Received: 6 April 2023 | Revised: 25 June 2023 | Accepted: 1 August 2023

DOI: 10.1111/jnc.15933

Journal of Neurochemistry JNC The Official Journal of the International Society for Neurochemistry WILEY

REVIEW

Receptor–ligand interaction controls microglial chemotaxis and amelioration of Alzheimer's disease pathology

Shun-Fat Lau[1,2] | Amy K. Y. Fu[1,2,3] | Nancy Y. Ip[1,2,3]

[1]Division of Life Science, State Key Laboratory of Molecular Neuroscience, Molecular Neuroscience Center, The Hong Kong University of Science and Technology, Hong Kong, China

[2]Hong Kong Center for Neurodegenerative Diseases, Hong Kong, China

[3]Guangdong Provincial Key Laboratory of Brain Science, Disease and Drug Development, HKUST Shenzhen Research Institute, Shenzhen–Hong Kong Institute of Brain Science, Shenzhen, China

Correspondence
Nancy Y. Ip, Division of Life Science, State Key Laboratory of Molecular Neuroscience, Molecular Neuroscience Center, The Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong, China.
Email: boip@ust.hk

Funding information
Areas of Excellence Scheme of the University Grants Committee, Grant/Award Number: AoE/M-604/16; Collaborative Research Fund, Grant/Award Number: C6027-19GF; Fundamental Research Program of Shenzhen Virtual University Park, Grant/Award Number: 2021Szvup137; RGC General Research Fund, Grant/Award Number: HKUST16103017 and HKUST16100418; Guangdong Provincial Key S&T Program Grant, Grant/Award Number: 2018B030336001; Innovation and Technology Commission Grant, Grant/Award Number: InnoHK and ITCPD/17-9; National Key R&D Program of China Grants, Grant/Award Number: 2021YFE0203000; the Guangdong

Abstract

Microglia maintain brain homeostasis through their ability to survey and phagocytose danger-associated molecular patterns (DAMPs). In Alzheimer's disease (AD), microglial phagocytic clearance regulates the turnover of neurotoxic DAMPs including amyloid beta (Aβ) and hyperphosphorylated tau. To mediate DAMP clearance, microglia express a repertoire of surface receptors to sense DAMPs; the activation of these receptors subsequently triggers a chemotaxis-to-phagocytosis functional transition in microglia. Therefore, the interaction between microglial receptors and DAMPs plays a critical role in controlling microglial DAMP clearance and AD pathogenesis. However, there is no comprehensive overview on how microglial sensome receptors interact with DAMPs and regulate various microglial functions, including chemotaxis and phagocytosis. In this review, we discuss the important axes of receptor–ligand interaction that control different microglial functions and their roles in AD pathogenesis. First, we summarize how the accumulation and structural changes of DAMPs trigger microglial functional impairment, including impaired DAMP clearance and aberrant synaptic pruning, in AD. Then, we discuss the important receptor–ligand axes that restore microglial DAMP clearance in AD and aging. These findings suggest that targeting microglial chemotaxis—the first critical step of the microglial chemotaxis-to-phagocytosis state transition—can promote microglial DAMP clearance in AD. Thus, our review highlights the importance of microglial chemotaxis in promoting microglial clearance activity in AD. Further detailed investigations are essential to identify the molecular machinery that controls microglial chemotaxis in AD.

KEYWORDS
amyloid-beta, chemotaxis, danger-associated molecular patterns, microglia, phagocytosis, synapse

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta; ApoE, apolipoprotein E; CD33, sialic acid-binding Ig-like lectin 3; CNS, central nervous system; DAMP, danger-associated molecular pattern; DAP-12, TYRO protein tyrosine kinase-binding protein; IL, interleukin; IL-1RAP, IL-1 receptor accessory protein; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; IRS, insulin receptor substrate; SH2, Src homology 2; SHP, SH2-domain-containing phosphatase; Siglec, sialic acid-binding immunoglobulin-like lectin; Syk, spleen tyrosine kinase; sST2, soluble ST2; TNF, tumor necrosis factor; TREM2, triggering receptor expressed on myeloid cells 2.

Provincial Fund for Basic and Applied Basic Research, Grant/Award Number: 2019B1515130004; Theme-Based Research Scheme, Grant/Award Number: T13-605/18W

1 | INTRODUCTION

The functional transition of microglia plays a central role in controlling Alzheimer's disease (AD) pathogenesis. Along AD progression, neurotoxic amyloid beta (Aβ), hyperphosphorylated tau, dystrophic neurites, and proinflammatory cytokines—referred to as "danger-associated molecular patterns" (DAMPs)—accumulate in the central nervous system (CNS). These DAMPs trigger the activation of microglia and stimulate their functional changes (Heneka et al., 2015; Holmes et al., 2009). Specifically, activated microglia undergo a stepwise functional transition in which they first migrate toward a specific stimulus (i.e., chemotaxis), which leads to contact-dependent activities such as phagocytosis (Gomez-Nicola & Perry, 2015; Lau et al., 2021; Perry & Holmes, 2014). Ineffective phagocytic clearance of DAMPs results in their accumulation in the CNS, leading to chronic activation and detrimental microglial functions, including aberrant synaptic pruning. However, a comprehensive understanding of how microglial functions, including chemotaxis and phagocytosis toward DAMPs, are regulated and contribute to AD pathogenesis is lacking.

To sense DAMPs in CNS milieus, microglia express various surface sensome receptors to detect extracellular protein aggregates and soluble factors (Hickman et al., 2013). Therefore, the expression and functions of sensome receptors are critical for controlling the capacity of microglia to detect DAMPs and triggering the functional transition of microglia, which leads to the clearance of those DAMPs. The importance of sensome receptors in the regulation of microglial functions and AD pathogenesis is further supported by genetics studies. For instance, large-cohort genetic analyses demonstrate that many AD risk variants are located near or within the coding regions of microglial sensome receptors, including *CD33* and *TREM2* (Guerreiro et al., 2013; Hollingworth et al., 2011; Lambert et al., 2013; Naj et al., 2011). These variants alter the expression or function of the corresponding microglial receptors and are associated with dysregulated microglial Aβ clearance (Gratuze et al., 2018; Griciuc et al., 2013, 2019; Yuan et al., 2016). These findings collectively show that microglial DAMP clearance in AD requires proper expression and functioning of microglial sensome receptors.

Therefore, it is important to study how sensome receptor–DAMP interactions control the functional transition of microglia and result in beneficial outcomes in AD. Accordingly, in this review, we first summarize how the aberrant accumulation and changes of DAMPs (including Aβ and hyperphosphorylated tau) dysregulate microglial functions (including impaired DAMP clearance and excessive synaptic loss) in AD. The current literature suggests that effective DAMP clearance by microglia significantly contributes to the amelioration of AD pathology. Then, we discuss the important axes of receptor–ligand interaction (including CD33, TREM2, cytokine, and chemokine signalings) that regulate the functional transition and effective DAMP clearance of microglia in AD. Furthermore, we highlight the inhibitory effect of aging on microglial DAMP clearance, especially through increasing the levels of circulating decoy proteins. All presented evidence collectively suggests that microglial chemotaxis—the first critical step of DAMP clearance—is impaired by dysregulated receptor–ligand interactions in aging and AD. Therefore, we suggest that interventions aiming to ameliorate AD pathology could target the regulatory mechanisms of microglial chemotaxis.

2 | ACCUMULATION OF DANGER-ASSOCIATED MOLECULAR PATTERNS IMPAIRS MICROGLIAL CHEMOTACTIC AND PHAGOCYTIC CAPACITY IN ALZHEIMER'S DISEASE

The accumulation of DAMPs including Aβ and hyperphosphorylated tau occurs years before cognitive impairment in patients with AD (Selkoe & Hardy, 2016). Therefore, it is important to understand how the accumulating DAMPs stimulate functional changes of brain cells and contribute to disease pathogenesis in AD. While recent single-nucleus transcriptome profiling of AD brains highlights that nearly all types of brain cells undergo cell type-specific transcriptomic changes (Grubman et al., 2019; Lau, Cao, et al., 2020; Mathys et al., 2019), the field still lacks a comprehensive understanding of how these AD-associated DAMPs trigger cellular changes, especially in microglia, to alter the homeostatic functions of those cells. Here, we first provide an overview on how AD pathological hallmarks, including Aβ and hyperphosphorylated tau, change along disease progression and lead to the functional impairment of microglia.

2.1 | Structural changes of amyloid-beta plaques inhibit microglial chemotaxis and clearance

In AD, Aβ is a major biological signal that triggers microglial activation. Specifically, the extracellular aggregation of Aβ leads to the formation of Aβ plaques and creates a concentration gradient of Aβ that stimulates microglial activation. However, the structures of Aβ plaques are highly heterogeneous and change dynamically along AD progression (Chen et al., 2017; Selkoe & Hardy, 2016). Therefore, it is necessary to delineate the changes that occur in Aβ plaques to understand how they regulate microglial activation and functions.

Aβ plaques first appear in a filamentous form and gradually change into compact and finally inert forms (Yuan et al., 2016). This

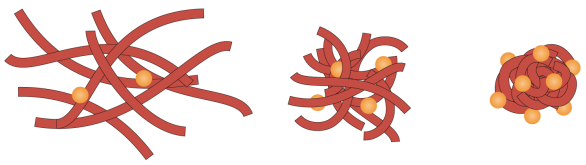
structural transition of Aβ plaques is not autonomous and requires the regulation of Aβ plaque-associated factors, such as apolipoprotein E (APOE). Mass spectrometry analyses reveal that many glial-derived proteins, lipoproteins, and apolipoproteins, accumulate in Aβ plaques in AD (Bai et al., 2020; Blank & Hopf, 2021; Xiong et al., 2019). Among these Aβ plaque-associated factors, APOE has received the most attention because of its genetic contribution to late-onset AD (Corder et al., 1993; Zhou et al., 2019). The accumulation of APOE in Aβ plaques facilitates the seeding and growth of these plaques because of the interaction between APOE and Aβ (Chen et al., 2021; Huynh et al., 2017; Liu et al., 2017). Moreover, the deposition of APOE also increases the compactness of Aβ plaques and converts them into compact and inert plaques (Bales et al., 1997; Liao et al., 2018). Studies using a humanized APOE mouse model show that APOE4 stimulates amyloid seeding more effectively than APOE3 (Lin et al., 2018; Liu et al., 2017). Besides APOE, many glia-derived factors, such as ASC, facilitate Aβ seeding and control amyloid pathology in an amyloidosis mouse model (Venegas et al., 2017). These findings demonstrate that structural changes of Aβ plaques along AD progression involve complex interactions between Aβ and Aβ plaque-associated factors. Nevertheless, further investigation is required to understand the therapeutic potential of targeting these factors. In short, Aβ plaques undergo extensive changes, including changes to their structure and composition, along AD progression.

