



TLR4 Cross-Talk With NLRP3 Inflammasome and Complement Signaling Pathways in Alzheimer's Disease

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Amyloid plaques, mainly composed of abnormally aggregated amyloid β -protein (A β) in the brain parenchyma, and neurofibrillary tangles (NFTs), consisting of hyperphosphorylated tau protein aggregates in neurons, are two pathological hallmarks of Alzheimer's disease (AD). A β fibrils and tau aggregates in the brain are closely associated with neuroinflammation and synapse loss, characterized by activated microglia and dystrophic neurites. Genome-wide genetic association studies revealed important roles of innate immune cells in the pathogenesis of late-onset AD by recognizing a dozen genetic risk loci that modulate innate immune activities. Furthermore, microglia, brain resident innate immune cells, have been increasingly recognized to play key, opposing roles in AD pathogenesis by either eliminating toxic A β aggregates and enhancing neuronal plasticity or producing proinflammatory cytokines, reactive oxygen species, and synaptotoxicity. Aggregated A β binds to toll-like receptor 4 (TLR4) and activates microglia, resulting in increased phagocytosis and cytokine production. Complement components are associated with amyloid plaques and NFTs. Aggregated A β can activate complement, leading to synapse pruning and loss by microglial phagocytosis. Systemic inflammation can activate microglial TLR4, NLRP3 inflammasome, and complement in the brain, leading to neuroinflammation, A β accumulation, synapse loss and neurodegeneration. The host immune response has been shown to function through complex crosstalk between the TLR, complement and inflammasome signaling pathways. Accordingly, targeting the molecular mechanisms underlying the TLR-complement-NLRP3 inflammasome signaling pathways can be a preventive and therapeutic approach for AD.

Keywords: TLR4, Alzheimer's disease, inflammasome, complement, amyloid, synapse

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INTRODUCTION

Alzheimer's disease (AD) is characterized by two neuropathological hallmarks, extracellular amyloid β (A β) deposits in the brain parenchyma (amyloid plaques) and cerebral blood vessels (cerebral amyloid angiopathy, CAA) and abnormal aggregates of hyperphosphorylated tau protein in brain neurons (neurofibrillary tangles, NFTs). Amyloid plaques and NFTs are accompanied with neuroinflammation including activated microglia and increased levels of cytokines (1). Profound loss of neurons and synapses is also found in AD dementia. Except a small subset of

early-onset familial AD cases, the causes for the vast majority of AD cases are unknown and satisfactory therapeutic and preventive measures for AD are unavailable. Therefore, an urgent need exists to identify the molecular mechanisms that increase the risk for the vast majority of AD cases and to develop the preventive and therapeutic measures. Increasing lines of evidence indicate that central and systemic inflammation promotes AD progression and even initiates neurodegeneration (2–7). Indeed, recent genetic studies on late-onset AD have discovered about a dozen risk alleles that modulate innate immune activities and are highly expressed in brain-resident macrophages, microglia, highlighting the importance of immune responses and microglia in the pathogenesis of late-onset AD (8–10). Aging is the largest known risk factor for AD and represents chronic, systemic inflammation (inflamm-aging) (6, 11–13). Additionally, almost all highly ranked, modifiable risk factors for AD such as diabetes, obesity, hyperlipidemia, and hypertension are characterized by chronic, systemic inflammation (14–19). Inflammation caused by certain bacterial and viral infections is a risk factor of dementia (20–23). However, the precise molecular mechanisms by which inflammation increases the risk of AD remain to be elucidated. Here we discuss the impact of three innate immune signaling pathways including TLR4, NLRP3 inflammasome, and complement on the pathogenesis of AD.

TLRS AND ITS SIGNALING PATHWAYS

In responses to a variety of invading pathogens and tissue damages, the innate immune system initiates inflammatory responses through activation of pattern recognition receptors (PRRs) (24). PRRs recognize pathogen-associated molecular patterns (PAMPs), conserved structures commonly identified among different microorganisms, as well as damage-associated molecular patterns (DAMPs), molecules shed by injured cells. Currently identified classes of PRR families comprise the Toll-like receptors (TLRs) and C-type lectin receptors (CLRs), the Retinoic acid-inducible gene (RIG)-I-like receptors (RLRs) and the nucleotide-binding oligomerization domain (NOD)-Leucine Rich Repeats (LRR)-containing receptors (NLRs), and secreted proteins such as complement proteins (25, 26). TLRs are composed of an extracellular and cytoplasmic domain that belongs to a type I transmembrane receptor and recognize TLR ligands through the extracellular domain. TLR ligands can be either exogenous (PAMPs) or endogenous (DAMPs). At least 10 and 12 functional TLRs have been reported in human and mouse, respectively. The activation of TLRs by TLR ligands initiates both innate and adaptive immune responses (25, 27). TLR ligation initiates a signaling cascade that leads to activation of transcription factors that upregulate a number of target genes encoding cytokines, chemokines, growth factors, and other inflammatory mediators. Activation of TLR by pathogens and injured cells also induces phagocytic activities of macrophages/microglia and clears pathogens, damaged tissues and buildup wastes (28–31). The cytoplasmic domain of TLRs is termed Toll/interleukin-1 (IL-1) receptor (TIR) domain. TLR activation by TLR ligands initiates interaction of TLR's TIR domain with TIR domains of adaptors such as MyD88 and TRIF. Different TLRs utilize distinctive adaptor

molecules, resulting in different signaling responses (**Figure 1**). TLR1, TLR2, TLR4, TLR5, and TLR6 are located on the cell surface membrane and recognize mostly bacterial products. TLR3, TLR7, TLR8, and TLR9 sense mostly bacterial and viral nucleic acids and are localized to intracellular vesicles including the endoplasmic reticulum, endosomes, lysosomes, and endolysosomes (32). All TLRs, with the exception of TLR3, use MyD88 as an adaptor. The ligation of TLR2 and TLR4 culminates in activation of transcription factors, NF- κ B and AP1, through the MyD88-dependent pathway that is essential for expression of cytokines, chemokines and co-stimulatory molecules, such as TNF- α , IL-1 β , IL-6, IL-8, IL-12, and MIP1 α . TLR3 and TLR4 ligation can mediate signaling through the MyD88-independent (TRIF-dependent) pathway, leading to the activation of interferon regulatory factor 3 (IRF3). The activation of IRF3 induces expression of type I interferon (IFN) genes such as IFN β and IFN-inducible genes (**Figure 1**). TLR3 and TLR4 ligation can activate NF- κ B, also, via the TRIF-dependent pathway, resulting in induction of inflammatory cytokines (**Figure 1**). In TRIF-dependent signal transduction, the TLR4-lipopolysaccharide (LPS) complex on the plasma membrane is internalized to endosomes, where it triggers TRIF-dependent signal transduction (33). Importantly, although robust expression of inflammatory cytokines via MAP kinase and NF- κ B activation is achieved by synergistic activation of both TRIF-dependent and MyD88-dependent pathways, TLR4 ligands can produce type I IFN solely through TRIF-dependent pathway activation (27, 34). TLR9 and TLR7 ligation can activate both IRF7 and NF- κ B, leading to induction of type I IFNs and inflammatory cytokines, respectively [**Figure 1**; (25, 27)]. TLR signaling produce a number of genes involved in phagocytosis and inflammation through activation of transcription factors such as NF- κ B, IRF3 and IRF7 (25, 35, 36).

