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Innate Immunity in Alzheimer's disease: a Complex Affair

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Abstract

Alzheimer's disease (AD) is characterized by three major histopathological hallmarks: β-amyloid plaques, neurofibrillary tangles and gliosis. While neglected for decades, neuroinflammatory processes coordinated by microglia are now accepted as etiologic events in AD evolution. Microglial cells are found in close vicinity to amyloid plaques and display various activation phenotypes determined by expression of a wide range of cytokines, chemokines, and innate immune cell surface receptors. During the development of AD pathology, microglia fail to restrict amyloid plaques and may contribute to neurotoxicity and cognitive deficit. Nevertheless, under specific conditions, microglia can participate in cerebral amyloid clearance. This review focuses on the complex relationship between microglia and Aβ pathology, and highlights both deleterious and beneficial roles of microglial activation in the context of AD. A deeper understanding of microglial biology will hopefully pave the way for next-generation AD therapeutic approaches aimed at harnessing these enigmatic innate immune cells of the central nervous system.

Keywords

Alzheimer disease; Amyloid-β peptide; Chemokine; Cytokine; Gliosis; Inflammation; Innate Immunity; Microglia; Neuroinflammation; Phagocytosis

Introduction

Alzheimer's disease (AD), the most common form of dementia, currently affects more than five million Americans and newly diagnosed cases are expected to reach 15 million by the year 2050. Pathological features include large-scale damage to the entorhinal cortex, hippocampus and basal forebrain, leading to memory impairment, temporal and spatial disorientation and altered cognitive function. The disease is earmarked by presence of two histopathological lesions: extracellular amyloid deposits [chiefly composed of amyloid-β (Aβ) peptides] and intracellular neurofibrillary tangles [NFTs, made up primarily of abnormally folded tau protein]. Over the last hundred years, intense focus has been directed toward understanding AD pathoetiology and potential treatment approaches aimed at controlling these two hallmark pathologies.

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In 1906, Alois Alzheimer described post-mortem analysis of Auguste Deter, a 51-year-old female patient that suffered from dementia. In this first report, he identified a third pathological feature of the disease that would later bear his name. What he termed "*gliose*", we now know as gliosis, or inflammation of the brain's glial support cells [1]. At the light microscopic level, gliosis in the AD brain is characterized by presence of reactive microglia and astrocytes that typically surround "senile" β-amyloid plaques [2]. Interestingly, microglial cells found in close proximity to amyloid plaques express the human leukocyte antigen-DR surface immune marker for mononuclear phagocyte activation as well as pro-inflammatory cytokines including interleukin(IL)-1β and IL-6 [3, 4]. While once regarded as epiphenomenon, more recent clinico-pathological studies show a strong association between microglial abundance and disease severity, and suggest that microglial activation is an early event in AD pathogenesis [5–8]. These results suggest that reactive microglia play both active and essential roles in the pathophysiology of AD [3, 9, 10]. In this review, we examine the broader implications of gliosis and innate immunity in the pathobiology of AD. A complex relationship emerges whereby the interactions between microglia and Aβ are characterized by discrete phases of attraction, interaction and activation, leading to context-dependent detrimental or beneficial outcomes in AD.

Attraction of microglia to amyloid plaques

As resident innate immune cells of the central nervous system (CNS), microglia play an indispensible role in surveying the brain milieu and form a first line of defense against invading pathogens. To carry out these important functions, microglia utilize: phagocytosis, cytokine production, activation of the protein complement cascade, and production of oxyradicals [11]. But before microglia can mount a response to a stimulus, they must first be attracted to the tissue site. The attraction process is often mediated by the interaction of chemokines and cytokines with their receptors, both of which are expressed by microglial cells. In the context of AD, several lines of evidence support the notion that β-amyloid plaque-associated factors, including misfolded Aβ peptides themselves, act as microglial attractants.

Indeed, the numerous chemokine receptors expressed by microglia and corresponding chemokines produced by Aβ-stimulated cells indicate that these macromolecules play an important role in microglia accumulation in the AD brain. More precisely, chemokine receptors such as CCR2, CCR3, CCR5 and CX3CR1 are all present on microglia *in vitro* as well as in AD patient brains, and CXCR2 and CXCR3 are expressed in close vicinity of neuritic plaques [12, 13]. That microglial cells readily express these chemokine receptors implies that they are primed to respond to cognate chemokine ligands. In this regard, *in vitro* experiments reveal that Aβ-stimulated microglia can induce mRNA and secretion of several chemokines, including CCL4 and CXCL2, CCL3, CXCL8 and CCL5 [14], suggesting an autocrine mode of chemokine signaling. Furthermore, several cell types appear to be a source of CCL2 in response to Aβ stimulation: astrocytes, neurons, oligodendrocytes and microglial cells themselves [14–16]. In fact, the central role of CCR2-CCL2 interaction in attraction of microglia towards Aβ deposits has been demonstrated in mouse models. For example, 3xTg-AD mice carrying amyloid precursor protein "Swedish" (APPsw), presenilin 1 (PS1) M146V and Tau P301L mutant human transgenes [17] have increased CCL2 levels in entorhinal cortex correlating with recruitment of microglia/macrophages to this brain region [18]. Furthermore, aged mice bearing human mutant APP and PS1 transgenes (designated PSAPP mice) develop β-amyloid plaques accompanied by activated microglial cells expressing CCL2 [19]. These data are clinically strengthened by post-mortem analysis of AD patient brains, indicating that CCL2 is expressed in microglia present in mature senile plaques [20]. Additionally, El Khoury and collaborators established that CCR2 deficiency leads to reduced accumulation of microglia in brains of aged transgenic APPsw mice (line

Tg2576) [21, 22]. Moreover, intracerebral injections of Aβ into wild-type mice induces accumulation of microglia at the injection site that is completely abolished in CCR2$^{-/-}$ mice. These data confirm that CCR2 is required *in vivo* for the recruitment of microglia to sites of Aβ deposition. Another chemokine receptor, CX3CR1 (also known as fractalkine receptor) is exclusively expressed on microglia whereas its ligand, CX3CL1, is highly expressed on neurons [23, 24]. The CX3CL1/CX3CR1 pathway is implicated in neuronal-microglial cross-talk, and may play a role in microglia attraction to amyloid plaques. In support, CX3CR1 deficiency reduces numbers of total and activated microglia surrounding amyloid plaques in two different mouse models of cerebral amyloidosis: PSAPP and R1–40 [25–27]. Furthermore, CX3CR1 deletion rescues microglial-dependent neuronal loss observed in 3xTg-AD mice [28].