The structural heterogeneity of Aβ plaques results in differential microglial responses toward the various Aβ plaque subtypes. Structurally, filamentous plaques exhibit more sprouting of amyloid fibrils than compact or inert plaques (number of sprouting amyloid fibrils: filamentous > compact > inert). Interestingly, microglia react to the different forms of Aβ plaques to different extents (i.e., filamentous > compact > inert) (Yuan et al., 2016), possibly because of their differential responses to the sprouting amyloid fibrils (Sebastian Monasor et al., 2020; Sondag et al., 2009). As AD progresses, the proportion of compact and inert plaques gradually increases, which reduces the level of sprouting amyloid fibrils that can stimulate microglial chemotaxis and phagocytosis. While detailed investigation is required to understand why microglia exhibit a preferential response toward sprouting amyloid fibrils, the abovementioned findings collectively show that the continuous accumulation of Aβ plaque-associated factors, such as APOE, increases Aβ plaque compactness and prevents further microglial chemotaxis and clearance of Aβ plaques (Figure 1).

2.2 | Tau triggers microglial activation and exacerbates tau spreading via microglial exosomes

Tau is an intracellular, microtubule-associated protein that is predominantly found in axons. Tau plays a crucial role in maintaining the integrity of the cytoskeleton and axonal transport (Ballatore et al., 2007). Tau hyperphosphorylation and aggregation are found in the brains of patients with AD and are correlated with the disease progression. While further investigation is required to understand the exact cause(s) of tau microtubule detachment, hyperphosphorylation, and aggregation, intracellular tau aggregates to form neurofibrillary tangles, resulting in neuronal functional impairment and death in AD.

Tau pathology progresses in a stereotypic manner, spreading from the entorhinal cortex to the hippocampus and finally to the neocortex (Braak & Braak, 1991). Several hypotheses aim to explain why tau pathology spreads through anatomically connected regions, including the release of tau from dystrophic/dying neurons, trans-synaptic transmission of tau, and microglia-dependent transmission of tau (Asai et al., 2015; Brunello et al., 2020; Takeda, 2019). In particular, activated microglia control the spread of tauopathy. Extracellular diffusible tau first triggers microglial activation by activating NF-κB-dependent transcriptomic reprogramming, which leads to the production of proinflammatory cytokines (Das et al., 2020; Jin et al., 2021; Morales et al., 2013; Wang et al., 2022). In turn, activated microglia facilitate the spread of tau through the



	Filamentous	Compact	Inert
Sprouting amyloid fibrils	+++	++	+
Changes along AD progression	↓	↑	↑
Aβ plaque-associated factors (e.g., ApoE)	+	++	+++
Ability to trigger microglial chemotaxis	+++	++	+

FIGURE 1 Characteristics of amyloid-beta plaque subtypes and changes along Alzheimer's disease progression. Diagram summarizing the characteristics of three Aβ plaque subtypes, including the levels of sprouting amyloid fibrils, changes of these subtypes along AD progression, accumulation of Aβ plaque-associated factors, and ability to trigger microglial chemotaxis. The levels are indicated as follows: +++, highest level; +, lowest level. Aβ, amyloid beta; AD, Alzheimer's disease.

exosome-mediated release of phagocytosed tau (Asai et al., 2015). However, further investigation is needed to understand why activated microglia fail to degrade phagocytosed tau and release them via exosomes. Together, these findings suggest that tau-mediated microglial activation contributes to the spread of tau pathology and exacerbates AD pathogenesis.

3 | ACTIVATED MICROGLIA MEDIATE NEURONAL DYSFUNCTION IN ALZHEIMER'S DISEASE

The accumulation of DAMPs, including Aβ and tau, can stimulate the activation of microglia and alter their homeostatic functions, including synaptic pruning. Homeostatic microglia regulate synaptic pruning via various mechanisms including the phagocytic engulfment of synapses, phagocytic clearance of the perisynaptic extracellular matrix, or even non-phagocytic mechanisms (Cheadle et al., 2020; Nguyen et al., 2020; Schafer & Stevens, 2015). Recent evidence further suggests that microglia-mediated synaptic pruning exhibits selectivity toward excitatory and inhibitory synapses by sensing the specific neurotransmitter released (Favuzzi et al., 2021). Therefore, the proper level of synaptic pruning by microglia is required for homeostatic neuronal functions.

However, in early AD stage, aberrant microglial activation results in detrimental synaptic remodeling and neuronal dysfunction. Here, we discuss the important axes of receptor–ligand interaction that regulate microglia-mediated synaptic loss in AD.

3.1 | Microglia-derived complement proteins lead to synaptic loss

The complement system is a crucial host defense mechanism for eliminating pathogens. Complement system signaling comprises a series of proteolytic events that lead to the formation of the membrane attack complex on the cell surface of pathogens, which results in their lysis (Dunkelberger & Song, 2010). Three major pathways can activate the complement system: the classical, lectin, or alternative pathway. Among these activation pathways, the classical pathway—which involves the conversion of C1 complex (comprising C1q, C1r, and C1s) to C3 convertase and the subsequent cleavage of C3 to generate the opsonin C3b—plays a role in microglia-mediated synaptic pruning in AD.

While C1q and C3 expressions are maintained at low levels in microglia in the homeostatic state, their levels increase significantly upon oligomeric Aβ stimulation or Aβ plaque accumulation (Hong et al., 2016; Schafer et al., 2012; Schafer & Stevens, 2015; Shi et al., 2017). Increased C1q level is associated with increased phagocytic activity and synaptic engulfment by microglia in AD (Hong et al., 2016). Concordantly, inhibiting complement signaling by genetic ablation or antibody neutralization of complement proteins (i.e., C1qa or C3) or their receptor (i.e., C3R) rescues the synaptic loss and impaired synaptic plasticity (i.e., long-term potentiation) in a mouse model of tauopathy or upon oligomeric Aβ stimulation (Dejanovic et al., 2018; Hong et al., 2016). These findings collectively show that the complement system is critical for microglia-mediated synaptic loss in AD.

How do complement proteins regulate synaptic pruning? Super-resolution imaging analysis shows that in a transgenic mouse model of amyloid deposition, complement proteins (e.g., C1q) colocalize with postsynaptic PSD95 puncta (Hong et al., 2016), suggesting that C1q could serve as a molecular tag on synapses, priming them for microglial phagocytosis. However, further investigation is needed to understand how the secreted complement proteins recognize synapses and guide microglial chemotaxis toward C1q-tagged synapses. Nevertheless, these findings suggest that in AD, Aβ stimulates the excessive production of complement proteins (i.e., C1q and C3)—the aberrant accumulation of which in synapses leads to excessive microglia-mediated synaptic loss.

3.2 | Microglia-derived cytokines induce neurotoxic astrocytes and lead to neuronal dysfunction

Besides mediating synaptic loss through the complement system, chronically activated microglia produce soluble factors that lead to neuronal dysfunction. In AD, the chronic activation of microglia results in the prolonged production of proinflammatory cytokines (e.g., tumor necrosis factor [TNF]-α, interleukin [IL]-1 α, IL-1β, and IL-6), reactive oxygen species, and nitric oxide. Increased levels of these soluble factors can induce excitotoxicity and tau hyperphosphorylation, which result in neuronal dysregulation. For example, IL-1β administration promotes the surface trafficking of NMDA receptors by NR2A/B phosphorylation (Viviani et al., 2003). In turn, this sensitizes neurons to glutamate, increases glutamate-induced Ca^{2+} influx, and leads to excitotoxicity (Allan et al., 2005; Mishra et al., 2012; Viviani et al., 2006). Apart from their direct effects on synaptic impairment, proinflammatory cytokines mediate the neurotoxicity of oligomeric Aβ. For example, TNF-α signaling regulates oligomeric Aβ-induced memory impairment via insulin receptor substrate (IRS-1) signaling (Lourenco et al., 2013). Furthermore, microglial proinflammatory cytokines promote the differentiation of homeostatic astrocytes into neurotoxic reactive astrocytes (Liddelow et al., 2017), which lose their neurotrophic support and mediate neuronal death. Recent findings further suggest that neurotoxic astrocytes secrete saturated lipids, which contain APOE and ApoJ lipoparticles, to mediate neuronal death (Guttenplan et al., 2021).

Together, these findings reveal that microglia-secreted factors, such as complement proteins and proinflammatory cytokines, contribute to neuronal dysfunction by directly acting on neurons or indirectly by activating neurotoxic reactive astrocytes in AD.

4 | DYSREGULATED MICROGLIAL CHEMOTAXIS INHIBITS THE MICROGLIAL PHAGOCYTIC CLEARANCE OF DANGER-ASSOCIATED MOLECULAR PATTERNS

Once microglia are activated by accumulating DAMPs, they undergo transcriptomic reprogramming (Mathys et al., 2017; McQuade et al., 2020) and a multistate functional transition in which they first adopt a transient but essential chemotactic state before transiting to a phagocytic state (Heneka et al., 2015; Lau et al., 2021; Perry et al., 2010). This stepwise transition also shows that chemotaxis (i.e., the directed migration of microglia) and phagocytosis occur in sequential order. Microglia can only mediate phagocytic clearance when they are in contact with Aβ plaques or tau aggregates after chemotaxis. Therefore, successful chemotaxis is a prerequisite for all contact-based microglial functions including phagocytosis and DAMP clearance.

Mechanistically, microglial chemotaxis requires the precise interaction between a receptor and a ligand (i.e., chemoattractant) in which the concentration gradient of the chemoattractant directs microglial migration (SenGupta et al., 2021; Shellard & Mayor, 2020). However, the continuous changes in AD brain milieus strongly inhibit microglial receptor-mediated chemotaxis, contributing to impaired microglial Aβ phagocytosis and clearance. Here, we review the key changes in the ligand–chemoattractant interactions along AD progression—including alterations of microglial receptors, extrinsic cytokine and chemokine signalings, and aging factors—that dysregulate microglial chemotaxis in AD.