Neurodegenerative diseases are characterized by progressive loss of specific synapses and neurons as well as abnormally aggregated proteins such as A β in AD (amyloid plaques) and α -synuclein in Parkinson's disease (Lewy bodies). Microglia are the principal innate immune cells in the CNS and modulate brain development, homeostasis and neuroinflammation in diseases and aging. Microglia express multiple classes of PRRs including all TLRs and respond to a variety of PAMPs and DAMPs through PRRs (37). DAMPs released from damaged or degenerating neurons and abnormally aggregated A β and α -synuclein (38, 39) activate microglia via PRRs, which may modulate progression of neurodegenerative diseases. Since aggregated A β has been shown to activate innate immune cells by interacting with several TLRs (see below), it may be possible to reduce A β load and neuronal injuries in the AD brain by regulating TLR signaling. However, it remains to be determined which TLR signaling pathways and effectors are involved in modulation of A β deposition, clearance and neuronal injuries in the brain.

ROLE OF TLR4 SIGNALING IN ALZHEIMER'S DISEASE BRAIN

Large-scale genome-wide association studies on late-onset AD have discovered a dozen genetic risk alleles that are

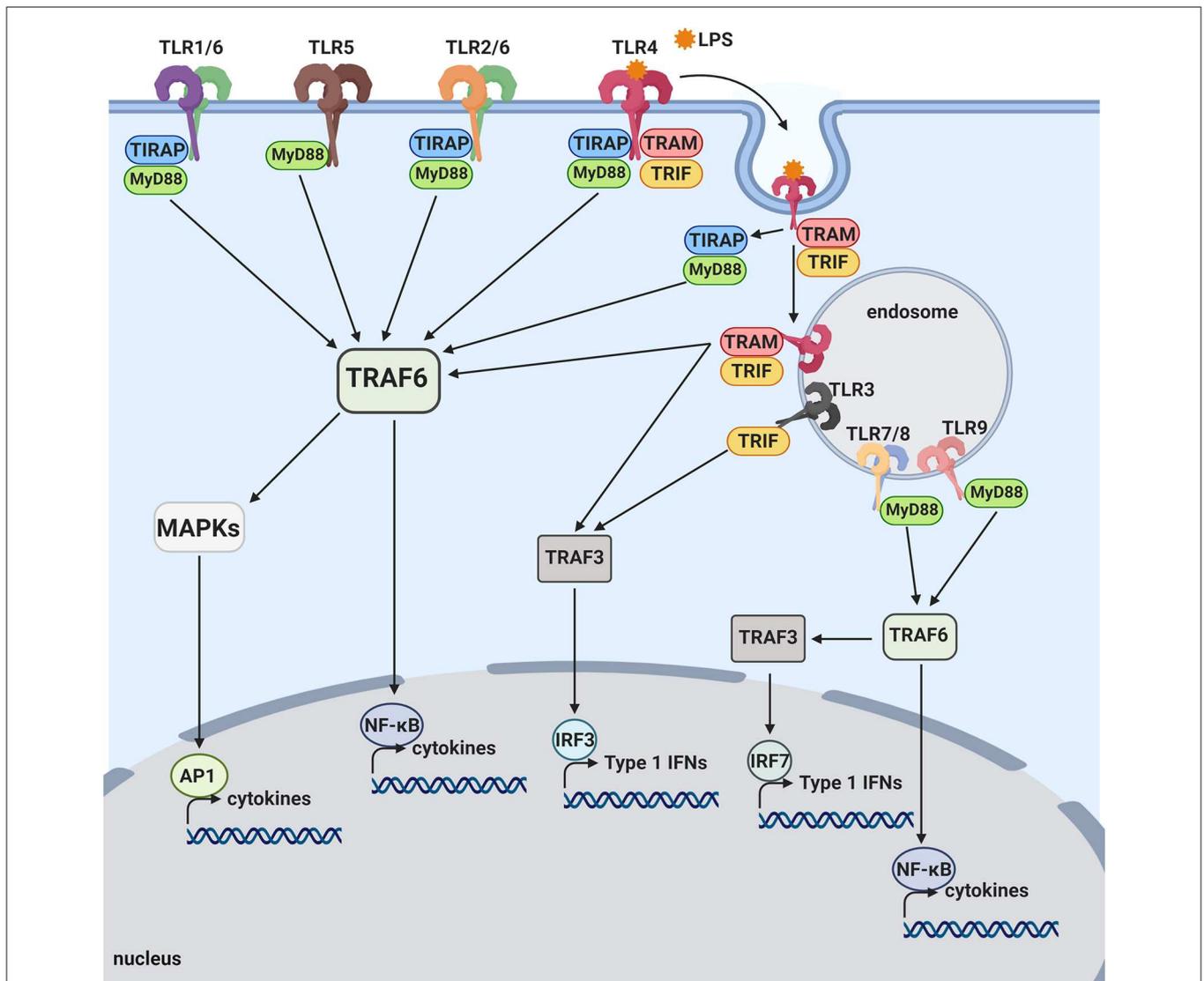


FIGURE 1 | Toll-like receptor pathways. TLR1, TLR2, TLR4, TLR5, and TLR6 are mostly expressed on the cell surface and bind to bacterial products. When activated by LPS, TLR4 is internalized onto an endosome surface. The internalization triggers the release of TIRAP/MyD88, activating the TRAF6 pathway and resulting in activation of transcription factors, NF- κ B and AP-1. The release of TIRAP/MyD88 from TLR4 allows for the signaling by TRAM/TRIF to commence from the endosome, also activating NF- κ B as well as the transcription factor, IRF3. TLR3, TLR7, TLR8, and TLR9 are located on internal vesicles and bind to bacterial and viral nucleic acids. TLR7, TLR8, and TLR9 each activate NF- κ B, as well as the transcription factor, IRF7, through the MyD88 pathway. TLR3 is the only toll-like receptor that does not activate via the MyD88 pathway and instead activates NF- κ B and IRF3 through the TRIF pathway.