Cytokines have also been suggested to be involved in chemoattraction of microglia to amyloid lesions. Interestingly, elevated $A\beta_{1–40}$ and $A\beta_{1–42}$ levels in aging Tg2576 and PSAPP transgenic mice are associated increased pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), IL-6, IL-1α and granulocyte macrophage-colony stimulating factor (GM-CSF) [29]. These results suggest that pathological accumulation of Aβ is a key factor leading to neuroinflammatory responses in AD [29]. In addition, *in vitro* experiments demonstrate that exposure of cultured microglia to pre-aggregated $A\beta_{1–42}$ increases production of proinflammatory cytokines (*i.e.*, pro-IL-1β, IL-6, TNF-α), macrophage inflammatory peptide (MIP-1α) and macrophage colony-stimulating factor (M-CSF) [30]. These molecules are all classically associated with monocyte chemoattraction, and others have implicated IL-6, IL-34 and M-CSF as microglial mitogens [31–33]. Furthermore, M-CSF levels in the plasma and CNS of AD patients are significantly increased compared to age-matched healthy controls or patients with mild cognitive impairment (MCI) [34]. Thus, there is little doubt that Aβ accumulation and perhaps neuronal injury endorse signals that trigger microglial recruitment and proliferation. This strong attraction of microglia towards Aβ prompts the question of how microglia immunologically respond once recruited to these lesions.

Activation of microglia in response to Aβ

Once microglia have moved toward Aβ deposits, they express various cell surface receptors allowing them to recognize and interact with misfolded Aβ peptides. In this context, the scavenger receptors (SRs) have garnered attention, as they can bind diverse ligands and affect the activation level, inflammatory status and phagocytic function of microglia [35]. Class A and B scavenger receptors were first described to bind Aβ in fibrillar or oligomeric conformations [36–39]. Several members of this family seem to be implicated in microglial interaction with Aβ. A prototypical example is CD36, which is expressed by microglia *in vitro* and in AD brain and endorses secretion of reactive oxygen species (ROS) by microglia in response to Aβ [14, 40]. Furthermore, in microglial cells isolated from CD36 null mice, fibrillar Aβ-induced secretion of cytokines, chemokines and ROS is reduced. Additionally, intracerebral injection of fibrillar Aβ results in significantly lower recruitment of microglia in brains of CD36$^{-/-}$ mice compared to wild-type mice [14]. Finally, Bamberger and collaborators described a receptor complex including CD36, the integrin-associated protein CD37 and the α6β1 integrin, which interacts with Aβ fibrils and activates microglial secretion of ROS [41]. Another key SR, the receptor for advanced glycation end products (RAGE), has also been identified on CD68^{+} microglial cells close to senile plaques in AD patient brains and in cultured rat and mouse microglia [42]. *In vitro*, RAGE is expressed on the surface of microglial cells and is able to bind Aβ [42]. Furthermore, Alarcon and colleagues reported that SRs expressed on neonatal rat microglia endorse binding of both fibrillar and non-fibrillar Aβ and another SR, MARCO, specifically mediates fibrillar Aβ binding [43]. Furthermore, APP23 transgenics have elevated levels of the SR SCARA-1 on

microglia around Aβ plaques. Thus, SCARA-1 also seems to be implicated in microglial recognition of Aβ. Finally, other reports suggest that the low density lipoprotein receptor-related protein, expressed on microglial cells, may function as an Aβ clearance receptor [44, 45].

Another family of innate immune receptors, the Toll-like receptors (TLRs), function as sensors for pathogen-associated molecular patterns (PAMPs) and can also recognize pathogenic endogenous proteins. TLR engagement initiates intracellular signaling pathways resulting in pro-inflammatory cytokine and chemokine secretion as well as nitric oxide (NO) release [46]. Remarkably, TLRs and associated receptors (*e.g.*, CD14) are highly expressed by microglia in close proximity to plaques in AD patient brains and in mouse models of the disease [47–51]. Aβ infusion into hippocampi of wild-type mice increases TLR2 expression, supporting these observations made in human AD [52]. Several reports suggest that TLRs are involved in recognition of amyloid peptides by microglia. For example, in a mouse model of AD, TLR4 deficiency modulates activation of microglia [53]. Others have reported that the hydrophobic β-sheet conformation is recognized and binds to the TLR-associated receptor CD14, initiating microglial secretion of NO, IL-6 and other neurotoxic factors [48–50]. This hypothesis is consistent with observations that TLR2 or TLR4 inhibition reduces Aβ-mediated microglial production of NO, TNF-α, IL-6 and IL-1β [49, 54, 55], and that CD14 deficiency in PSAPP mice inhibits microgliosis and lowers CD45 immunoreactivity [56]. At some level, these observations in mouse models have been corroborated by genetic studies showing that TLR4 or CD14 polymorphisms that attenuate inflammatory responses decrease AD risk [57, 58].