4.1 | Receptor dysfunction impairs microglial amyloid-beta chemotaxis and subsequent clearance in Alzheimer's disease

Many AD genetic risk variants are located near genes that encode microglial receptors. These risk variants alter the expression levels or functions of microglial receptors, including TREM2 and CD33, thereby impairing microglial chemotaxis toward Aβ, which is the first critical step of Aβ clearance (Griciuc et al., 2013; Guerreiro et al., 2013; Hollingworth et al., 2011; Yuan et al., 2016; Zhou et al., 2020). In addition, phagocytic receptors, such as the TAM receptors Axl and Mer, regulate microglial clearance of Aβ plaques (Fourgeaud et al., 2016; Huang et al., 2021). These findings show that the proper functioning of microglial receptors is crucial for microglial Aβ clearance and limiting AD pathogenesis, which we discuss below.

4.1.1 | The TREM2 axis

TREM2 (triggering receptor expressed on myeloid cells 2) is a single-pass transmembrane protein that is specifically expressed by microglia in the CNS. TREM2 signaling, which is activated through the downstream adapter protein DAP12, regulates various microglial functions including survival, migration, and phagocytosis (Ulland & Colonna, 2018). Whole-exome and whole-genome sequencing analyses have identified a rare R47H variant of TREM2 that carries an increased risk of AD (odds ratio = ~4.5) (Guerreiro et al., 2013; Ulland & Colonna, 2018). In AD carriers of this variant, microglial migration toward Aβ plaques is decreased and microglia exhibit a reduced reactive signature marked by reduced expression of *CHI3L1*, *HLA-DRA*, and *CA2* (Yuan et al., 2016; Zhou et al., 2020).

How does TREM2 regulate microglial Aβ chemotaxis? In vitro screening shows that TREM2 can bind to various lipoproteins and apolipoproteins such as APOE and ApoJ/CLU (Song et al., 2017; Wang et al., 2015; Yeh et al., 2017). Given that Aβ plaques have an abundance of these apolipoproteins, TREM2 can regulate the microglial sensing of Aβ plaque-associated factors and affect microglial Aβ chemotaxis. Indeed, genetic ablation of TREM2 restrains microglial migration toward Aβ plaques (Wang et al., 2015; Yuan et al., 2016). Genetic analysis and in vitro screening further support the notion that this dysregulated TREM2-mediated apolipoprotein sensing in microglia plays a detrimental role in Aβ chemotaxis. The R47H TREM2 risk variant reduces the binding affinity of TREM2 to lipoproteins and apolipoproteins (e.g., LDL, CLU, and APOE), suggesting that this variant increases AD risk by reducing the microglial sensing of Aβ plaque-associated apolipoproteins and impairing microglial Aβ chemotaxis (Wang et al., 2015; Yuan et al., 2016). Together, these findings highlight that TREM2 is a crucial regulator of microglial Aβ chemotaxis through its ability to recognize Aβ plaque-associated APOE in AD.

4.1.2 | The CD33 axis

CD33 (also called "Siglec-3") is a member of the sialic acid-binding immunoglobulin-like lectins (siglecs) and is expressed by microglia in the brain (Crocker et al., 2007). Its association with AD risk was first demonstrated by two large genome-wide association studies showing that two CD33 variants—rs3826656 and rs3865444—are associated with late-onset AD (Bertram et al., 2008; Hollingworth et al., 2011; Naj et al., 2011). Specifically, rs3865444 is a protective variant that can lower the protein expression of CD33 and enhance $A\beta_{42}$ phagocytosis in microglia; indeed, among patients with AD, carriers of this variant have lower $A\beta_{42}$ levels than non-carriers (Griciuc et al., 2013).

To understand why reduced CD33 leads to enhanced $A\beta_{42}$ uptake, we need to first elucidate the role of CD33 in microglial activation. Human CD33 has immunoreceptor tyrosine-based inhibitory motifs (ITIMs) that can suppress the activation of receptors containing immunoreceptor tyrosine-based activation motifs (ITAMs) in microglia (Crocker et al., 2007). Upon activation, receptors with ITIMs function as docking sites for recruiting SH2 (Src homology 2) domain-containing tyrosine and inositol phosphatases, which in turn can suppress ITAM-containing receptor-mediated signaling (Crocker

et al., 2007; Ravetch & Lanier, 2000). Two notable tyrosine and inositol phosphatases, SHP1 (SH2 domain-containing protein tyrosine phosphatase 1) and SHP2, bind to ITIM-containing receptors. These findings collectively suggest that CD33 plays an immunosuppressive role in the regulation of microglial functions through the inhibition of ITAM signaling (Figure 2a).

Among all types of ITAM signaling, TREM2/DAP12 signaling is the most implicated in AD (Gratuze et al., 2018; Konishi & Kiyama, 2018; Ulland & Colonna, 2018). Given that both the transcript and protein levels of microglial CD33 are up-regulated in AD (Griciuc et al., 2013), an increased CD33 level potentially attenuates TREM2-mediated microglial chemotaxis. Indeed, functional studies demonstrate that TREM2 signaling is required for CD33 genetic ablation to confer its beneficial effects in 5xFAD transgenic mice, including memory improvement and Aβ clearance (Griciuc et al., 2019). While CD33 loss can enhance microglial recruitment toward Aβ plaques, this is dampened by TREM2 knockout. These findings suggest that CD33 and TREM2 signalings regulate microglial Aβ chemotaxis in an antagonistic manner (Figure 2b). Importantly, CD33 inhibits TREM2-dependent Aβ chemotaxis in microglia in AD.

Besides sensing Aβ plaque-associated factors, some microglial receptors regulate microglial chemotaxis through sensing extrinsic signals. Indeed, the stimulation of microglial Aβ chemotaxis requires factors, including interleukins and chemokines, from other brain cell types. Single-nucleus transcriptome analysis of AD brains reveals that astrocytes are the major cellular source of alarmin cytokines, including HMGB1 and IL-33, which alert neighboring cells to injury (Lau, Cao, et al., 2020). Besides alarmins, astrocytes secrete other interleukins, such as IL-3, to regulate microglial Aβ chemotaxis in AD (McAlpine et al., 2021). Here, we discuss how astrocyte–microglia communication, exemplified by IL-3 and IL-33, can regulate microglial Aβ chemotaxis in AD.

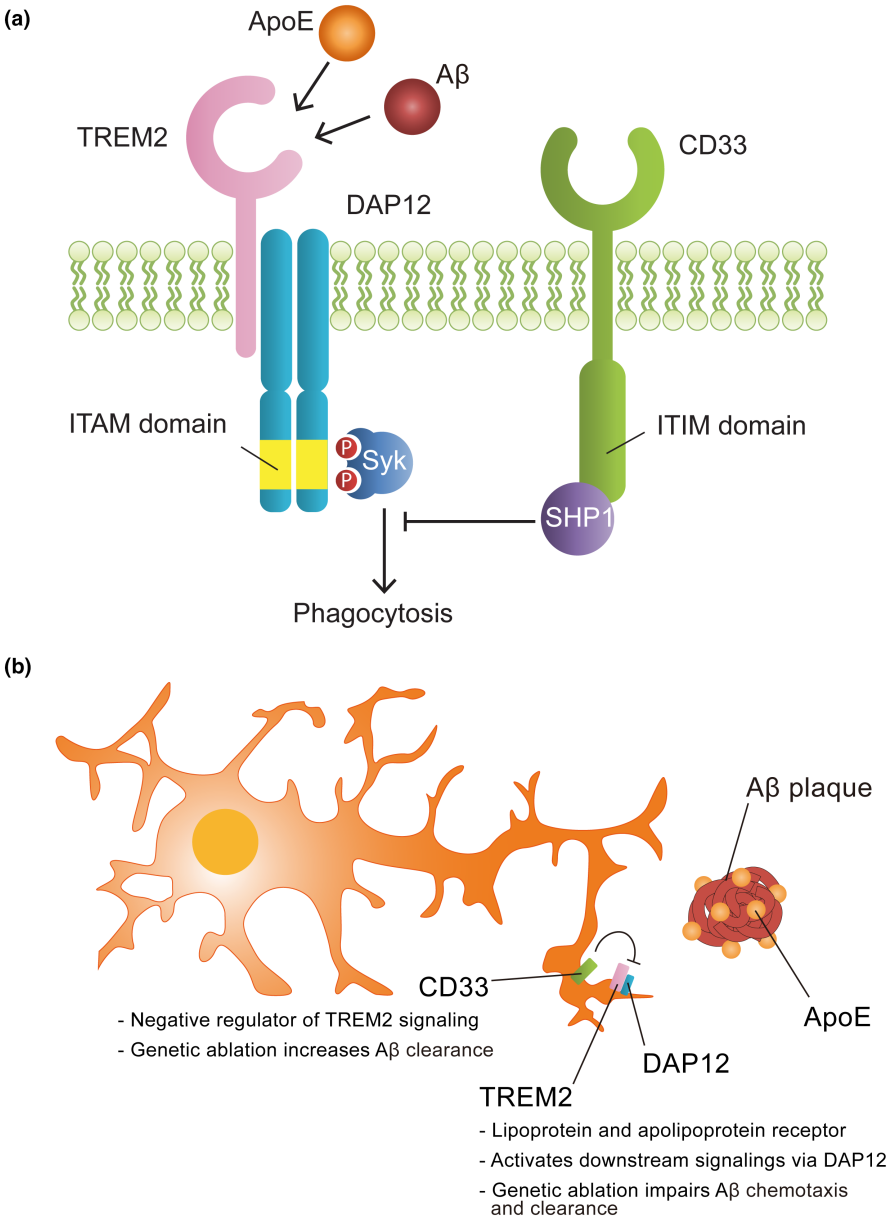


FIGURE 2 CD33/TREM2 pathways regulate microglial amyloid-beta chemotaxis and clearance. (a, b) Diagrams summarizing the interplay between CD33 and TREM2 signalings (a) at the signaling level and (b) at the cellular level in microglia that regulate Aβ chemotaxis and clearance in the progression of Alzheimer's disease. Aβ, amyloid beta; ApoE, apolipoprotein E; CD33, sialic acid-binding Ig-like lectin 3; DAP12, TYRO protein tyrosine kinase-binding protein; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; TREM2, triggering receptor expressed on myeloid cells; SHP1, Src homology region 2 domain-containing phosphatase-1; Syk, spleen tyrosine kinase.