involved in immune/inflammatory responses and highly expressed in microglia, highlighting the importance of microglial inflammatory responses in the pathogenesis of late-onset AD. Such risk loci include APOE, TREM2, CLU, CR1, MS4A6A, MS4A4E, CD33, ABCA7, EPHA1, HLA-DRB5 & DRB1, INPP5D, and MEF2C (8, 9). Their potential roles and functions in TLR4-complement-NLRP3 signaling, are summarized in **Table 1**. Particularly, APOE (43), CD33 (47), INPP5D (57), and TREM2 (66) have been shown to negatively regulate TLR4 signaling. CR1 can inhibit inflammasome activation by suppressing the complement activation pathways (52). However,

activation of microglial CR1 induces neurotoxic cytokines and reactive oxygen species (53). Although TREM2 is found to upregulate complement components during aging (69), it can inhibit inflammasome activation (67). CD33 may induce NLRP3 inflammasome assembly (48). APOE (46) and CLU (50) inhibit complement activation and reduce inflammation.

Previously, a coding variant of TLR4 (rs4986790) was reported to increase longevity and reduce an AD risk in Italian cohorts (71, 72). Recently, this observation has been confirmed in independent cohorts (Quebec Founder Population and presymptomatic individuals with a parental history of

TABLE 1 | AD risk genes involved in inflammatory responses.

Genes	TLR4	References	Inflammasome	References	Complement	References	Functions
ABCA7	No		No		No		Involved in lipid homeostasis; enhances A β clearance by macrophages (40, 41)
APOE	Yes	(42–44)	Maybe	(45)	Maybe	(46)	Involved in lipid metabolism (42–44)
CD33	Yes	(47)	Maybe	(48)	Maybe	(49)	Inhibitory receptor exclusive to immune cells (47)
CLU	No		No		Yes	(50)	Inhibitor of complement receptors (50)
CR1	Yes	(51)	Yes	(52)	Yes	(53)	Influences complement cascade; binds C1q; inhibits formation of MAC (52, 54)
EPHA1	No		No		No		Promotes permeability of the blood-brain barrier (55, 56)
HLA-DRB1	No		No		No		Creates beta chain 1 of the MHC class II protein complex
HLA-DRB5	No		No		No		Creates beta chain 5 of the MHC class II protein complex
INPP5D	Yes	(57, 58)	No		No		Binds DAP12 which inactivates the TREM2-DAP12 signaling complex (59)
MEF2C	Maybe	(60)	No		No		Regulates apoptosis of T cells and is necessary for transcriptional activation of IL-2 (61, 62)
MS4A cluster (MS4A4E and MS4A6A)	Maybe	(63)	No		Maybe	(63)	Ligand binding promotes calcium conductance; may modulate TREM2 expression (and TLR/complement through TREM2) (63)
TLR4 variant (rs4986790)	Yes		Yes		No		Altered ability to recruit MyD88 and TRIF (64)
TREM2	Yes	(65, 66)	Maybe	(67)	Yes	(68, 69)	Found on myeloid cells and alters inflammatory functions (70)

AD), demonstrating the association of the TLR4 variant with a reduced AD risk, better visuospatial and constructional skills, an increased cortical thickness in visual cortices, and stable IL-1 β levels in cerebrospinal fluid (CSF) over time (73). Additionally, certain TLR4 gene variants are associated with an increased risk of AD in the Chinese population (74–76). These associations of TLR4 with AD in different populations indicate an important role of TLR4 in the AD pathogenesis.

Microglia, brain resident phagocytes in the innate immune system, are thought to be macrophages in the central nervous system. Fibrillar A β deposits are closely associated with activated microglia in the brain (1). Microglia interact with fibrillary A β through their cell surface receptor complexes leading to A β phagocytosis and inflammation. Using cultured microglia, the receptor complexes of microglia, which recognize A β fibrils, have been shown to contain TLR2, TLR4 and their co-receptor, CD14, as indispensable constituents of the receptor (77–79). Activation of microglia by TLR2, TLR3, TLR4, TLR7, and TLR9 ligands boosts ingestion and/or clearance of A β by microglia *in vitro* (78, 80–84). In line with these *in vitro* experiments, an acute (one-time) injection of LPS, a TLR4 ligand, into the brains of AD mouse models activated microglia and decreased A β plaques (85–87). Additionally, activation of microglia by intracerebroventricular injection of CpG-oligodeoxynucleotides (ODN), a TLR9 ligand, reduced brain A β deposits and ameliorated cognitive deficits in Tg2576 mice (an AD mouse model) (80, 88–91). However, sustained brain injection of

LPS induced premature cerebral A β deposits and cognitive impairments in AD mouse models (92–94).

APP/PS1 mice (an AD mouse model) homozygous for a loss-of-function mutation (Tlr^{Lps-d}/Tlr^{Lps-d}) of TLR4 had greater cerebral A β load and poorer spatial learning than APP/PS1 mice with TLR4 wild-type alleles (81, 95). AD mouse models show increases in brain cytokine levels including TNF- α , IL-1 β , IL-17, and IL-10. Such increases in the brain cytokines were abolished in APP/PS1 mice with the TLR4 mutation, indicating TLR4-dependent upregulation of the cytokines in APP/PS1 mice (96). However, TLR4-dependent upregulation of cytokines and microglial activation were not observed in young APP/PS1 mice before A β deposition (95, 96). Additionally, TLR2 deficiency in an AD mouse model [APP^{Swe}/PS1(A246E)] increased brain A β 42 levels (toxic form of A β) and accelerated spatial and contextual memory impairments (97). These *in vivo* data suggest that activation of certain TLRs can be therapeutic option for AD. However, APP/PS1 mice defective for CD14 (CD14 gene knockout), a co-receptor for TLR4, showed a decrease in A β plaques (98). MyD88 deficiency decreased cerebral A β load and improved behavioral deficits in APP/PS1 mice (99). Additionally, transplantation of bone marrow cells with MyD88 deficiency in an AD mouse model ameliorated brain A β levels and cognitive deficits much better than MyD88-sufficient bone marrow cells (100). The latter experiments indicate that activation of certain TLRs can be detrimental to the AD progression. These experimental results also indicate that the *in vitro* data can be misleading perhaps due to oversimplification

of the *in vitro* systems as well as difficulties in mimicking chronic activation of TLRs in the *in vitro* systems. Accordingly, *in vivo* experiments in detail in TLR ligand treatment regimen, age, sex and genetic background of experimental animals are indispensable for a better understanding of the roles of the TLR signaling pathways in the AD pathogenesis.