Activation of immune cells typically requires co-stimulatory signals in addition to the primary stimulus. CD40 is an immunoregulatory cell surface glycoprotein which, upon stimulation with its cognate ligand, CD40 ligand (CD40L), promotes activation of microglia and production of inflammatory proteins [59]. Interestingly, AD patient brains exhibit elevated abundance of microglial-associated CD40 concomitant with astrocyte-derived CD40L in and around amyloid plaques [60, 61]. Furthermore, Aβ stimulated microglia co-challenged with CD40L or agonistic CD40 antibody produce copious amounts of TNF-α that injure primary cortical neurons *in vitro* [62, 63]. In cultured microglial cells, CD40-CD40L interaction stimulates release of pro-inflammatory cytokines, inhibits Aβ phagocytosis, and promotes loading of Aβ peptides onto immunostimulatory major histocompatibility class II molecules [64]. Broadly then, concomitant stimulation with Aβ plus CD40L shifts microglial activation from a beneficial phagocytic phenotype to a potentially deleterious pro-inflammatory state endorsing antigen-presenting cell function. Furthermore, microglial cells derived from CD40L–deficient PSAPP AD model mice have reduced expression of TNF-α compared to control PSAPP littermates, and exhibit attenuated cell surface markers of activation [65]. Interestingly, CD40L–induced pro-inflammatory immune responses can be blocked by stimulation of the microglial transmembrane protein tyrosine phosphatase, CD45 [66, 67]. Complementarily, CD45 deficient PSAPP mice present a pro-inflammatory microglial phenotype accompanied by elevated levels of TNF-α and IL-1β, indicating that CD45 is a negative regulator of microglial activation [68]. Remarkably, CD45 is expressed by microglia in the frontal cortex and hippocampus of normal aging individuals and is markedly increased in close vicinity of β-amyloid plaques in AD patient brains [69], possibly representing a compensatory response in an attempt to reduce Aβ-mediated microgliosis.

Just recently, the list of potential Aβ innate immune receptors has grown. Of particular interest is the concept that misfolded Aβ peptides may in fact mimic activators of the prototypical NOD-like receptor 3 (NLRP3) pathway. NLRP3 is a cytoplasmic receptor that associates with an adapter protein, apoptosis-associated speck-like protein, and caspase-1 to

form a multiprotein complex known as the “Inflammasome” [70]. Interestingly, a recent report showed that Inflammasome activation is initiated after Aβ phagocytosis by microglia. The interaction between Aβ and the NLRP3 Inflammasome leads to release of IL-1β, the cardinal downstream Inflammasome effector cytokine [71]. We await further confirmation of these exciting results linking Aβ-induced microglial activation to the Inflammasome cascade.

Heterogeneity of microglial activation states

In the healthy adult CNS, microglial cells display a classic “ramified” or resting morphology characterized by a small soma with fine cellular processes. While often associated with a quiescent state, contrary to what the name implies, this ramified morphology is actually an active state in which microglia dynamically scan the brain milieu by extending and retracting many cytoplasmic extensions [72, 73]. This phenotype shifts to a reactive state in case of disturbance in homeostasis, injury or recognition of danger signals- when rapid changes in morphology, gene expression and function occur. The purpose of this shift toward activation is to allow microglia to divide, acquire mobility, and mount innate immune responses. Once activated, microglia present with a characteristic enlarged cytoplasm and shortened processes, morphologically referred to as “amoeboid” [74]. The activation states of microglia have been discretely classified into: classical activation (M1), alternative activation (M2), and acquired deactivation. However, a complementary concept is that a continuum of functional phases exist between two extremes, designated M1 and M2 [75]. Microglial activation is both characterized and modulated by cytokines, cell surface antigen interactions, and the inflammatory milieu. Classical activation is earmarked by elevated proinflammatory cytokines including TNF-α, IL-1, IL-6, IL-12 and IL-18, cell surface receptors, NO and prostaglandins accompanied by poor phagocytic capacity [76]. The M2 state is characterized by secretion of the anti-inflammatory cytokines IL-4, IL-10, IL-13 and TGF-β, and elevated phagocytic capacity without supraphysiologic production of toxic NO [77–79]. In neurodegenerative diseases, heterogeneity of microglial activation states is likely to impact the development of the disorder [80]. In the brain of AD patients or mouse models, microglia surrounding plaques exhibit both M1 and M2 activation markers, indicating that a shift from one state to the other could occur during the progression of the disease or that one or several intermediate activation states are involved [81, 82]. This perspective is particularly interesting in view of the complex relationship between microglia and amyloid deposits, detailed below.

Inappropriate activation of microglia: reinforcement of amyloid load and neurotoxicity

In health, microglia are immunocompetent cells that survey the brain milieu and, if needed, become acutely activated in order to repair tissue damage. However, in the context of AD, microglia fail in this primary function, as 1) Aβ deposits are not cleared despite abundant microgliosis surrounding amyloid plaques, 2) it is not evident that microglia are capable of degrading Aβ, and 3) chronic microglial activation is damaging to neurons, via production of numerous cytokines and acute-phase reactants. This inappropriate activation of microglia in the AD brain is represented in Figure 1.

Several studies have cast doubt on the effectiveness of microglia in amyloid clearance. Poor microglial Aβ clearance aptitude could be at least partially due to age-related structural deterioration and cellular senescence of microglia [83]. Another explanation involves the particular phenotype that microglia adopt during the course of the disease, which fails to avail these cells of the appropriate molecular tools for amyloid clearance [82]. This line of reasoning is supported by Hickman and collaborators, who reported that aged PSAPP mice

have reduced expression of Aβ-binding receptors including scavenger receptor A (SR-A), CD36, the receptor for advanced glycation endproducts (RAGE) and Aβ degrading enzymes such as insulin degrading enzyme (IDE), neprilysin (NEP), and matrix metalloprotease 9 (MMP9) [84]. *Ex vivo* experiments indicate that microglia from aged mice secrete constitutively high amounts of the pro-inflammatory cytokines IL-6 and TNF-α, and this is associated with reduced capacity to internalize Aβ peptide compared to younger mouse microglia [85]. This evidence supports the above-mentioned concept that microglia committed to a strong inflammatory response are less efficient at phagocytosing Aβ [78]. All together, these data suggest that the aging process biases microglial activation toward an M1-like state that fails to restrict AD pathology. Furthermore, even if microglia are able to take up Aβ during the early stage of the disease, there is a paucity of evidence to suggest that these cells effectively degrade the peptide. In this regard, it is interesting to note that, *in vitro*, the majority of Aβ internalized by mouse microglia is still not degraded after 72 hours [86]. Furthermore, Aβ extracted from human AD patients and phagocytosed by primary cultured canine microglia can be detected in phagosomes for up to 19 days [87], and others have shown that non-degraded Aβ is released by microglia [88]. While opsonisation of Aβ with Immunoglobulin G or complement improves Aβ phagocytic receptor binding, this approach fails to improve phagolysosomal degradation of the peptide [89].