4.1.3 | The IL-3/IL-3R axis

IL-3 is a member of the colony-stimulating factor family and controls immune response and tissue homeostasis through its receptor complexes IL-3Rα and IL-3Rβ (Mindur & Swirski, 2019). Along AD progression, plasma IL-3 level decreases while microglial IL-3R expression increases, which are correlated with disease stage (McAlpine et al., 2021; Ravetti & Moscato, 2008; Ray et al., 2007). These findings show that IL-3/IL-3R signaling is dysregulated in AD.

This dysregulated signaling in AD impairs microglial Aβ chemotaxis and exacerbates Aβ pathology. Genetic ablation of either astrocytic IL-3 or microglial IL-3R reduces microglial migration toward Aβ plaques, leading to increased Aβ plaque levels, a reduced disease-associated microglia gene signature, and impaired cognitive functions (McAlpine et al., 2021). Meanwhile, replenishment of IL-3 can rescue the functional impairment of microglia in AD. For example, recombinant IL-3 treatment promotes microglial Aβ chemotaxis in 5xFAD mice and a 3D human triculture system (McAlpine et al., 2021). However, further detailed and independent investigations are required to understand the mechanisms by which IL-3/IL-3R signaling promotes microglial state transition and modifies microglial receptor–chemoattractant interaction. Of note, IL-3R signaling has crosstalk with TREM2 signaling, as TREM2 genetic ablation inhibits IL-3R expression in microglia. Together, these findings highlight the beneficial role of astrocytic IL-3 in the regulation of Aβ chemotaxis and clearance through the microglial IL-3 receptor in AD.

4.1.4 | The IL-33/ST2 axis

IL-33, a member of the IL-1 cytokine family, triggers its downstream signaling through the induction of the dimerization of ST2 and IL-1 receptor accessory protein (IL-1RAP) (Liew et al., 2016). In AD, IL-33/ST2 signaling is dysregulated and associated with disease pathogenesis. Along AD progression, the brain transcript level of *IL33* is reduced and the plasma level of soluble ST2 (sST2), a decoy IL-33 receptor, is increased (Chapuis et al., 2009; Fu et al., 2016), resulting in reduced IL-33/ST2 activation. Indeed, the replenishment of IL-33 in AD transgenic mouse models promotes microglial Aβ chemotaxis and clearance, leading to the amelioration of amyloid pathology and improved cognitive performance (Fu et al., 2016; Lau, Chen, et al., 2020).

How does IL-33/ST2 signaling modulate microglial Aβ chemotaxis? The activation of this signaling leads to the nuclear translocation of NF-κB and stimulates transcriptional reprogramming in microglia similar to the classical IL-1 receptor signaling cascade (Lau et al., 2021). Our recent work shows that IL-33 promotes microglial Aβ chemotaxis and clearance through the remodeling of the microglial epigenetic landscape, including chromatin accessibility and the PU.1 binding landscape (Lau, Chen, et al., 2020). In that study, inhibiting PU.1 transcriptional control in microglia using a small molecule inhibitor abolished microglial recruitment toward Aβ and attenuated Aβ clearance after IL-33 treatment in APP/PS1 mice. However, further investigation is required to clarify the molecular basis by which specific cytokines (e.g., IL-3 and IL-33) promote microglial Aβ chemotaxis. Specifically, it is of great interest to understand which receptor(s) is induced in microglia upon IL-3/IL-33 treatment to regulate the enhanced Aβ chemotaxis.

In conclusion, these studies underscore the roles of astrocytic factors, including IL-3 and IL-33, play in instructing and maintaining microglial Aβ chemotaxis through their corresponding microglial receptors (Figure 3).

4.1.5 | The CCL2/CCR2 axis

Chemokine signaling is another important axis that regulates the chemotaxis of migrating cells. Chemokine secretion by stationary

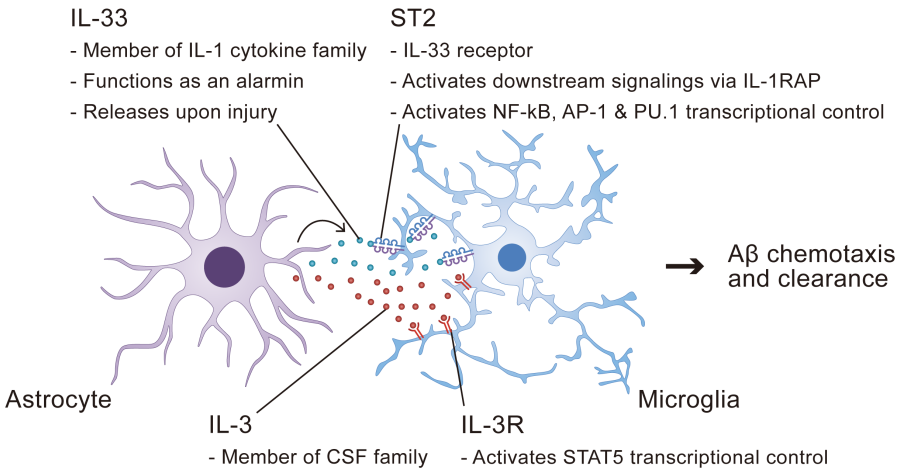


FIGURE 3 Astrocyte-derived interleukin 3 and interleukin 33 instruct microglial amyloid-beta chemotaxis and clearance. Diagram summarizing how astrocyte-derived IL-3 and IL-33 regulate microglial functions to promote Aβ chemotaxis and clearance. IL-3 and IL-33 stimulate the activation of gene expression profiles through specific transcription factors. Aβ, amyloid beta; AP-1, activator protein 1; CSF, colony-stimulating factor; IL, interleukin; IL-1RAP, IL-1 receptor accessory protein; STAT, signal transducer and activator of transcription.

cells functions as a chemoattractant or chemorepellent to regulate the directionality of chemotaxis (SenGupta et al., 2021; Shellard & Mayor, 2020). However, this concept is not completely applicable to Aβ chemotaxis, in which Aβ plaques are the destination of migrating microglia. In Aβ chemotaxis, Aβ plaques and Aβ plaque-associated factors including astrocytic and microglial APOE act as chemoattractants for migrating microglia. Therefore, we hypothesize that chemokine signaling is involved in microglial chemotaxis by depositing more chemoattractants in Aβ plaques or regulating the expression levels of other Aβ receptors in microglia. Interestingly, the dysregulation of various chemokine signalings—including CCL2, CCL5, CXCL10, and CX3CL1 signalings—are reported in patients with AD (Gschwandtner et al., 2019; Guedes et al., 2018); among these, CCL2/CCR2 signaling is the most extensively investigated in AD. Here, we summarize the role of chemokine signaling in the regulation of microglial Aβ chemotaxis, which is exemplified by CCL2/CCR2 signaling.

CCL2 was initially found to be derived from tumor cells to attract immune cells including monocytes, natural killer cells, and dendritic cells (di Liberto et al., 2018). To mediate its chemoattractant effect, CCL2 binds to its high-affinity receptor CCR2. The activation of CCL2/CCR2 signaling can trigger various downstream signalings—including Ras/Rac, JAK, and PI3K signalings—and result in the activation of AP-1, STAT, and NF-κB transcription factors (Fei et al., 2021; Gschwandtner et al., 2019; Hao et al., 2020). These findings suggest that activation of the CCL2/CCR2 axis can directly drive chemotaxis by functioning as a chemotactic receptor or indirectly by inducing the expression of other chemotactic receptors.

In AD, increased CCL2 chemokine levels are observed in the brain, cerebrospinal fluid, and plasma and are positively correlated with disease progression (Guedes et al., 2018). CCR2, the CCL2 receptor, is critical for regulating Aβ chemotaxis. Genetic ablation of CCR2 increases Aβ accumulation in blood vessels (el Khoury et al., 2007). Interestingly, CCR2 itself does not reduce Aβ binding to microglia but is required for microglial Aβ chemotaxis. These findings suggest that CCR2 potentially regulates the expression of other Aβ receptors that are required for Aβ recognition and chemotaxis.

Given the importance of chemokine signaling in the regulation of microglial chemotaxis, detailed investigation is required to further understand how chemokine signaling regulates the molecular signature of microglia and how it enhances their chemotactic capacity.

5 | THE EXPRESSION OF DECOY RECEPTORS IN BRAIN MILIEUS IS INCREASED IN AGING AND ALZHEIMER'S DISEASE

Aging is an important risk factor for AD. Aging increases AD risk in part by changing the levels of aging factors (i.e., circulating proteins) in the CNS milieu, which in turn modifies microglial response toward DAMPs. Given the prognostic value of using these factors as biomarkers to predict the staging or severity of AD, many studies have conducted proteome profiling of plasma in aged populations and patients with AD, yielding promising results (Jiang, Zhou, Ip, et al., 2022; Ray et al., 2007). Intriguingly, many of the differentially expressed factors are truncated cell-surface receptors—including soluble VCAM1, sST2, and soluble TREM2—that regulate microglial chemotactic and phagocytic responses (Henjum et al., 2016; Jiang, Wong, et al., 2022; Jiang, Zhou, Ip, et al., 2022; Yousef et al., 2019).