ROLE OF TLR4 SIGNALING IN SYSTEMIC INFLAMMATION IN ALZHEIMER'S DISEASE (AD)

There are increasing lines of evidence that systemic inflammation promotes AD progression and initiates microglial activation and neurodegeneration (2–7). Aging is the largest known risk factor for AD and is characterized by chronic, systemic low-grade inflammation, referred to as “inflamm-aging” (11–13). Additionally, highly ranked, modifiable risk factors for AD such as depression, hypertension, diabetes, obesity, and hyperlipidemia are characterized by a chronic, systemic low-grade inflammation (14–19). For example, visceral adipose tissue of obese subjects contains innate and adaptive immune cells and shows low-grade chronic inflammation, which is identified as a major contributor to the advancement of metabolic diseases including type 2 diabetes mellitus and coronary heart diseases (101, 102). Indeed, when a diabetic AD mouse model was produced by crossing APP23 mice (an AD model) with leptin-deficient (*ob/ob*) mice, the onset of diabetes exacerbated cognitive deficits, cerebral amyloid angiopathy, and cerebrovascular inflammation (103). A high-fat diet increased insoluble cerebral A β and soluble tau in the brains of 3xTg-AD mice (an AD model) (104). Low-grade inflammation plays a pivotal role in the initiation, progression, and propagation of the atherosclerotic process (105, 106). Atherogenic diet exacerbated cognitive deficits and cerebral A β deposits in Tg2576 mice (an AD mouse model) and the aortic atherosclerotic lesion area positively correlated with cerebral A β deposits (107). Certain peripheral, as well as CSF inflammatory markers, such as IL-6 and C-reactive protein (CRP) have been reported to forecast dementia or decline in cognitive functions many years before their onset (106, 108–113). These AD risk factors have been shown to be associated with altered TLR4 signaling. The TLR4 +896A/G coding variant (rs4986790) is underrepresented in patients with myocardial infarction, Alzheimer's disease or prostate cancer, whereas it is more frequently found in centenarians in Italian and Canadian cohorts (71–73). Their blood samples produce less IL-6, TNF- α , and eicosanoids (PGE2 and LTB4) in response to LPS, compared to other TLR4 genotypes (114). Anti-aging effects of caloric restriction is associated with downregulation of the TLR4/MyD88/NF- κ B pathway in rodents (115). Apolipoprotein E (ApoE)-deficient mice are prone to high-fat diet-induced atherosclerosis, which is reduced in additional TLR4-deficiency or MyD88-deficiency, indicating an important role of TLR4/MyD88 signaling in atherosclerosis (116). Activation of TLR4 contributes to insulin resistance by impairing insulin signal transduction via inhibitory phosphorylation on serine residues in insulin receptor substrate

(IRS) (117). Therefore, these AD risk factors may contribute to the AD development via TLR4 signaling.

Systemic infections are also associated with AD although not all studies found such associations. Infection of certain bacteria including *Helicobacter pylori*, *Porphyromonas gingivalis*, *Chlamydia pneumoniae*, and *Borrelia burgdorferi*, has been found to be risk factors for the development of dementia (20–22, 118, 119). In an AD mouse model (APP/PS1 mice), *Bordetella pertussis* respiratory challenge led to T cell infiltration into the brain and increased microglial activation and A β deposition (120). Peripheral injections of TLR ligands such as LPS and poly I:C, TLR4 and TLR3 ligand, into animals and humans have been commonly implemented to mimic bacterial and viral infections, respectively. Repeated peripheral LPS injection in wild type mice led to cognitive deficits and increases in cerebral A β levels and apoptotic cells (121, 122). A single intravenous poly I:C injection into 4-month-old 3xTg-AD mice increased cerebral A β deposits and altered tau phosphorylation at age 15 months. Additionally, systemic exposure to poly I:C during late gestation in wild type mice increased cerebral APP (A β precursor protein) levels, altered tau phosphorylation and cognitive function in old ages and these phenotypic alterations were exacerbated when the prenatal exposure was followed by a second challenge during their adulthood (123). Repeated systemic injection of LPS induced premature cerebral A β deposits and cognitive impairments in AD mouse models (92–94). Repeated intraperitoneal injection of LPS activated microglia and increased tau phosphorylation in an AD mouse model (3xTg-AD) (124). Daily intraperitoneal LPS injection in Kunming mice for 7 days induced microglia activation, upregulation of proinflammatory cytokines (both mRNA and protein) including IL-1 β , TNF- α , and IL-6, synapse loss, and impairment of learning and memory (125). Acute intraperitoneal LPS injection also increased tau phosphorylation in the hippocampal neurons of C57BL/6 mice (126, 127). Furthermore, periodontitis evoked by inoculation of *Porphyromonas gingivalis* exacerbated brain A β deposition and cognitive deficits in an AD mouse model (J20 PDGF-APP^{Sw-Ind} mice) (128). Repeated intraperitoneal injection of LPS derived from *Porphyromonas gingivalis* induced cognitive deficits, intraneuronal A β accumulation, microglial activation, and increases in IL-1 β in middle-aged (12 months) wild-type C57BL/6 mice but not in young (2 months) mice (129). These findings support the hypothesis that systemic inflammation promotes AD progression and even initiates AD-like pathological changes. Indeed, peripheral LPS administration has been widely used to model neuroinflammation and neurodegenerative diseases including AD in rodents and the lists of such experimental models are found in the following review papers (130–133). Importantly, TLR4 in brain-resident immune cells plays a predominant role in sustained neuroinflammation including IL-1 β upregulation, which is induced by systemic LPS administration rather than TLR4 in peripheral immune cells (134). However, the precise mechanisms by which systemic inflammation contributes to AD initiation and progression remain to be elucidated.

So far, as we discussed above, almost all chronic, systemic inflammatory events predominantly exert pro-inflammatory

responses in brain microglia, leading to exacerbation of neurodegenerative diseases including AD. Recently, Wendeln et al. (135) reported that one-time peritoneal injection of LPS prior to brain A β deposition (at 3 months of age) in an AD mouse model primed microglia and exacerbated the brain A β load 6 months later while 4 consecutive peritoneal injections of LPS (0.5 mg/kg) induced tolerance and reduced the A β load. Additionally, chronic intraperitoneal administration of CpG-ODN (TLR9 ligand) and monophosphoryl lipid A (MPL, TLR4 ligand) reduced A β plaques and NFTs, and restored cognitive deficits in AD mouse models (80, 88–91). However, the precise mechanisms, by which the repeated TLR ligand treatments improve AD-like pathophysiology are unclear. One possible explanation is that the repeated TLR ligand treatments increase stress resistance or adaptation/tolerance of microglia, leading to reduced inflammatory responses of microglia, alleviation of AD-like pathology, and cognitive deficits (136). It is important to understand that systemic inflammatory events as well as peripheral treatment with TLR ligands can shape the phenotype of microglia in the CNS. These results suggest that modulation of brain microglial phenotype by peripheral treatment with certain TLR ligands at appropriate doses and treatment intervals can be therapeutic and/or preventive to AD.