This inability of microglia to efficiently phagocytose and degrade Aβ during the evolution of AD has been termed “frustrated phagocytosis.” Part and parcel of this response is persistent release of pro-inflammatory molecules, ROS, cytokines and chemokines [90]. Importantly, this maladaptive phenotype not only negatively impacts Aβ clearance, but can also be neurotoxic. For example, in microglial/neuronal co-culture or in organotypic slice cultures, the ratio of dead to live neurons is increased by microglial Aβ stimulation [91, 92]. In these experiments, presence of microglia in the culture is obligatory for the deleterious effects on neurons. These experimental results are not without validation from human AD cases. In fact, high levels of the cardinal proinflammatory cytokine IL-1β are detected in microglial cells surrounding Aβ plaques in AD patient brains and cerebrospinal fluid (CSF) [93, 94]. *In vitro*, IL-1β is released by activated microglia after stimulation with Aβ [95], and in turn induces expression of the astrocyte pro-inflammatory cytokine-like molecule, S100β, which is implicated in neuritic plaque formation. Forced expression of S100β accelerates AD-like pathology in Tg2567 mice by increasing amyloidogenic APP cleavage, astrocytosis, microgliosis and pro-inflammatory cytokine abundance [96]. IL-1β can, at least under certain circumstances, favor Aβ deposition by modulating APP expression and proteolysis [97]. This phenomenon sets off a vicious loop leading to chronic cytokine-mediated neuronal injury and subsequent microglial activation.

There are multiple lines of evidence suggesting that the pro-inflammatory milieu present in the AD brain and in transgenic mouse models of the disease is damaging. For instance, risk for conversion from mild cognitive impairment to AD is high in subjects presenting with elevated CSF abundance of the pro-inflammatory cytokine TNF-α and decreased anti-inflammatory TGF-β levels [98]. Accordingly, TgCRND8 AD model mice have enhanced expression of TNF-α, NO and the pro-apoptotic protein Bax, while the anti-apoptotic protein Bcl-2 is decreased [99]. Elevated expression of additional cytokines/chemokines and innate immune receptors favor an M1-like activation state in the context of AD. For example, in neuron-microglia co-cultures, the synergistic action of Aβ with either interferon-gamma (IFN-γ) or CD40L triggers TNF-α secretion and production of ROS that is neurotoxic [62, 100]. Furthermore, CD40L deficiency in Tg2576 mice results in decreased microgliosis and tau hyperphosphorylation– a key index of neuronal stress [62]. As pharmacologic validation of this genetic approach, intracerebroventricular delivery of CD40L depleting antibody to PSAPP AD model mice leads to striking reduction of β-amyloid pathology associated with decreased amyloidogenic processing of APP and brain-

to-blood Aβ efflux. Taken together then, these data indicate that the CD40-CD40L interaction favors a pathogenic form of microglial activation in the context of AD [62]. In addition, the innate immune receptor, TLR4, is responsible for elevated levels of TNF-α and MIP-1α in AD model mice [53]. As the disease progresses in association with persistent production of pro-inflammatory cytokines such as TNF-α and IL-1β, unresolved neuroinflammation leads to chronicity. Deregulation of the stress responsive cyclin-dependent kinase 5 (Cdk5) is also involved in the development of AD-like pathology, including glial activation and MIP-1α, TNF-α, TGF-β and IL-1β secretion [101]. This form of neuroinflammation is deleterious, as the Cdk5/p25 complex induces hyperphosphorylation of tau, NFT formation and aberrant APP processing [102–107].

Finally, it deserves mentioning that Aβ-induced M1-type activation of microglia via SRs, TLRs or M-CSF leads to oxidative stress by release of NO and other ROS. Oxidative stress is well-known to provoke various types of damage including: apoptosis [108, 109], tau hyperphosphorylation and NFT formation, and increased β- and γ-secretase expression and activity associated with amyloidogenic APP metabolism [110, 111]. Furthermore, via stimulation of microglia and astrocytes, oxidative stress induces release of pro-inflammatory cytokines including IL-1, TNF-α and IL-6 that enhance Aβ generation [112–115]. Thus, oxidative stress is also a key perpetrator of the chronic, vicious cycle triggered by Aβ and reactive microglia.

Appropriate activation of microglia: resolution of cerebral amyloidosis

The primary goal of inflammation is to resolve injury or defend against foreign invaders while minimizing damage to surrounding tissues. In the case of AD, this would theoretically consist of clearing the brain of damaging forms of Aβ peptides. Several studies suggest that appropriate activation of microglia can be achieved and lead to resolution of cerebral amyloidosis in AD mouse models [68, 116–119]. The importance of microglia for restricting and remodeling Aβ plaques is underscored by transplantation of exogenous microglia into rat brains. Once transplanted, these cells migrate into the parenchyma and clear intracerebrally injected Aβ peptides [120]. Bone marrow-derived microglia also have an important role in plaque clearance via Aβ phagocytosis, when appropriately activated [121]. For instance, under defined conditions, microglia can internalize Aβ [78, 119, 122, 123] via macropinocytosis for soluble Aβ peptides, phagocytosis for insoluble aggregated species [124] and by phosphatidylserine-dependent internalization of exosomes [125]. Evidence supporting beneficial activation of microglia in the context of AD is summarized in Figure 2 and detailed below.