These truncated cell-surface receptors, also known as decoy receptors, act as extracellular molecular traps that silence the signaling receptor complex (Mantovani et al., 2001). These decoy receptors contain an extracellular domain that can bind the ligand (i.e., agonist) with high affinity but are unable to trigger intracellular signaling. They can be produced by the proteolytic cleavage of a full-length surface receptor (e.g., VCAM1 or TREM2) (Garton et al., 2003; Thornton et al., 2017) or transcribed through an alternative promoter (e.g., ST2) (Iwahana et al., 1999). Genetics studies highlight the contributions of decoy receptors to AD pathogenesis. In particular, a genetic variant of ST2 protects against AD risk by reducing the level of sST2 in cerebrospinal fluid (Jiang, Wong, et al., 2022). Moreover, patients with AD carrying this ST2 protective variant exhibit increased microglial activation and infiltration into Aβ plaques than non-carriers. Recent evidence also suggests that these decoy receptors can modify microglial phagocytosis in aging. For example, lowering the protein level of soluble VCAM1 in the blood through genetic knockout or antibody neutralization can improve microglial phagocytic responses (indicated by increased CD68 level) in aged mice and restore the detrimental effects of aged blood transfusion in young mice (Yousef et al., 2019). However, the exact mechanisms by which elevated decoy protein levels interfere with microglial chemotactic and phagocytic responses to impair ligand–chemoattractant interactions are unclear. Further research should focus on clarifying how these aging-related decoy receptors inhibit the microglial detection of specific chemoattractants in the contexts of aging and AD.

What are the cellular sources of these decoy receptors? To address this, comprehensive transcriptome profiling of brain cell types at the single-cell level along aging and in AD is required. Recent advancements in single-nucleus transcriptome analysis enable this type of profiling, as they use more easily accessible frozen postmortem brain tissue from aged individuals and patients with AD. Several studies provide useful single-nucleus transcriptome databases for more detailed examinations of the cell type specific transcriptomic changes in AD across brain regions, including the prefrontal and entorhinal cortices (Grubman et al., 2019; Lau, Cao, et al., 2020; Mathys et al., 2019; Zhou et al., 2020). While these decoy receptors can be produced within the brain, they can also enter the brain through the damaged blood–brain barrier in the contexts of aging and AD (Sweeney et al., 2018). Accordingly, the blood–brain barrier is more permeable in aged humans (Montagne et al., 2015). Therefore, future investigations should consider the roles of peripheral factors in brain aging.

6 | CONCLUDING REMARKS

AD is the leading type of dementia and remains incurable partly because of our incomplete understanding of the molecular basis of its pathogenesis. In this review, we discussed the critical roles of various receptor–ligand axes in controlling microglial activation and their functional state transition (i.e., chemotaxis to phagocytosis) in AD. Based on these findings, we provide novel insights into the therapeutic potential of restoring microglial chemotaxis and phagocytosis by administration of agonist antibodies that activate microglial receptor signalings or neutralizing antibodies against Aβ plaque-associated factors, immune signalings, or decoy receptors. In line with our idea, there are ongoing clinical trials that target microglial chemotactic receptors, such as TREM2, suggesting their therapeutic potential in ameliorating AD pathogenesis. However, detailed investigation of the interactions between the repertoire of microglial receptors and chemoattractants is required to identify precise molecular targets to restore the microglial chemotactic response and for the development of microglia-targeting therapies for AD.

AUTHOR CONTRIBUTIONS

Shun-Fat Lau, Amy K. Y. Fu, and Nancy Y. Ip conceived and wrote the manuscript.

ACKNOWLEDGMENTS

We thank Ka Chun Lok for the excellent illustrations as well as all other members of the Ip Laboratory for many helpful discussions. This study was supported in part by the National Key R&D Program of China Grants (2021YFE0203000); the Research Grants Council of Hong Kong (the Collaborative Research Fund [C6027-19GF], the Theme-Based Research Scheme [T13-605/18W], and the General Research Fund [HKUST16103017 and HKUST16100418]); the Areas of Excellence Scheme of the University Grants Committee (AoE/M-604/16); the Innovation and Technology Commission Grant (InnoHK and ITCPD/17-9); the Guangdong Provincial Key S&T Program Grant (2018B030336001); the Guangdong Provincial Fund for Basic and Applied Basic Research (2019B1515130004); Fundamental Research Program of Shenzhen Virtual University Park (2021Szvup137). S.-F.L. is a recipient of the Hong Kong Postdoctoral Fellowship Award.

CONFLICT OF INTEREST STATEMENT

All authors declare no competing interests.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/jnc.15933.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Shun-Fat Lau https://orcid.org/0000-0002-8527-3205
Amy K. Y. Fu https://orcid.org/0000-0003-4085-6201
Nancy Y. Ip https://orcid.org/0000-0002-2763-8907

REFERENCES

Allan, S. M., Tyrrell, P. J., & Rothwell, N. J. (2005). Interleukin-1 and neuronal injury. *Nature Reviews. Immunology*, *5*, 629–640. https://doi.org/10.1038/nri1664

Asai, H., Ikezu, S., Tsunoda, S., Medalla, M., Luebke, J., Haydar, T., Wolozin, B., Butovsky, O., Kügler, S., & Ikezu, T. (2015). Depletion of microglia and inhibition of exosome synthesis halt tau propagation. *Nature Neuroscience*, *18*, 1584–1593. https://doi.org/10.1038/nn.4132

Bai, B., Wang, X., Li, Y., Chen, P. C., Yu, K., Dey, K. K., Yarbro, J. M., Han, X., Lutz, B. M., Rao, S., Jiao, Y., Sifford, J. M., Han, J., Wang, M., Tan, H., Shaw, T. I., Cho, J. H., Zhou, S., Wang, H., … Peng, J. (2020). Deep multilayer brain proteomics identifies molecular networks in Alzheimer's disease progression. *Neuron*, *105*, 975–991.e7. https://doi.org/10.1016/j.neuron.2019.12.015

Bales, K. R., Verina, T., Dodel, R. C., du, Y., Altstiel, L., Bender, M., Hyslop, P., Johnstone, E. M., Little, S. P., Cummins, D. J., Piccardo, P., Ghetti, B., & Paul, S. M. (1997). Lack of apolipoprotein E dramatically reduces amyloid β-peptide deposition. *Nature Genetics*, *17*, 263–264. https://doi.org/10.1038/ng1197-263

Ballatore, C., Lee, V. M. Y., & Trojanowski, J. Q. (2007). Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. *Nature Reviews. Neuroscience*, *8*, 663–672. https://doi.org/10.1038/nrn2194

Bertram, L., Lange, C., Mullin, K., Parkinson, M., Hsiao, M., Hogan, M. F., Schjeide, B. M. M., Hooli, B., DiVito, J., Ionita, I., Jiang, H., Laird, N., Moscarillo, T., Ohlsen, K. L., Elliott, K., Wang, X., Hu-Lince, D., Ryder, M., Murphy, A., … Tanzi, R. E. (2008). Genome-wide association analysis reveals putative Alzheimer's disease susceptibility loci in addition to APOE. *American Journal of Human Genetics*, *83*, 623–632. https://doi.org/10.1016/j.ajhg.2008.10.008

Blank, M., & Hopf, C. (2021). Spatially resolved mass spectrometry analysis of amyloid plaque-associated lipids. *Journal of Neurochemistry*, *159*, 330–342. https://doi.org/10.1111/jnc.15216

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica*, *82*, 239–259. https://doi.org/10.1007/BF00308809

Brunello, C. A., Merezhko, M., Uronen, R. L., & Huttunen, H. J. (2020). Mechanisms of secretion and spreading of pathological tau protein. *Cellular and Molecular Life Sciences*, *77*, 1721–1744. https://doi.org/10.1007/s00018-019-03349-1

Chapuis, J., Hot, D., Hansmannel, F., Kerdraon, O., Ferreira, S., Hubans, C., Maurage, C. A., Huot, L., Bensemain, F., Laumet, G., Ayral, A. M., Fievet, N., Hauw, J. J., DeKosky, S. T., Lemoine, Y., Iwatsubo, T., Wavrant-Devrièze, F., Dartigues, J. F., Tzourio, C., … Lambert, J. C. (2009). Transcriptomic and genetic studies identify IL-33 as a candidate gene for Alzheimer's disease. *Molecular Psychiatry*, *14*, 1004–1016. https://doi.org/10.1038/mp.2009.10

Cheadle, L., Rivera, S. A., Phelps, J. S., Ennis, K. A., Stevens, B., Burkly, L. C., Lee, W. C. A., & Greenberg, M. E. (2020). Sensory experience engages microglia to shape neural connectivity through a non-phagocytic mechanism. *Neuron*, *108*, 451–468.e9. https://doi.org/10.1016/j.neuron.2020.08.002

Chen, G. F., Xu, T. H., Yan, Y., Zhou, Y. R., Jiang, Y., Melcher, K., & Xu, H. E. (2017). Amyloid beta: Structure, biology and structure-based therapeutic development. *Acta Pharmacologica Sinica*, *38*, 1205–1235. https://doi.org/10.1038/aps.2017.28

Chen, Y., Strickland, M. R., Soranno, A., & Holtzman, D. M. (2021). Apolipoprotein E: Structural insights and links to Alzheimer disease

pathogenesis. *Neuron*, *109*, 205–221. https://doi.org/10.1016/j.neuron.2020.10.008

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., Roses, A. D., Haines, J. L., & Pericak-Vance, M. A. (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*, *261*, 921–923. https://doi.org/10.1126/science.8346443

Crocker, P. R., Paulson, J. C., & Varki, A. (2007). Siglecs and their roles in the immune system. *Nature Reviews. Immunology*, *7*, 255–266. https://doi.org/10.1038/nri2056

Das, R., Balmik, A. A., & Chinnathambi, S. (2020). Phagocytosis of full-length tau oligomers by Actin-remodeling of activated microglia. *Journal of Neuroinflammation*, *17*, 1–15. https://doi.org/10.1186/s12974-019-1694-y

Dejanovic, B., Huntley, M. A., de Mazière, A., Meilandt, W. J., Wu, T., Srinivasan, K., Jiang, Z., Gandham, V., Friedman, B. A., Ngu, H., Foreman, O., Carano, R. A. D., Chih, B., Klumperman, J., Bakalarski, C., Hanson, J. E., & Sheng, M. (2018). Changes in the synaptic proteome in tauopathy and rescue of tau-induced synapse loss by C1q antibodies. *Neuron*, *100*, 1322–1336.e7. https://doi.org/10.1016/j.neuron.2018.10.014

di Liberto, G., Pantelyushin, S., Kreutzfeldt, M., Page, N., Musardo, S., Coras, R., Steinbach, K., Vincenti, I., Klimek, B., Lingner, T., Salinas, G., Lin-Marq, N., Staszewski, O., Costa Jordão, M. J., Wagner, I., Egervari, K., Mack, M., Bellone, C., Blümcke, I., … Merkler, D. (2018). Neurons under T cell attack coordinate phagocyte-mediated synaptic stripping. *Cell*, *175*, 458–471.e19. https://doi.org/10.1016/j.cell.2018.07.049