NLRP3 INFLAMMASOME AND AGING

Inflammasomes consist of multimeric protein complexes in the cytoplasm, which mediate activation of IL-1 β and IL-18 and induce pyroptosis, a programmed cell death. Inflammasomes are involved in initiation and sustainment of the innate immune response (137). The NLRP3 inflammasome consists of a sensor (NLRP3), and adaptor (ASC or PYCARD) and an effector (caspase 1) (138). Activation of the NLRP3 inflammasome and the production of IL-1 β are tightly regulated and require two triggering steps, a priming step and an activation step (Figure 2). In the priming step, expression of the inflammasome components (NLRP3, caspase 1 and pro-IL-1 β) needs to be upregulated to their suitable expression levels for inflammasome activation. This upregulation can be induced by various PAMPs or DAMPs, including LPS or amyloid, respectively, through activation of PRRs and cytokine receptors, including TLRs and IL-1R, respectively (138). In the activation step, NLRP3 can be activated by a large number of stimuli such as endogenous DAMPs, PAMPs, efflux of potassium (K⁺) or chloride (Cl⁻) ions and flux of calcium ions (Ca²⁺) (138).

The biggest risk factor for Alzheimer's disease is advanced age (139). Aging is characterized by systemic low-grade inflammation, referred to as "inflamm-aging" (11–13) and senescent cells are characterized by the senescence-associated secretory phenotype (SASP), indicating proinflammatory characteristics including increased secretion of IL-1 β , IL-6, IL-8, TGF- β , and TNF- α (140). IL-1 β production increases during aging in the mouse brain, which is exacerbated by intraperitoneal injection of LPS (1 mg/kg), (141, 142). IL-1 β , IL-6, TGF- β , and TNF- α levels are elevated in AD brain tissue,

as well as in AD patients' CSF and serum (143). Fibrillar A β induces more IL-1 β production in microglia isolated from aged mice than those derived from young mice (144). NLRP3 deficiency ameliorates central and peripheral low-grade inflammation and SASP and improves cognitive function and motor performance in aged mice (141). IL-1R deficiency (Il1r^{-/-}) also ameliorates cognitive decline associated with aging in mice (141). Thus, inhibition of NLRP3 inflammasome can be a therapeutic and preventive target for age-related chronic diseases including AD.

ROLE OF NLRP3 INFLAMMASOMES IN ALZHEIMER'S DISEASE BRAIN

Fibrillar A β can induce IL-1 β release from cultured microglia in an NLRP3-dependent and ASC-dependent manner, where NLRP3 serves as a sensor of aggregated A β for inflammasome activation (145). ASC deficiency decreases brain A β deposits and improves cognitive deficits in APP/PS1 mice. Injection of ASC specks induces spreading of A β deposits in APP/PS1 mice. However, this is not observed in ASC-deficient APP/PS1 mice, and co-administration of anti-ASC antibody blocks the spreading of A β pathology. Thus, ASC specks released from pyroptotic microglia induce seeding and spreading of A β oligomers and aggregates, leading to AD progression (146). NLRP3 or caspase-1 deficiency in APP/PS1 mice leads to reduced brain caspase-1 and IL-1 β activation, increased microglial A β phagocytosis, reduced brain A β load, and protection of neuronal spine loss, long-term potentiation (LTP) decline, and cognitive deficits (147). However, the reduced A β load in NLRP3-deficient APP/PS1 mice is discernible at 16 months of age but not at 4 months of age (147). In patients with early AD or mild cognitive impairment due to AD, levels of IL-1 β and caspase-1 activity are significantly increased (147, 148) and ASC-bound A β is found in AD patients' brains (146). These observations suggest that NLRP3 inflammasome activation represents an early pathogenic event in AD. Intrastriatal injection of fibrillar A β in mice causes microglial activation, which is inhibited in mice with MyD88 deficiency, ASC deficiency, caspase-1 deficiency, or IL-1R deficiency (145), suggesting that aggregated A β initiates a signaling cascade involving MyD88, NLRP3 inflammasome, and IL-1 β . In line with these observations, MyD88-deficiency decreases microglial activation and cerebral A β load and improves behavioral deficits in APP/PS1 mice (99, 149). Moreover, MyD88 deficiency enhances A β phagocytosis by microglia/macrophages *in vitro* and bone marrow reconstitution by MyD88-deficient cells reduces A β load and improves cognitive functions more efficiently compared with MyD88-sufficient cells in AD mouse models including APP/PS1 and TgCRND8 mice (100). Expression levels of IL-1 β mRNA and protein are upregulated in the brains of APP/PS1 mice compared to those in age-matched APP/PS1 mice with a loss-of-function TLR4 mutation at 9–15 months of age but not at 5 months (95, 96). These findings suggest that TLR4/MyD88 signaling is involved in the priming step of NLRP3 inflammasome activation in AD mouse models (Figure 2).