It is now appreciated that targeting specific receptors involved in microglial recognition of Aβ can lead to beneficial phagocytic activation. A good example of this is genetic deletion of the chemokine receptor, CCR2, in Tg2576 mice. These crossed mice manifest reduced migration of microglia towards amyloid plaques and higher cerebral Aβ levels associated with increased mortality [21]. Another study in PSAPP mice confirmed that lack of CCR2 aggravates amyloid pathology and behavioral deficit. In this model, expression is enhanced of the typical anti-inflammatory molecules TGF-β1 ligand and TGF-β receptors [126]. These results suggest that CCR2-mediated activation of microglia promotes brain Aβ clearance and protects mice from neurotoxicity, a concept further supported by a study designed to overexpress IL-1β in PSAPP mouse brains. Interesting, these animals have dramatic elevation of CCL2, increased microglial accumulation and activation, and reduced AD-like pathology [127]. Furthermore, the scavenger receptor SCARA-1 is also implicated in this mechanism, as its deficiency in mouse-derived microglia drastically reduces Aβ uptake [9, 39, 43, 128]. TLR-mediated activation of microglia also seems to impact Aβ clearance. For instance, in mouse models of AD, TLR2 deficiency or expression of a TLR4 mutant

increases Aβ deposition and worsens cognitive impairment [52, 129, 130]. Similarly, intrahippocampal injections of the TLR4 ligand, lipopolysaccharide, promote Aβ clearance in PSAPP mice [131]. In primary neuron-microglia co-cultures, activation of microglia via interaction between TLR9 and its ligand, unmethylated CpG DNA, mediates oligomeric Aβ clearance by microglial cells and attenuates $A\beta_{1–42}$ oligomer-induced neurotoxicity. These observations were accompanied by high levels of the antioxidant enzyme, heme oxygenase-1, and absence of potentially neurotoxic NO and glutamate. Those authors further confirmed these effects *in vivo*, by demonstrating that intracerebroventricular injection of CpG DNA ameliorates impaired associative learning and cognition induced by oligomeric Aβ in Tg2576 mice [132]. When taken together, these reports indicate that selective targeting of innate immune receptors can favor microglial Aβ uptake and support a protective form of activation.

Cytokines are also powerful modulators of neuroinflammation and can impact microglial Aβ clearance. Two good examples are M-CSF and granulocyte-colony stimulating factor (G-CSF), which are reported to promote Aβ phagocytic clearance by microglia and to rescue learning and memory deficits in mouse models [133, 134]. Additionally, unilateral hippocampal injection of M-CSF, G-CSF or GM-CSF in transgenic AD model mice reduces amyloid load when compared to the (control) contralateral hemisphere. Furthermore, chronic GM-CSF subcutaneous injection reduces Aβ burden, ameliorates cognitive deficit, and increases hippocampal synaptic area [135]. GM-CSF binding to its receptor promotes proliferation of human fetal and adult microglia in primary cultures and acts as a neurotrophic factor without enhancing Aβ-induced microglial secretion of potentially damaging pro-inflammatory cytokines [136]. These experimental results are even more valid when considering that GM-CSF receptor expression is reduced in the hippocampus of AD patients compared to age-matched controls [137]. However, when Manczak and colleagues administered GM-CSF neutralizing antibody to a mouse model of AD, they observed suppression of microglial activation and decreased $A\beta_{1–42}$ levels [138]. Interestingly, stimulation of pro-inflammatory signaling via treatment of microglial cells with IFN-γ and IL-1β results in increased $A\beta_{1–42}$ uptake concomitant with enhanced IL-6 secretion [139], and pharmacological induction of IL-6 and TNF-α secretion by microglia favors Aβ peptide uptake [140]. Similarly, overexpression of IL-6 in TgCRND8 or Tg2567 model mice induces massive gliosis accompanied by increased expression of the phagocytosis marker, CD68, resulting in microglial clearance of amyloid aggregates [141]. Furthermore, in primary neuron and microglia co-cultures, an M-CSF-related cytokine modulator of inflammation, IL-34, promotes microglial proliferation and clearance of soluble oligomeric Aβ. Moreover, intracerebroventricular injection of IL-34 in PSAPP mice reduces oligomeric Aβ levels and improves learning and memory [33].

While often regarded as pro-inflammatory molecules, NO and components of the protein complement cascade can also play beneficial roles in the context of AD pathobiology. NO is inducibly generated in the brain by the inducible nitric oxide synthase (iNOS) enzyme, encoded by the NOS2 gene. Strikingly, NOS2 deficiency diminishes NO levels and exacerbates cerebral amyloidosis, tauopathy and neuronal loss in AD model mice [142, 143]. Those authors suggested that AD-like pathology was directly related to NO abundance, where high levels produced by microglia were neuroprotective whereas NO deficiency favored development of AD-like pathology [144]. Regarding the protein complement pathway, components of this cascade have been found to colocalize with amyloid plaques and tangles and may also participate in beneficial effects of microglia in AD [145]. Thus, inhibition of complement C3 activation or genetic ablation of C3 in a transgenic mouse model of AD activates microglia, augments Aβ deposition and promotes neuronal degeneration [146, 147]. Additionally, *in vitro* experiments showed that synthetic Aβ peptides enhance C3 production by cultured microglial cells [148]. Finally, despite the

controversy surrounding degradation of fibrillar Aβ by microglia, it has been demonstrated that activation of microglial cells by M-CSF or other inflammatory stimuli increases their ability to degrade internalized fibrillar Aβ *in vitro*. In this regard, it is interesting that quiescent microglial cells have unusually high lysosomal pH (which does not support optimal Aβ degradation), while activated cells have acidification of these compartments, endorsing efficient degradation of Aβ [149].

Harnessing beneficial microglial responses to Aβ: a therapeutic perspective

In past decades, one of the key therapeutic strategies for AD has been aimed at reducing cerebral Aβ load. In one embodiment, preventive therapy would target β- and γ-secretases, preventing amyloidogenic APP metabolism and thereby reducing Aβ generation. However, because the secretases: 1) target a variety of substrates and 2) have negative side-effects and associated adverse events, the scientific community has asked for consideration of alternative therapeutic approaches. One such approach has been to target the other side of the equation: Aβ clearance. This alternate approach may be even more important when considering a recent report strongly suggesting that failure in Aβ clearance machinery rather than overproduction of the peptides may be the etiologic culprit in human AD [150].