Dunkelberger, J. R., & Song, W. C. (2010). Complement and its role in innate and adaptive immune responses. *Cell Research*, *20*, 34–50. https://doi.org/10.1038/cr.2009.139

el Khoury, J., Toft, M., Hickman, S. E., Means, T. K., Terada, K., Geula, C., & Luster, A. D. (2007). Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer-like disease. *Nature Medicine*, *13*, 432–438. https://doi.org/10.1038/nm1555

Favuzzi, E., Huang, S., Saldi, G. A., Binan, L., Ibrahim, L. A., Fernández-Otero, M., Cao, Y., Zeine, A., Sefah, A., Zheng, K., Xu, Q., Khlestova, E., Farhi, S. L., Bonneau, R., Datta, S. R., Stevens, B., & Fishell, G. (2021). GABA-receptive microglia selectively sculpt developing inhibitory circuits. *Cell*, *184*, 4048–4063.e32. https://doi.org/10.1016/j.cell.2021.06.018

Fei, L., Ren, X., Yu, H., & Zhan, Y. (2021). Targeting the CCL2/CCR2 axis in cancer immunotherapy: One stone, three birds? *Frontiers in Immunology*, *12*, 4657. https://doi.org/10.3389/fimmu.2021.771210

Fourgeaud, L., Través, P. G., Tufail, Y., Leal-Bailey, H., Lew, E. D., Burrola, P. G., Callaway, P., Zagórska, A., Rothlin, C. V., Nimmerjahn, A., & Lemke, G. (2016). TAM receptors regulate multiple features of microglial physiology. *Nature*, *532*, 240–244. https://doi.org/10.1038/nature17630

Fu, A. K. Y., Hung, K. W., Yuen, M. Y. F., Zhou, X., Mak, D. S. Y., Chan, I. C. W., Cheung, T. H., Zhang, B., Fu, W. Y., Liew, F. Y., & Ip, N. Y. (2016). IL-33 ameliorates Alzheimer's disease-like pathology and cognitive decline. *Proceedings of the National Academy of Sciences of the United States of America*, *113*, E2705–E2713. https://doi.org/10.1073/pnas.1604032113

Garton, K. J., Gough, P. J., Philalay, J., Wille, P. T., Blobel, C. P., Whitehead, R. H., Dempsey, P. J., & Raines, E. W. (2003). Stimulated shedding of vascular cell adhesion molecule 1 (VCAM-1) is mediated by tumor necrosis factor-α-converting enzyme (ADAM 17). *The Journal of Biological Chemistry*, *278*, 37459–37464. https://doi.org/10.1074/jbc.M305877200

Gomez-Nicola, D., & Perry, V. H. (2015). Microglial dynamics and role in the healthy and diseased brain: A paradigm of functional plasticity. *The Neuroscientist*, *21*, 169–184. https://doi.org/10.1177/1073858414530512

Gratuze, M., Leyns, C. E. G., & Holtzman, D. M. (2018). New insights into the role of TREM2 in Alzheimer's disease. *Molecular Neurodegeneration*, *13*, 1–16. https://doi.org/10.1186/s13024-018-0298-9

Griciuc, A., Patel, S., Federico, A. N., Choi, S. H., Innes, B. J., Oram, M. K., Cereghetti, G., McGinty, D., Anselmo, A., Sadreyev, R. I., Hickman, S. E., el Khoury, J., Colonna, M., & Tanzi, R. E. (2019). TREM2 acts downstream of CD33 in modulating microglial pathology in Alzheimer's disease. *Neuron*, *103*, 820–835.e7. https://doi.org/10.1016/j.neuron.2019.06.010

Griciuc, A., Serrano-Pozo, A., Parrado, A. R., Lesinski, A. N., Asselin, C. N., Mullin, K., Hooli, B., Choi, S. H., Hyman, B. T., & Tanzi, R. E. (2013). Alzheimer's disease risk gene cd33 inhibits microglial uptake of amyloid beta. *Neuron*, *78*, 631–643. https://doi.org/10.1016/j.neuron.2013.04.014

Grubman, A., Chew, G., Ouyang, J. F., Sun, G., Choo, X. Y., McLean, C., Simmons, R. K., Buckberry, S., Vargas-Landin, D. B., Poppe, D., Pflueger, J., Lister, R., Rackham, O. J. L., Petretto, E., & Polo, J. M. (2019). A single-cell atlas of entorhinal cortex from individuals with Alzheimer's disease reveals cell-type-specific gene expression regulation. *Nature Neuroscience*, *22*, 2087–2097. https://doi.org/10.1038/s41593-019-0539-4

Gschwandtner, M., Derler, R., & Midwood, K. S. (2019). More than just attractive: How CCL2 influences myeloid cell behavior beyond chemotaxis. *Frontiers in Immunology*, *10*, 2759. https://doi.org/10.3389/fimmu.2019.02759

Guedes, J. R., Lao, T., Cardoso, A. L., & El Khoury, J. (2018). Roles of microglial and monocyte chemokines and their receptors in regulating Alzheimer's disease-associated amyloid-β and tau pathologies. *Frontiers in Neurology*, *9*, 549. https://doi.org/10.3389/fneur.2018.00549

Guerreiro, R., Wojtas, A., Bras, J., Carrasquillo, M., Rogaeva, E., Majounie, E., Cruchaga, C., Sassi, C., Kauwe, J. S., Younkin, S., Hazrati, L., Collinge, J., Pocock, J., Lashley, T., Williams, J., Lambert, J. C., Amouyel, P., Goate, A., Rademakers, R., … Alzheimer Genetic Analysis Group. (2013). TREM2 variants in Alzheimer's disease. *The New England Journal of Medicine*, *368*, 117–127. https://doi.org/10.1056/nejmoa1211851

Guttenplan, K. A., Weigel, M. K., Prakash, P., Wijewardhane, P. R., Hasel, P., Rufen-Blanchette, U., Münch, A. E., Blum, J. A., Fine, J., Neal, M. C., Bruce, K. D., Gitler, A. D., Chopra, G., Liddelow, S. A., & Barres, B. A. (2021). Neurotoxic reactive astrocytes induce cell death via saturated lipids. *Nature*, *599*, 102–107. https://doi.org/10.1038/s41586-021-03960-y

Hao, Q., Vadgama, J. V., & Wang, P. (2020). CCL2/CCR2 signaling in cancer pathogenesis. *Cell Communication and Signaling: CCS*, *18*, 1–13. https://doi.org/10.1186/s12964-020-00589-8

Heneka, M. T., Carson, M. J., el Khoury, J., Landreth, G. E., Brosseron, F., Feinstein, D. L., Jacobs, A. H., Wyss-Coray, T., Vitorica, J., Ransohoff, R. M., Herrup, K., Frautschy, S. A., Finsen, B., Brown, G. C., Verkhratsky, A., Yamanaka, K., Koistinaho, J., Latz, E., Halle, A., … Kummer, M. P. (2015). Neuroinflammation in Alzheimer's disease. *Lancet Neurology*, *14*, 388–405. https://doi.org/10.1016/S1474-4422(15)70016-5

Henjum, K., Almdahl, I. S., Årskog, V., Minthon, L., Hansson, O., Fladby, T., & Nilsson, L. N. (2016). Cerebrospinal fluid soluble TREM2 in aging and Alzheimer's disease. *Alzheimer's Research & Therapy*, *8*, 1–11. https://doi.org/10.1186/s13195-016-0182-1

Hickman, S. E., Kingery, N. D., Ohsumi, T. K., Borowsky, M. L., Wang, L. C., Means, T. K., & el Khoury, J. (2013). The microglial sensome revealed by direct RNA sequencing. *Nature Neuroscience*, *16*, 1896–1905. https://doi.org/10.1038/nn.3554

Hollingworth, P., Harold, D., Sims, R., Gerrish, A., Lambert, J. C., Carrasquillo, M. M., Abraham, R., Hamshere, M. L., Pahwa, J. S., Moskvina, V., Dowzell, K., Jones, N., Stretton, A., Thomas, C., Richards, A., Ivanov, D., Widdowson, C., Chapman, J., Lovestone,

S., … Williams, J. (2011). Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nature Genetics*, *43*, 429–436. https://doi.org/10.1038/ng.803

Holmes, C., Cunningham, C., Zotova, E., Woolford, J., Dean, C., Kerr, S., Culliford, D., & Perry, V. H. (2009). Systemic inflammation and disease progression in alzheimer disease. *Neurology*, *73*, 768–774. https://doi.org/10.1212/WNL.0b013e3181b6bb95

Hong, S., Beja-Glasser, V. F., Nfonoyim, B. M., Frouin, A., Li, S., Ramakrishnan, S., Merry, K. M., Shi, Q., Rosenthal, A., Barres, B. A., Lemere, C. A., Selkoe, D. J., & Stevens, B. (2016). Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science*, *352*, 712–716. https://doi.org/10.1126/science.aad8373

Huang, Y., Happonen, K. E., Burrola, P. G., O'Connor, C., Hah, N., Huang, L., Nimmerjahn, A., & Lemke, G. (2021). Microglia use TAM receptors to detect and engulf amyloid β plaques. *Nature Immunology*, *22*, 586–594. https://doi.org/10.1038/s41590-021-00913-5

Huynh, T. P. V., Liao, F., Francis, C. M., Robinson, G. O., Serrano, J. R., Jiang, H., Roh, J., Finn, M. B., Sullivan, P. M., Esparza, T. J., Stewart, F. R., Mahan, T. E., Ulrich, J. D., Cole, T., & Holtzman, D. M. (2017). Age-dependent effects of apoE reduction using antisense oligonucleotides in a model of β-amyloidosis. *Neuron*, *96*, 1013–1023.e4. https://doi.org/10.1016/j.neuron.2017.11.014

Iwahana, H., Yanagisawa, K., Ito-Kosaka, A., Kuroiwa, K., Tago, K., Komatsu, N., Katashima, R., Itakura, M., & Tominaga, S. I. (1999). Different promoter usage and multiple transcription initiation sites of the interleukin-1 receptor-related human ST2 gene in UT-7 and TM12 cells. *European Journal of Biochemistry*, *264*, 397–406. https://doi.org/10.1046/j.1432-1327.1999.00615.x