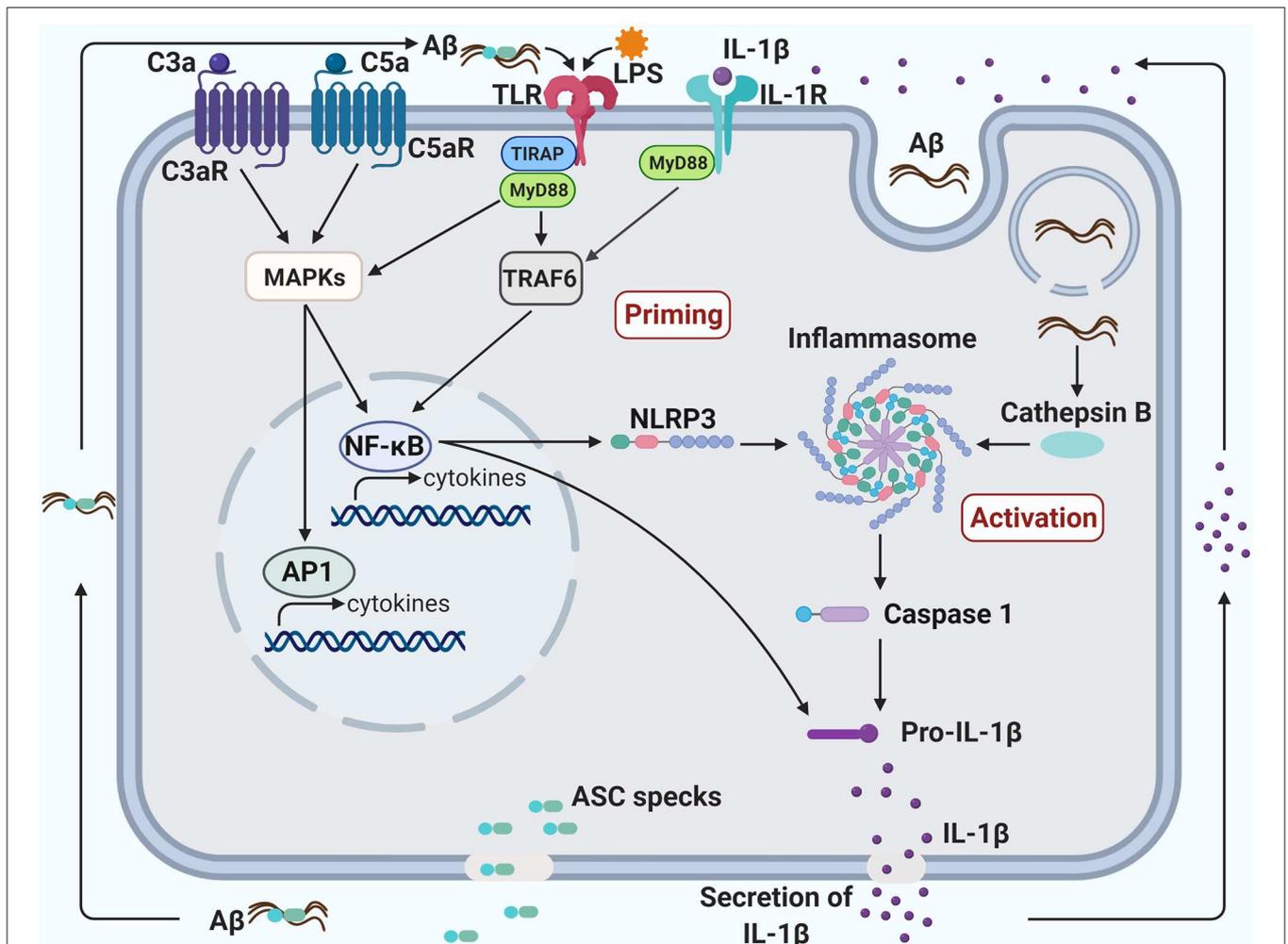


FIGURE 2 | Crosstalk between TLR4, NLRP3 inflammasome, and complement promotes neuroinflammation in Alzheimer’s disease. Priming of the inflammasome occurs when the transcription factor, NF-κB, is activated, triggering the production of both NLRP3 and Pro-IL-1β. NF-κB can be activated via the TLR/IL-1R MyD88-dependent pathway and the C3/C5 MAPK pathway. The TLR pathway can be induced by a bacterial component, such as LPS, and the MAPK pathway can be induced by C3a/C5a binding to their respective receptors. The activation of NF-κB through complement, TLR and IL-1R pathways may create a synergistic increase in pro-inflammatory factors. The inflammasome can be activated in several ways, including an increase of endogenous damage-associated and pathogen-associated molecular patterns or an efflux of potassium or chloride ions. Additionally, aggregated fibrillary Aβ engulfed by the microglia can damage the lysosome and leak into the cytoplasm, also contributing to the activation of the inflammasome. Activation of the inflammasome can induce pyroptosis, leading to the secretion of IL-1β and ASC specks. ASC specks bind to Aβ and seed the surrounding parenchyma leading to further Aβ aggregation. Aggregated Aβ can also bind to TLR and induce activation of the MyD88 pathway. Likewise, IL-1β secreted from the pyroptotic microglia can bind to IL-1R and induce activation of the MyD88 pathway. The induction of the MyD88 pathway through the by-products of microglial pyroptosis may lead to a vicious cycle of inflammasome priming, inflammasome activation and pyroptosis that will exacerbate Aβ pathology.

In addition to a crucial role of the NLRP3 inflammasome in Aβ pathophysiology in AD, tau pathology is influenced by NLRP3 activation (150). NLRP3 or ASC deficiency decreases tau hyperphosphorylation and aggregation by regulating tau kinases (GSK-3β and CaMKII-α) and phosphatases (PP2A) in Tau22 mice that express tau mutations found in frontotemporal dementia. Intracerebral injection of fibrillar Aβ-containing brain homogenates enhances tau phosphorylation and aggregation in Tau22 mice, which is blocked by NLRP3 or ASC deficiency (150), suggesting that Aβ-induced NLRP3 inflammasome activation exacerbates tau pathology in AD and its animal models.

ROLE OF NLRP3 INFLAMMASOMES IN SYSTEMIC INFLAMMATION IN ALZHEIMER’S DISEASE

LPS is a potent TLR4 ligand and its systemic administration is widely used to model systemic inflammation. A list of animal models summarizing the effects of LPS treatment on NLRP3 inflammasome activation is found in an excellent review article by Heneka et al. (151). Several papers have reported microglial NLRP3 inflammasome activation after peripheral LPS injection. Single intraperitoneal injection of LPS (5 mg/kg) in

C57BL/6 (B6) mice induced microglial activation, upregulation of NLRP3, ASC, caspase-1p10, and IL-1 β in the hippocampus, leading to behavioral alterations (depression like behavior and memory deficits) for 29 days after LPS injection, which were inhibited by a NLRP3 inhibitor (152). Intraperitoneal injection of LPS (3.5 mg/kg) in B6 mice induced activation of microglia and NLRP3 inflammasome, and increased IL-1 β expression in CNS, which were exacerbated by microglia-specific A20 (NF- κ B inhibitor) deficiency but not by deficiency in other cell types (neuron, astrocyte, and oligodendrocytes) (153). Intraperitoneal injection of LPS (0.5 mg/kg) in B6 mice induced activation of microglia, increases in NLRP3, ASC, caspase-1 and IL-1 β in the hippocampus, and depressive behavior (154) and such effects by LPS (1 mg/kg) were inhibited in NLRP3-deficient mice (155). Intraperitoneal injection of LPS (1 mg/kg) in APP/PS1 mice at 15 months of age induced decreases in A β uptake by microglia, increases in the number and size of A β deposits and in peripheral myeloid cells that infiltrated into the brain but not at 5 months of age (156). Such changes by intraperitoneal LPS injection were blocked by NLRP3 deficiency. These results suggest that systemic LPS administration induces microglial NLRP3 inflammasome activation, increased brain A β load and brain infiltration of peripheral myeloid cells in an age dependent manner, leading to exacerbation of AD pathophysiology.