In a seminal report, Schenk and colleagues reported that so-called “active” vaccination with $A\beta_{1–42}$ peptide plus QuilA adjuvant strikingly ameliorated cerebral Aβ load in PDAPP AD model mice, and Bard and coworkers followed-up by showing that “passive” transfer of Aβ antibodies produced a similar result [151, 152]. These exciting results led to an early developmental clinical trial, AN-1792 (Elan Pharmaceuticals/Wyeth) which revealed Aβ antibody-dependent microglial clearance of amyloid plaques in post-mortem analyses of a limited AD patient cohort [153]. Unfortunately though, this phase IIa trial was prematurely halted after 4 months of treatment, when ~6 % of the patients developed a severe form of brain inflammation known as aseptic meningoencephalis [154]. This adverse event was believed to have been caused by T helper type 1 (Th1) cells that infiltrated the brain and mounted an autoaggressive response to cerebral Aβ. Furthermore, even though patients that received AN-1792 produced Aβ-specific antibodies and had reduced amyloid plaques, they did not demonstrate durable improvement in cognitive function. It is interesting to note that immunization with $A\beta_{1–42}$ plus Freund’s adjuvant in either Tg2576 or wild-type mice results in decreased Th1 cytokines IL-2 and IFN-γ and elevated Th2 cytokines IL-4 and IL-10 concomitant with attenuation of Aβ burden [155]. These data suggest that the choice of adjuvant is a critical determinant of the character of the Aβ-specific immune response. Other studies have shown similar Th2 responses to active Aβ vaccines in transgenic AD mice associated with robust reduction of Aβ deposits [156–158], while less efficient clearance of Aβ is typically observed in immunization approaches that favor a Th1 response [159]. Although imperfect, the AN-1792 trial has nonetheless paved the way for additional immunotherapeutic studies aiming at preventing plaque formation by the use of Aβ-specific antibodies.

Broadly stated, one such approach has been to convert microglial activation from harmful M1-like neurotoxic to helpful M2-like pro-phagocytic phenotype– and not simply to suppress inflammatory processes all together. Numerous *in vitro* and *in vivo* studies, detailed below, provide evidence that microglial phagocytosis of amyloid peptide can, in fact, be successfully achieved.

One such approach has been to selectively target receptor complexes that bind Aβ and induce inflammatory responses. Peroxisome proliferator-activated receptor gamma (PPARγ) is involved in the regulation of apolipoprotein E and acts as a molecular chaperone for Aβ.

Oral treatment of PSAPP mice with a synthetic PPARγ agonist causes phenotypic polarization of microglial cells from pro- to anti-inflammatory, enhances phagocytosis of soluble and insoluble Aβ peptides, and ameliorates memory deficits [160, 161]. Another example is inhibition of RAGE receptor in transgenic AD model mice, which reduces β-secretase activity and Aβ production, suppresses microglial activation and inflammatory responses, and ameliorates cognitive performance [162]. Blockade of TLR2 also reduces inflammation and increases Aβ uptake by shifting microglia from M1 to M2 activation states [163]. Furthermore, inhibition of CD36-dependent microglial activation results in beneficial blockade of ROS production [164].

A different strategy that has shown promise is modulation of cytokines. TGF-βs are key cytokine regulators of inflammation that also play cardinal roles in immune homeostasis and tissue repair [165]. In brains of AD mouse models, several studies indicate that overexpression of TGF-β1 promotes microgliosis and accelerates Aβ deposition [166, 167], while others have show resolution of microglial activation [168] and clearance of Aβ deposits via phagocytosis in this scenario [119, 169, 170]. Another report demonstrated that neuronal reduction of TGF-β signaling in a mouse model of AD induces Aβ accumulation, dendritic loss and age-dependent neurodegeneration, suggesting that increasing neuronal TGF-β signaling may be beneficial in AD by being neurotrophic [171]. More recently, Tichauer and collaborators evaluated the participation of the TGF-β-Smad3 pathway on expression of SRs and activation of wild-type rat-derived microglia in culture. They reported that TGF-β1 increased SR-A but decreased SR-B1 expression, and had no effect on SR-MARCO or CD36. In addition, microglial activation by TGF-β1 leads to increased clearance of Aβ and reduced neurotoxicity [172]. Nevertheless, in AD patient brains, TGF-β1 is increased while Aβ clearance is reduced. Interestingly, TGF-β1, nuclear Smad7 and β-catenin are strikingly augmented in cortical brain regions of TgCRND8 AD model mice. Furthermore, interaction between Smad7 and β-catenin, as revealed by coimmunoprecipitation, is enhanced in TgCRND8 mice. In mouse primary cortical neuronal cultures, exposure to $A\beta_{1-42}$ peptide induces TGF-β1 and elevates nuclear β-catenin and Smad7. Moreover, addition of TGF-β1 to mouse cortical neuron cultures increases apoptosis via a Smad7 and β-catenin-dependent pathway. These data suggest that TGF-β1 amplifies $A\beta_{1-42}$-mediated neurodegeneration via a Smad7/β-catenin-dependent mechanism [173].

Our group developed a transgenic mouse model with blockade of TGF-β receptor and downstream Smad2/3 signaling on peripheral macrophages (designated CD11c–DNR mice) [174, 175]. When these mice were crossed with Tg2576 mice, doubly transgenic animals had betterment of behavioral impairment [176]. Importantly, these animals had striking reduction of Aβ deposits in brain parenchyma, accompanied by increased infiltration of peripheral macrophages in and around β-amyloid plaques. *In vitro*, CD11c–DNR-derived peripheral macrophages exhibit blockade of the classical TGF-β-activated Smad2/3 pathway accompanied by hyperactivation of the alternative Smad1/5/8 signaling cascade and marked increase in Aβ phagocytosis [176]. It is noteworthy that the peripheral macrophages implicated in this beneficial Aβ phagocytosis effect have increased levels of IL-10, characteristic of an anti-inflammatory M2-like phenotype. Taken together, these results indicate that blockade of TGF-β-Smad2/3 signaling in peripheral macrophages represents a new therapeutic target for AD [177, 178].