Jiang, Y., Zhou, X., Ip, F. C., Chan, P., Chen, Y., Lai, N. C. H., Cheung, K., Lo, R. M. N., Tong, E. P. S., Wong, B. W. Y., Chan, A. L. T., Mok, V. C. T., Kwok, T. C. Y., Mok, K. Y., Hardy, J., Zetterberg, H., Fu, A. K. Y., & Ip, N. Y. (2022). Large-scale plasma proteomic profiling identifies a high-performance biomarker panel for Alzheimer's disease screening and staging. *Alzheimer's & Dementia*, *18*, 88–102. https://doi.org/10.1002/alz.12369

Jiang, Y., Zhou, X., Wong, H. Y., Ouyang, L., Ip, F. C. F., Chau, V. M. N., Lau, S. F., Wu, W., Wong, D. Y. K., Seo, H., Fu, W. Y., Lai, N. C. H., Chen, Y., Chen, Y., Tong, E. P. S., Alzheimer's Disease Neuroimaging Initiative, Weiner, M. W., Aisen, P., Petersen, R., … Ip, N. Y. (2022). An IL1RL1 genetic variant lowers soluble ST2 levels and the risk effects of APOE-ε4 in female patients with Alzheimer's disease. *Nature Aging*, *2*, 616–634. https://doi.org/10.1038/s43587-022-00241-9

Jin, M., Shiwaku, H., Tanaka, H., Obita, T., Ohuchi, S., Yoshioka, Y., Jin, X., Kondo, K., Fujita, K., Homma, H., Nakajima, K., Mizuguchi, M., & Okazawa, H. (2021). Tau activates microglia via the PQBP1-cGAS-STING pathway to promote brain inflammation. *Nature Communications*, *12*, 1–22. https://doi.org/10.1038/s41467-021-26851-2

Konishi, H., & Kiyama, H. (2018). Microglial TREM2/DAP12 signaling: A double-edged sword in neural diseases. *Frontiers in Cellular Neuroscience*, *12*, 206. https://doi.org/10.3389/fncel.2018.00206

Lambert, J. C., Ibrahim-Verbaas, C. A., Harold, D., Naj, A. C., Sims, R., Bellenguez, C., Jun, G., DeStefano, A. L., Bis, J. C., Beecham, G. W., Grenier-Boley, B., Russo, G., Thornton-Wells, T. A., Jones, N., Smith, A. V., Chouraki, V., Thomas, C., Ikram, M. A., Zelenika, D., … Bihoreau, M.-T. (2013). Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nature Genetics*, *45*, 1452–1458. https://doi.org/10.1038/ng.2802

Lau, S. F., Cao, H., Fu, A. K. Y., & Ip, N. Y. (2020). Single-nucleus transcriptome analysis reveals dysregulation of angiogenic endothelial cells and neuroprotective glia in Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*, *117*, 25800–25809. https://doi.org/10.1073/pnas.2008762117

Lau, S. F., Chen, C., Fu, W. Y., Qu, J. Y., Cheung, T. H., Fu, A. K. Y., & Ip, N. Y. (2020). IL-33-PU.1 transcriptome reprogramming drives functional state transition and clearance activity of microglia in Alzheimer's disease. *Cell Reports*, *31*, 107530. https://doi.org/10.1016/j.celrep.2020.107530

Lau, S. F., Fu, A. K. Y., & Ip, N. Y. (2021). Cytokine signaling convergence regulates the microglial state transition in Alzheimer's disease. *Cellular and Molecular Life Sciences*, *78*, 4703–4712. https://doi.org/10.1007/s00018-021-03810-0

Liao, F., Li, A., Xiong, M., Bien-Ly, N., Jiang, H., Zhang, Y., Finn, M. B., Hoyle, R., Keyser, J., Lefton, K. B., Robinson, G. O., Serrano, J. R., Silverman, A. P., Guo, J. L., Getz, J., Henne, K., Leyns, C. E. G., Gallardo, G., Ulrich, J. D., … Holtzman, D. M. (2018). Targeting of nonlipidated, aggregated apoE with antibodies inhibits amyloid accumulation. *The Journal of Clinical Investigation*, *128*, 2144–2155. https://doi.org/10.1172/JCI96429

Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., Bennett, M. L., Münch, A. E., Chung, W. S., Peterson, T. C., Wilton, D. K., Frouin, A., Napier, B. A., Panicker, N., Kumar, M., Buckwalter, M. S., Rowitch, D. H., Dawson, V. L., Dawson, T. M., … Barres, B. A. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*, *541*, 481–487. https://doi.org/10.1038/nature21029

Liew, F. Y., Girard, J. P., & Turnquist, H. R. (2016). Interleukin-33 in health and disease. *Nature Reviews. Immunology*, *16*, 676–689. https://doi.org/10.1038/nri.2016.95

Lin, Y. T., Seo, J., Gao, F., Feldman, H. M., Wen, H. L., Penney, J., Cam, H. P., Gjoneska, E., Raja, W. K., Cheng, J., Rueda, R., Kritskiy, O., Abdurrob, F., Peng, Z., Milo, B., Yu, C. J., Elmsaouri, S., Dey, D., Ko, T., … Tsai, L. H. (2018). APOE4 causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types. *Neuron*, *98*, 1141–1154.e7. https://doi.org/10.1016/j.neuron.2018.05.008

Liu, C. C., Zhao, N., Fu, Y., Wang, N., Linares, C., Tsai, C. W., & Bu, G. (2017). ApoE4 accelerates early seeding of amyloid pathology. *Neuron*, *96*, 1024–1032.e3. https://doi.org/10.1016/j.neuron.2017.11.013

Lourenco, M. V., Clarke, J. R., Frozza, R. L., Bomfim, T. R., Forny-Germano, L., Batista, A. F., Sathler, L. B., Brito-Moreira, J., Amaral, O. B., Silva, C. A., Freitas-Correa, L., Espírito-Santo, S., Campello-Costa, P., Houzel, J. C., Klein, W. L., Holscher, C., Carvalheira, J. B., Silva, A. M., Velloso, L. A., … de Felice, F. G. (2013). TNF-α mediates PKR-dependent memory impairment and brain IRS-1 inhibition induced by Alzheimer's β-amyloid oligomers in mice and monkeys. *Cell Metabolism*, *18*, 831–843. https://doi.org/10.1016/j.cmet.2013.11.002

Mantovani, A., Locati, M., Vecchi, A., Sozzani, S., & Allavena, P. (2001). Decoy receptors: A strategy to regulate inflammatory cytokines and chemokines. *Trends in Immunology*, *22*, 328–336. https://doi.org/10.1016/S1471-4906(01)01941-X

Mathys, H., Adaikkan, C., Gao, F., Young, J. Z., Manet, E., Hemberg, M., de Jager, P. L., Ransohoff, R. M., Regev, A., & Tsai, L. H. (2017). Temporal tracking of microglia activation in neurodegeneration at single-cell resolution. *Cell Reports*, *21*, 366–380. https://doi.org/10.1016/j.celrep.2017.09.039

Mathys, H., Davila-Velderrain, J., Peng, Z., Gao, F., Mohammadi, S., Young, J. Z., Menon, M., He, L., Abdurrob, F., Jiang, X., Martorell, A. J., Ransohoff, R. M., Hafler, B. P., Bennett, D. A., Kellis, M., & Tsai, L. H. (2019). Single-cell transcriptomic analysis of Alzheimer's disease. *Nature*, *570*, 332–337. https://doi.org/10.1038/s41586-019-1195-2

McAlpine, C. S., Park, J., Griciuc, A., Kim, E., Choi, S. H., Iwamoto, Y., Kiss, M. G., Christie, K. A., Vinegoni, C., Poller, W. C., Mindur, J. E., Chan, C. T., He, S., Janssen, H., Wong, L. P., Downey, J., Singh, S., Anzai, A., Kahles, F., … Swirski, F. K. (2021). Astrocytic interleukin-3 programs microglia and limits Alzheimer's disease. *Nature*, *595*, 701–706. https://doi.org/10.1038/s41586-021-03734-6

McQuade, A., Kang, Y. J., Hasselmann, J., Jairaman, A., Sotelo, A., Coburn, M., Shabestari, S. K., Chadarevian, J. P., Fote, G., Tu, C. H., Danhash, E., Silva, J., Martinez, E., Cotman, C., Prieto, G. A., Thompson, L. M., Steffan, J. S., Smith, I., Davtyan, H., … Blurton-Jones, M. (2020). Gene expression and functional deficits underlie TREM2-knockout microglia responses in human models of Alzheimer's disease. *Nature Communications*, *11*, 1–17. https://doi.org/10.1038/s41467-020-19227-5

Mindur, J. E., & Swirski, F. K. (2019). Growth factors as immunotherapeutic targets in cardiovascular disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *39*, 1275–1287. https://doi.org/10.1161/ATVBAHA.119.311994

Mishra, A., Kim, H. J., Shin, A. H., & Thayer, S. A. (2012). Synapse loss induced by interleukin-1β requires pre-and post-synaptic mechanisms. *Journal of Neuroimmune Pharmacology*, *7*, 571–578. https://doi.org/10.1007/s11481-012-9342-7

Montagne, A., Barnes, S. R., Sweeney, M. D., Halliday, M. R., Sagare, A. P., Zhao, Z., Toga, A. W., Jacobs, R. E., Liu, C. Y., Amezcua, L., Harrington, M. G., Chui, H. C., Law, M., & Zlokovic, B. V. (2015). Blood-brain barrier breakdown in the aging human hippocampus. *Neuron*, *85*, 296–302. https://doi.org/10.1016/j.neuron.2014.12.032

Morales, I., Jiménez, J. M., Mancilla, M., & Maccioni, R. B. (2013). Tau oligomers and fibrils induce activation of microglial cells. *Journal of Alzheimer's Disease*, *37*, 849–856. https://doi.org/10.3233/JAD-131843