TLR/IL-1R/MYD88 SIGNALING IN SUSTAINED VICIOUS CIRCLE OF NLRP3 INFLAMMASOME ACTIVATION IN ALZHEIMER'S DISEASE

LPS is often used to prime NLRP3 inflammasome (157). LPS can induce canonical and non-canonical NLRP3 inflammasome activation (138). In canonical inflammasome priming, activated TLR4 by LPS signals through the adaptor protein, MyD88, culminating in activation of transcription factor, nuclear-factor- κ B (NF- κ B), that elevates pro-IL-1 β and NLRP3 expression (158, 159). Toll-like receptors (TLRs) including TLR2, TLR4, TLR6, and their co-receptor, CD14, are indispensable constituents of the receptor complexes for microglial activation by A β , leading to cytokine and chemokine production (78, 79, 95). Extracellular fibrillary A β can prime the canonical inflammasome pathway by activating the TLR/MyD88/NF- κ B signaling pathway [Figure 2; (160, 161)]. In the activation step, phagocytosed A β in microglia leads to lysosomal damage and liberation of cathepsin B and/or production of mitochondrial reactive oxygen species, which trigger formation of the NLRP3 inflammasome complex, causing caspase 1 activation, IL-1 β production and pyroptosis (145, 162). Oligomeric and fibrillar A β can directly interact with NLRP3 and ASC, resulting in NLRP3 inflammasome activation, also (163). ASC specks released by microglial pyroptosis quickly bind to extracellular A β and induce seeding and spreading of A β oligomers and aggregates (146). Aggregated A β further promotes microglial inflammasome priming via TLR/MyD88 signaling. Additionally, secreted IL-1 β also induces microglial inflammasome priming via IL-1R/MyD88 signaling (164). Thus, this vicious circle of NLRP3 inflammasome activation by

TLR/IL-1R/MyD88 signaling may lead to chronic/sustained inflammation and neurodegeneration in AD (Figure 2).

COMPLEMENT IN AGING BRAIN

Complements belong to the pattern recognition receptors in the innate immune system and involved in recognition and clearance of pathogens, damaged tissues, aggregated proteins, and toxic wastes (165, 166). Additionally, complement proteins have been implicated in diverse processes during brain development, aging and neurological diseases (26). Virtually all complement components are locally expressed in the brain and microglia express almost all classical complement components and their receptors including C1qR, CR3, C3aR, and C5aR (167, 168). Particularly, complement and microglia play an important role in synaptic pruning, that is, complement-tagged synapse elimination by microglia, during neural development, aging, and neurodegenerative diseases (169). In the normally developing brain, opsonization of synapses by complement factors (tagged by C1q, C3b, and C4) triggers microglial phagocytosis, resulting in elimination of the tagged synapses.

During normal brain aging in human and mouse, C1q protein levels dramatically increase in certain regions of the brain, including the hippocampus, substantia nigra, and piriform cortex. Aged mice with C1q deficiency exhibit significantly less cognitive and memory decline compared with wild-type mice (170). Marked increases in C1q levels are found in dendritic spines at synapses in the aged rhesus macaque dorsolateral prefrontal cortex as well as glia ensheathed synapses, suggesting C1q-tagged synapse elimination by glial phagocytosis as a possible mechanism for age-related degeneration (171). C57BL/6J (B6) mice (at 16 months of age) show age-dependent neuron loss in hippocampal CA3 but not in CA1, which is not observed complement C3-deficient B6 mice. Additionally, aged C3-deficient B6 mice show better cognition and LTP than wild-type B6 mice, implying that C3 is also involved in age-dependent synapse loss and cognitive decline (172).

ROLE OF COMPLEMENT IN ALZHEIMER'S DISEASE BRAIN

In AD, the degree of region-specific synapse loss better correlates with cognitive decline than amyloid plaques, NFTs and neuron loss (173, 174) and genetic variants of complement receptor 1 (CR1) and clusterin (CLU, apolipoprotein J), which are parts of the complement system, are identified as AD risk factors by genome wide association studies (175). Certain components of complements including C1q, C3, C4, and C5b-C9 (membrane attack complex, MAC) accumulate in amyloid plaques and NFT in the brains of AD patients (176–179). A positive correlation is found between expression levels of C3 and C3a receptor (C3aR1) in the brain and cognitive decline and Braak staging in AD patients (180). Additionally, CD57 that prevents MAC assembly is decreased in AD brain (181). CSF and plasma levels of certain complement proteins

have been reported as promising biomarkers for AD diagnosis and progression (182–186). These observations suggest that activation of the complement system may contribute to the AD pathogenesis.

C1q deficiency decreases plaque-associated glial activation and mitigates progressive decreases in synaptic markers in Tg2576 mice without changes in brain A β load (187). In J20 mice (an AD mouse model), upregulation and deposition of C1q onto synapses precedes synaptic loss in the hippocampus before overt amyloid plaque formation (188). The toxic effects of A β oligomers on synapse loss and LTP inhibition are blocked by C1q deficiency or its inhibitor in mice (188). C1q tags tau-affected synapses and microglia eliminate C1q-tagged synapses by engulfment in PS19 mice (a frontotemporal dementia model). This process is inhibited by C1q-blocking antibodies (189). LPS and A β increases production of C3 in primary microglial cultures in a dose dependent manner (190). A β oligomer-induced synaptic engulfment by microglia is inhibited by CR3 deficiency in adult mice and inhibition of C3 or microglial CR3 decreases A β oligomer-induced synapse loss (188). C3 deficiency ameliorates age-dependent loss of synapses and neurons, and cognitive deficits in aged APP/PS1 mice although it increases cerebral A β deposits (191). C3 deficiency mitigates amyloid plaque-associated synapse loss in another AD model mice, PS2APP, and rescues neuron loss and LTP deficits in PS19 mice (192). Similarly, C3aR1 deficiency mitigates tau pathology, neuroinflammation, synaptic deficits and neurodegeneration in PS19 mice (180). Activation of microglia by LPS or A β increases sialidase activity and desialylation of the microglial surface, leading to stimulation of CR3-mediated phagocytosis of neurons by microglia in primary glial-neuronal co-cultures. This neuronal loss by microglial phagocytosis is inhibited by a blocking antibody against CD11b (a component of CR3) and a sialidase inhibitor (193). Oral administration of a C5a receptor antagonist (PMX205) decreases A β deposition and glial activation in Tg2576 and 3xTg mice, improves cognitive deficits in Tg2576 mice and reduces tau hyperphosphorylation in 3xTg mice (194). These observations support the hypotheses that complement activation exacerbates the AD progression and that the complement signaling pathway that regulates pruning of excess synapses by microglia during brain development is inadequately initiated and mediates synapse loss and neurodegeneration in AD.