Concluding remarks

An impressive array of studies, reviewed here, clearly implicate the innate immune response in the pathobiology of AD. *In toto*, these reports reveal a highly complex relationship between microglia and Aβ that can either be deleterious or beneficial. If left unchecked, the chronic neuroinflammatory process can perpetrate bystander neuronal injury; but if

controlled, reactive microgliosis can be harnessed to clear the brain of damaging Aβ species. In mouse models of AD, targeted activation of microglia induces plaque clearance associated with improvement in learning and memory. Nevertheless, extensive microglial recruitment to plaques in human AD is accompanied by very little if any phagocytosis of Aβ, allowing plaques to accumulate over many years– or even decades. A central message that emerges is that the specific microglial activation profile is of utmost importance in determining whether the response is ultimately damaging or helpful. A key challenge in coming years will be to translate these basic science discoveries into potential AD therapeutics favoring pro-phagocytic activation of microglia and/or blocking the chronic, unresolved pro-inflammatory form of reactive microgliosis that wreaks havoc on the AD brain.

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List of abbreviations

Aβ	amyloid-β peptide
AD	Alzheimer's Disease
APP	Amyloid Precursor Protein
CDn	Cluster of Differentiation
CCL	Chemokine C-C motif Ligand
CCR	Chemokine C-C motif Receptor
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CXnCLn	Chemokine C-X-C motif Ligand
CXnCRn	Chemokine C-X-C motif Receptor
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
HLA-DR	Human Leukocyte Antigen
IFN	Interferon
IL	Interleukin
MCI	Mild Cognitive Impairment
M-CSF	Macrophage Colony-Stimulating Factor
MHC II	Major Histocompatibility Complex II
MIP-1α	Macrophage Inflammatory Peptide 1-alpha
NFT	Neurofibrillary Tangle
NO	Nitric Oxide

PPAR-γ	Peroxisome Proliferator-Activated Receptor-gamma
PS	presenilin
RAGE	Receptor for Advanced Glycation End product
ROS	Reactive Oxygen Species
SR	Scavenger Receptor
TGF-β	Transforming Growth Factor-β
Th2	T helper 2
TLRs	Toll Like Receptors
TNF-α	Tumor Necrosis Factor-alpha

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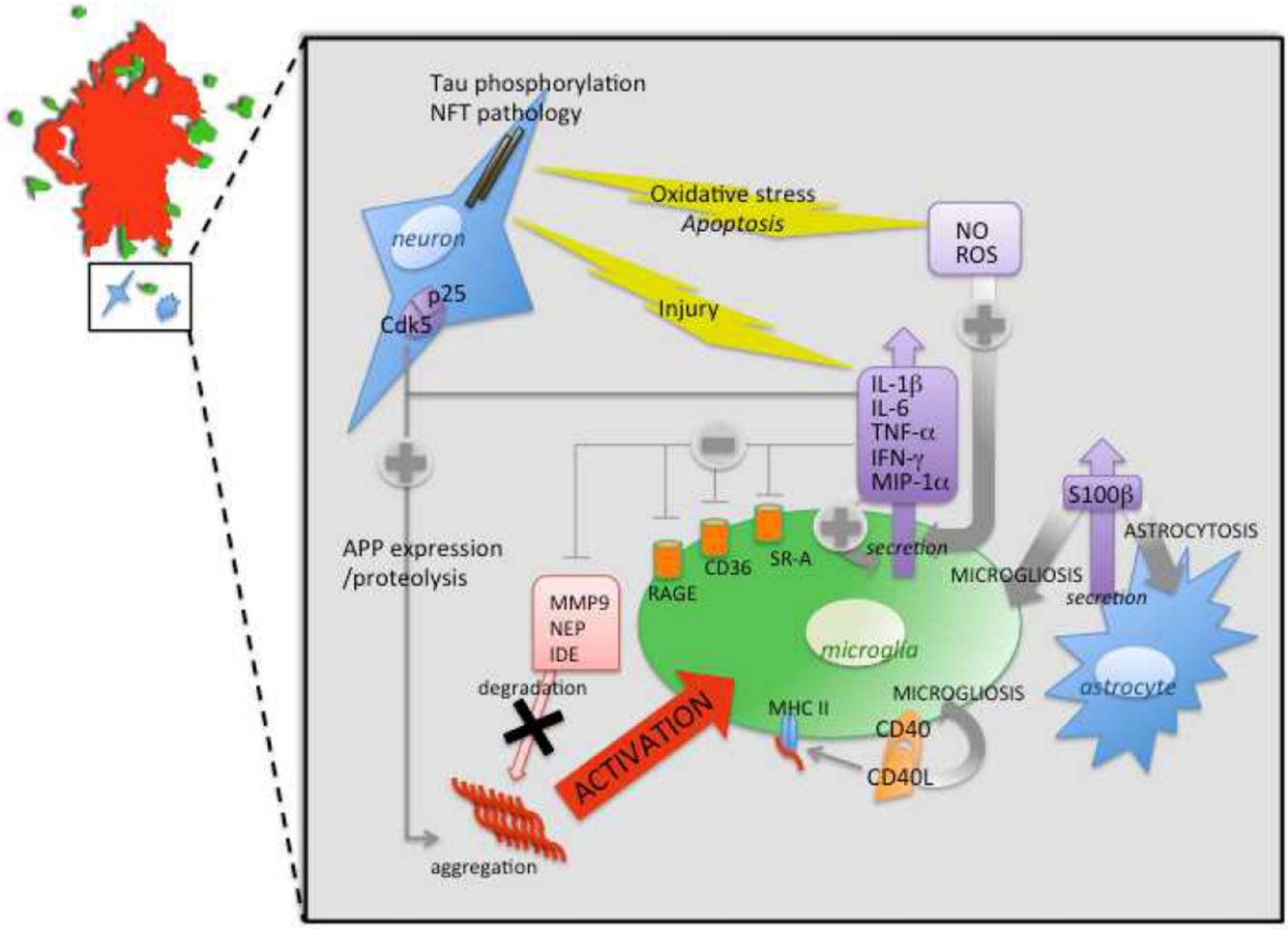

