complement Component 3d; C4: Complement Component 4; CD11b: Cluster of differentiation molecule 11B; CD33: Cluster of Differentiation 33; CR1: Complement Receptor 1; CR3: Complement Receptor 3; CSF: Cerebrospinal fluid; CX3CR1: C-X3-C motif chemokine receptor 1; CXCR1: C-X-C motif chemokine receptor 1; DAMP: Damage-associated molecular pattern; EP2: Prostaglandin E receptor 2 (or E-prostanoid 2 receptor); FD: Frontotemporal dementia; GM-CSF: Granulocyte-macrophage colony-stimulating factor; GSK3b: Glycogen Synthase Kinase 3 Beta; HD: Huntington's disease; HLADR: Human Leukocyte Antigen—DR isotype; IFN- α: Interferon Alpha; IL-1: Interleukin 1; IL-16: Interleukin 16; IL-4: Interleukin 4; LBD: Lewy body dementia; MHCI: Major Histocompatibility Complex Class I; MHCII: MHC Class II; NMDA: N-methyl-D-aspartate; NLRP3: Nucleotide-Binding Domain, Leucine-Rich–Repeating Pyrin Domain–Containing 3; OGD: oxygen-glucose deprivation; PAMP: Pathogen-associated molecular pattern; PD: Parkinson's disease; PGE2: Prostaglandin E2; PRRs: Pattern Recognition Receptor; S-100: A family of calcium-binding proteins, soluble in 100% saturated ammonium sulfate solution at neutral pH; SCD: Sickle cell disease; SIRT1: Silent Information Regulator 1 (also known as Sirtuin 1); SNAP25: Synaptosomal-Associated Protein 25; SNARE: N-ethylmaleimide-sensitive factor attachment protein receptor; TLR: Toll-like Receptor; NF-α: Tumor Necrosis Factor alpha; TREM2: Triggering Receptor Expressed

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on Myeloid Cells 2; TrkB: Tropomyosin receptor kinase B; TYRO: Tyrosine kinase-related proteins (the name TYRO is derived from tyrosine); TYROBP: TYRO protein tyrosine kinase binding protein; VD: Vascular dementia; WKS: Wernicke-Korsakoff Syndrome

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