In contrast with these hypotheses, the other investigators found beneficial effects of complement activation. C1q has been reported to have a protective effect against neurotoxic A β fibrils and oligomers by activating cAMP-response element-binding protein and AP-1, resulting in upregulation of LRP1B and G protein-coupled receptor 6 (GPR6), in cultured neurons as well as 3xTg mice (195). Additionally, genetic deficiency of C3 increases A β deposition and induces neurodegeneration and alternative activation (M2) of microglia in aged J20 mice (17 months) (196). Inhibition of C3 by overexpressing soluble complement receptor related protein γ (sCr γ) increases A β deposition and neurodegeneration in J20 mice (197). These findings support the notion that activation of these complement components is neuroprotective.

ROLE OF COMPLEMENT IN SYSTEMIC INFLAMMATION IN NEURODEGENERATION

Intraperitoneal administration of LPS (10 mg/kg) for 7 days induces marked upregulation of C1q and C3 by activating the classical complement pathway, microglial activation, synapse loss in the hippocampus, and cognitive deficits in Kunming mice (125). Repeated intraperitoneal administration of LPS (1 mg/kg/day for 4 consecutive days) induces dopaminergic neuron loss in the substantia nigra in mice but a single LPS injection does not. This loss of dopaminergic neurons is prevented in C3-deficient mice and associated with increased expression of genes involved in the classical and alternative complement (Itgam of CR3, C4, C3, and HF1) and phagosome (Fcer2b, Fcgr3, Fcgr4, Tyrobp, and Fcer1g) pathways in the brain, suggesting that repeated peripheral LPS administration induces complement-mediated elimination of dopaminergic neurons by microglial phagocytosis (198). Intraperitoneal injection of LPS (5 mg/kg) activates microglia and activated microglia induce A1 astrocytes by releasing TNF α , IL-1 α , and C1q in B6 mice. A1 astrocytes can drive neurodegeneration by releasing a neurotoxin and multiple complement components including C1q and C3, leading to microglial CR3-mediated synapse pruning and loss (199). A1 astrocytes are abundantly observed in diverse neurodegenerative diseases including AD (199). These findings indicate that systemic inflammation can activate brain complement and microglia, leading to loss of synapses and neurons, cognitive deficits, and neurodegeneration.

POTENTIAL COMPLEMENT AND TLR CROSSTALK IN NEUROINFLAMMATION AND ALZHEIMER'S DISEASE

As parts of the host defense innate immune system, TLRs and complements engage in synergistic or antagonistic signaling crosstalk to orchestrate immune responses. Indeed, most pathogens activate both TLRs and complements. TLR4 activation upregulates expression of complement components, potentially leading to complement activation (200, 201). In responses to TLR ligands including LPS (TLR4), zymosan (TLR2/6), and CpG-ODN (TLR9), mice deficient in a major membrane complement inhibitor, decay-accelerating factor (DAF), show striking elevation of plasma IL-1 β , IL-6, and TNF- α in a complement-dependent manner. This synergistic effect of complement on the cytokine production by TLRs in peripheral tissues has been attributed to activation of NF- κ B and mitogen-activated protein kinases (ERK1/2 and c-Jun N-terminal kinase) through the C5a-C5aR1 and C3a-C3aR signal pathways in mice [Figure 2; (200)]. Indeed, co-stimulation of human monocytes (THP-1 cell line) with aggregated A β and C5a markedly enhances secretion of IL-1 β and IL-6 through NF- κ B activation *in vitro* (202). Therefore, it is possible that activation of C5aR and C3aR signaling by C5a and C3a, respectively, synergistically enhances proinflammatory responses initiated by aggregated A β -induced TLR4 activation in the

brain, leading to AD initiation and progression. Additionally, the formation of the complement membrane attack complex (MAC) triggers increased cytosolic Ca^{2+} concentration, resulting in mitochondrial dysfunction and NLRP3 activation that causes caspase 1 activation and IL-1 β secretion *in vitro* (203), which may further promote a pathogenic cycle of the TLR4-complement-NLRP3 inflammasome interactions in AD.

In human monocytes, C5aR activation by C5a enhances LPS/TLR4-induced expression of IL-6 and TNF- α production while, in macrophages, C5a increases IL-10 secretion and inhibits LPS/TLR4-induced upregulation of IL-6 and TNF- α via C5aR/MEK/ERK signaling (204). This distinct regulation of LPS/TLR4 signaling by C5a in different cell types supports the concept that monocytes in circulation act as danger sensor and heighten inflammatory responses to PAMPs and DAMPs, while tissue macrophages restrain excess inflammation for host protection/tissue repair (204). Therefore, it is also possible that, in homeostatic/resting microglia, C5a and/or C3a synergistically enhance pro-inflammatory responses triggered by A β -TLR4 activation for removal of toxic A β aggregates while, in activated microglia, C5a and/or C3a antagonizes A β -TLR4-induced pro-inflammatory responses for neuroprotection. This host defense function of complement appears to be altered to host-offensive actions during aging (205). This detrimental alteration of complement-TLR signaling during aging may be exacerbated in AD.

CONCLUDING REMARKS

TLRs function as a host defense mechanism against pathogens and tissue damages. In peripheral tissues, complement and NLRP3 inflammasome modulate immune and inflammatory responses initiated by TLRs through crosstalk between their signaling pathways. TLR4 primes NLRP3 inflammasome in the peripheral tissues as well as in the central nervous system (CNS). As A β forms aggregates, a vicious cycle of A β -TLR4-NLRP3 inflammasome-IL-1 β in microglia sustains neuroinflammation in AD. Systemic inflammation can exacerbate neuroinflammation and neurodegeneration in AD via TLR4 and complement activation. In the peripheral

tissues, the crosstalk between TLR and complement is complex and contextual depending on cell type, tissue, species and disease models and complement seems to function as a molecular switch of TLR signaling (pro- or anti-inflammatory) and as a coordinator between innate and adaptive immune responses. However, such regulatory functions of complement have not been investigated in the CNS or brain-resident immune cells including microglia. One of the obstacles that hamper the investigation is that available microglial cell lines and primary microglia derived from the brain have characteristics different from brain resident microglia because microglia are sensitive to environmental changes. Such obstacles may be circumvented by use of new technologies such as the RiboTag and BacTRAP (Translating Ribosome Affinity Purification) methods (206, 207), single-nuclei or single cell RNAseq, genome editing tools, and iPSC-derived 3D co-culture brain models (208). Repeated failures of A β -targeted therapeutics indicate the need for a new approach for AD therapy and prevention based on disease mechanisms alternative to the amyloid cascade hypothesis. Inflammation and immune cells play a central role in the initiation and progression of AD. It is crucial to elucidate the molecular mechanisms by which inflammatory responses and immune cells drive the AD initiation and progression.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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