Figure 1. Inappropriate activation of microglia in Alzheimer's disease

A schematic representation is shown of a mature amyloid plaque (red) surrounded by activated microglia (green) and a neuron and astrocyte (shaded blue; top left corner). The inset summarizes the effects of Aβ-induced activation of microglia on cytokine/chemokine secretion, expression of cell surface immune receptors, oxidative stress, and the resultant deleterious vicious cycle reinforcing Aβ deposition and neurotoxicity. Abbreviations used: APP, amyloid precursor protein; Cdk5, cyclin-dependent kinase 5; IDE, insulin degrading enzyme; IFN-γ, interferon-gamma; IL, interleukin; MHC II, major histocompatibility complex, class II; MIP-1α, macrophage inflammatory protein, type 1alpha; MMP9, matrix metalloprotease, type 9; NEP, neprilysin; NFT, neurofibrillary tangle; NO, nitric oxide; RAGE, receptor for advanced glycation endproducts; ROS, reactive oxygen species; SR-A, scavenger receptor, type A, TNF-α, tumor necrosis factor-alpha.

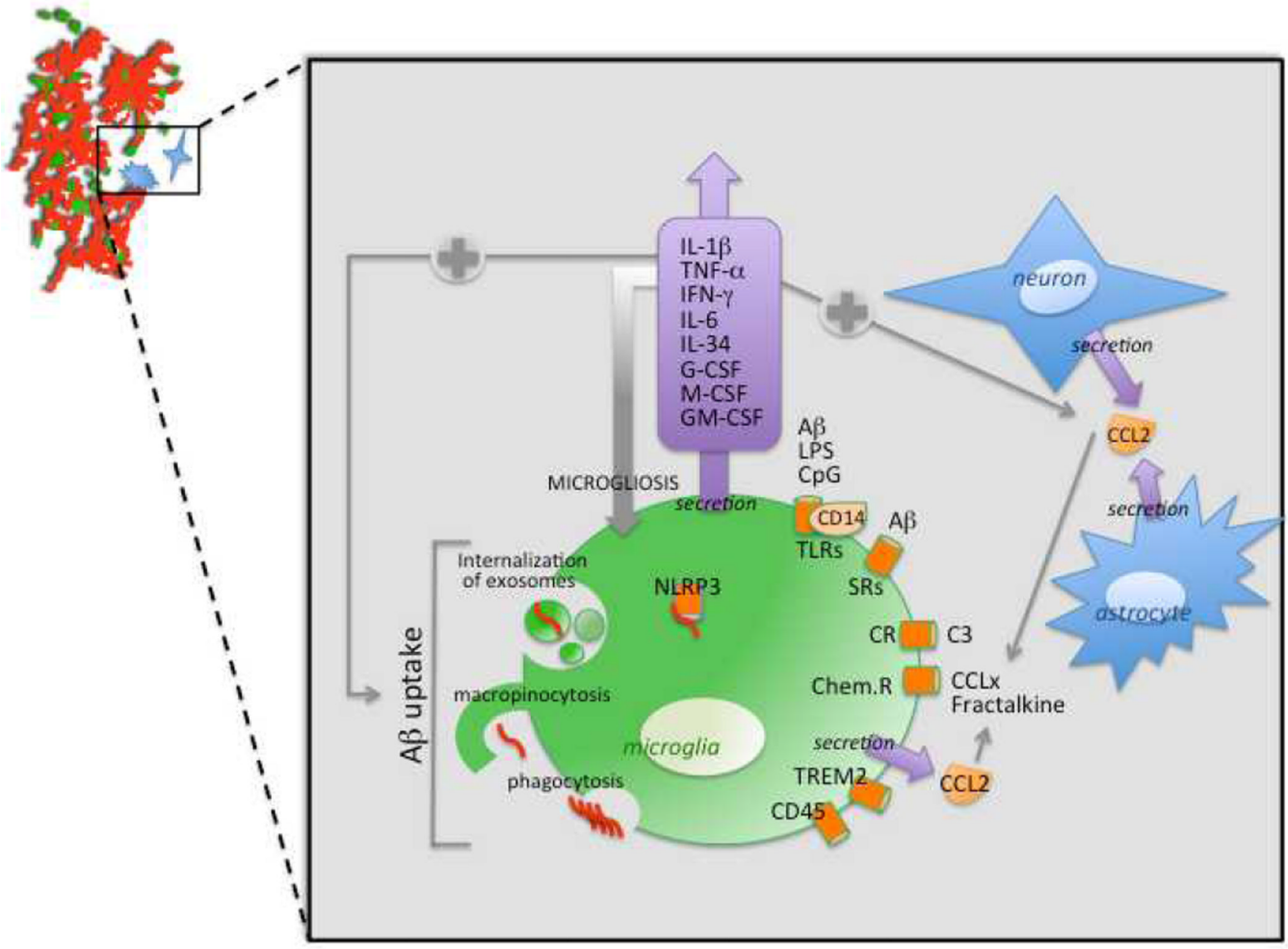

Figure 2. Beneficial activation of microglia in the context of Alzheimer's disease

A schematic representation of an amyloid plaque (red) being phagocytosed by appropriately-activated microglia (green) is shown in the top left corner. A neuron and an astrocyte are represented in blue. The inset summarizes the principle receptors and cytokines/chemokines that play roles in mediating Aβ clearance by microglia. Abbreviations used: CCL, chemokine ligand; Chem.R, chemokine receptor; CpG, unmethylated DNA containing CpG motifs; CRs, protein complement receptors; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN-γ, interferon-gamma; IL, interleukin; LPS, lipopolysaccharide; M-CSF, macrophage colony stimulating factor; NLRP3, NOD-like receptor, type 3; NO, nitric oxide; ROS, reactive oxygen species; SRs, scavenger receptors; TLRs, Toll-like receptors; TNF-α, tumor necrosis factor-alpha; TREM, triggering receptor expressed on myeloid cells; SRs, scavenger receptors.