Naj, A. C., Jun, G., Beecham, G. W., Wang, L. S., Vardarajan, B. N., Buros, J., Gallins, P. J., Buxbaum, J. D., Jarvik, G. P., Crane, P. K., Larson, E. B., Bird, T. D., Boeve, B. F., Graff-Radford, N. R., de Jager, P. L., Evans, D., Schneider, J. A., Carrasquillo, M. M., Ertekin-Taner, N., … Schellenberg, G. D. (2011). Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nature Genetics*, *43*, 436–443. https://doi.org/10.1038/ng.801

Nguyen, P. T., Dorman, L. C., Pan, S., Vainchtein, I. D., Han, R. T., Nakao-Inoue, H., Taloma, S. E., Barron, J. J., Molofsky, A. B., Kheirbek, M. A., & Molofsky, A. V. (2020). Microglial remodeling of the extracellular matrix promotes synapse plasticity. *Cell*, *182*, 388–403.e15. https://doi.org/10.1016/j.cell.2020.05.050

Perry, V. H., & Holmes, C. (2014). Microglial priming in neurodegenerative disease. *Nature Reviews. Neurology*, *10*, 217–224. https://doi.org/10.1038/nrneurol.2014.38

Perry, V. H., Nicoll, J. A. R., & Holmes, C. (2010). Microglia in neurodegenerative disease. *Nature Reviews. Neurology*, *6*, 193–201. https://doi.org/10.1038/nrneurol.2010.17

Ravetch, J. V., & Lanier, L. L. (2000). Immune inhibitory receptors. *Science*, *290*, 84–89. https://doi.org/10.1126/science.290.5489.84

Ravetti, M. G., & Moscato, P. (2008). Identification of a 5-protein biomarker molecular signature for predicting Alzheimer's disease. *PLoS ONE*, *3*, e3111. https://doi.org/10.1371/journal.pone.0003111

Ray, S., Britschgi, M., Herbert, C., Takeda-Uchimura, Y., Boxer, A., Blennow, K., Friedman, L. F., Galasko, D. R., Jutel, M., Karydas, A., Kaye, J. A., Leszek, J., Miller, B. L., Minthon, L., Quinn, J. F., Rabinovici, G. D., Robinson, W. H., Sabbagh, M. N., So, Y. T., … Wyss-Coray, T. (2007). Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. *Nature Medicine*, *13*, 1359–1362. https://doi.org/10.1038/nm1653

Schafer, D. P., Lehrman, E. K., Kautzman, A. G., Koyama, R., Mardinly, A. R., Yamasaki, R., Ransohoff, R. M., Greenberg, M. E., Barres, B. A., & Stevens, B. (2012). Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron*, *74*, 691–705. https://doi.org/10.1016/j.neuron.2012.03.026

Schafer, D. P., & Stevens, B. (2015). Microglia function in central nervous system development and plasticity. *Cold Spring Harbor Perspectives in Biology*, *7*, a020545. https://doi.org/10.1101/cshperspect.a020545

Sebastian Monasor, L., Müller, S. A., Colombo, A. V., Tanrioever, G., König, J., Roth, S., Liesz, A., Berghofer, A., Piechotta, A., Prestel, M., Saito, T., Saido, T. C., Herms, J., Willem, M., Haass, C., Lichtenthaler, S. F., & Tahirovic, S. (2020). Fibrillar aβ triggers microglial proteome alterations and dysfunction in alzheimer mouse models. *eLife*, *9*, 1–33. https://doi.org/10.7554/eLife.54083

Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Molecular Medicine*, *8*, 595–608. https://doi.org/10.15252/emmm.201606210

SenGupta, S., Parent, C. A., & Bear, J. E. (2021). The principles of directed cell migration. *Nature Reviews. Molecular Cell Biology*, *22*, 529–547. https://doi.org/10.1038/s41580-021-00366-6

Shellard, A., & Mayor, R. (2020). All roads lead to directional cell migration. *Trends in Cell Biology*, *30*, 852–868. https://doi.org/10.1016/j.tcb.2020.08.002

Shi, Q., Chowdhury, S., Ma, R., le, K. X., Hong, S., Caldarone, B. J., Stevens, B., & Lemere, C. A. (2017). Complement C3 deficiency protects against neurodegeneration in aged plaque-rich APP/PS1 mice. *Science Translational Medicine*, *9*, 9. https://doi.org/10.1126/scitranslmed.aaf6295

Sondag, C. M., Dhawan, G., & Combs, C. K. (2009). Beta amyloid oligomers and fibrils stimulate differential activation of primary microglia. *Journal of Neuroinflammation*, *6*, 1–13. https://doi.org/10.1186/1742-2094-6-1

Song, W., Hooli, B., Mullin, K., Jin, S. C., Cella, M., Ulland, T. K., Wang, Y., Tanzi, R. E., & Colonna, M. (2017). Alzheimer's disease-associated TREM2 variants exhibit either decreased or increased ligand-dependent activation. *Alzheimer's & Dementia*, *13*, 381–387. https://doi.org/10.1016/j.jalz.2016.07.004

Sweeney, M. D., Sagare, A. P., & Zlokovic, B. V. (2018). Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nature Reviews. Neurology*, *14*, 133–150. https://doi.org/10.1038/nrneurol.2017.188

Takeda, S. (2019). Tau propagation as a diagnostic and therapeutic target for dementia: Potentials and unanswered questions. *Frontiers in Neuroscience*, *13*, 1274. https://doi.org/10.3389/fnins.2019.01274

Thornton, P., Sevalle, J., Deery, M. J., Fraser, G., Zhou, Y., Ståhl, S., Franssen, E. H., Dodd, R. B., Qamar, S., Gomez Perez-Nievas, B., Nicol, L. S. C., Eketjäll, S., Revell, J., Jones, C., Billinton, A., St George-Hyslop, P. H., Chessell, I., & Crowther, D. C. (2017). TREM 2 shedding by cleavage at the H157-S158 bond is accelerated for the Alzheimer's disease-associated H157Y variant. *EMBO Molecular Medicine*, *9*, 1366–1378. https://doi.org/10.15252/emmm.201707673

Ulland, T. K., & Colonna, M. (2018). TREM2—A key player in microglial biology and Alzheimer disease. *Nature Reviews. Neurology*, *14*, 667–675. https://doi.org/10.1038/s41582-018-0072-1

Venegas, C., Kumar, S., Franklin, B. S., Dierkes, T., Brinkschulte, R., Tejera, D., Vieira-Saecker, A., Schwartz, S., Santarelli, F., Kummer, M. P., Griep, A., Gelpi, E., Beilharz, M., Riedel, D., Golenbock, D. T., Geyer, M., Walter, J., Latz, E., & Heneka, M. T. (2017). Microglia-derived ASC specks crossseed amyloid-β in Alzheimer's disease. *Nature*, *552*, 355–361. https://doi.org/10.1038/nature25158

Viviani, B., Bartesaghi, S., Gardoni, F., Vezzani, A., Behrens, M. M., Bartfai, T., Binaglia, M., Corsini, E., di Luca, M., Galli, C. L., & Marinovich, M. (2003). Interleukin-1β enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases. *The Journal of Neuroscience*, *23*, 8692–8700. https://doi.org/10.1523/jneurosci.23-25-08692.2003

Viviani, B., Gardoni, F., Bartesaghi, S., Corsini, E., Facchi, A., Galli, C. L., di Luca, M., & Marinovich, M. (2006). Interleukin-1β released by gp120 drives neural death through tyrosine phosphorylation and trafficking of NMDA receptors. *The Journal of Biological Chemistry*, *281*, 30212–30222. https://doi.org/10.1074/jbc.M602156200

Wang, C., Fan, L., Khawaja, R. R., Liu, B., Zhan, L., Kodama, L., Chin, M., Li, Y., le, D., Zhou, Y., Condello, C., Grinberg, L. T., Seeley, W. W., Miller, B. L., Mok, S. A., Gestwicki, J. E., Cuervo, A. M., Luo, W., & Gan, L. (2022). Microglial NF-κB drives tau spreading and toxicity

in a mouse model of tauopathy. *Nature Communications*, *13*, 1–19. https://doi.org/10.1038/s41467-022-29552-6

Wang, Y., Cella, M., Mallinson, K., Ulrich, J. D., Young, K. L., Robinette, M. L., Gilfillan, S., Krishnan, G. M., Sudhakar, S., Zinselmeyer, B. H., Holtzman, D. M., Cirrito, J. R., & Colonna, M. (2015). TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease model. *Cell*, *160*, 1061–1071. https://doi.org/10.1016/j.cell.2015.01.049

Xiong, F., Ge, W., & Ma, C. (2019). Quantitative proteomics reveals distinct composition of amyloid plaques in Alzheimer's disease. *Alzheimer's & Dementia*, *15*, 429–440. https://doi.org/10.1016/j.jalz.2018.10.006

Yeh, F. L., Hansen, D. V., & Sheng, M. (2017). TREM2, microglia, and neurodegenerative diseases. *Trends in Molecular Medicine*, *23*, 512–533. https://doi.org/10.1016/j.molmed.2017.03.008

Yousef, H., Czupalla, C. J., Lee, D., Chen, M. B., Burke, A. N., Zera, K. A., Zandstra, J., Berber, E., Lehallier, B., Mathur, V., Nair, R. V., Bonanno, L. N., Yang, A. C., Peterson, T., Hadeiba, H., Merkel, T., Körbelin, J., Schwaninger, M., Buckwalter, M. S., … Wyss-Coray, T. (2019). Aged blood impairs hippocampal neural precursor activity and activates microglia via brain endothelial cell VCAM1. *Nature Medicine*, *25*, 988–1000. https://doi.org/10.1038/s41591-019-0440-4

Yuan, P., Condello, C., Keene, C. D., Wang, Y., Bird, T. D., Paul, S. M., Luo, W., Colonna, M., Baddeley, D., & Grutzendler, J. (2016). TREM2 haplodeficiency in mice and humans impairs the microglia barrier function leading to decreased amyloid compaction and severe axonal dystrophy. *Neuron*, *90*, 724–739. https://doi.org/10.1016/j.neuron.2016.05.003

Zhou, X., Chen, Y., Mok, K. Y., Kwok, T. C. Y., Mok, V. C. T., Guo, Q., Ip, F. C., Chen, Y., Mullapudi, N., Alzheimer's Disease Neuroimaging Initiative, Giusti-Rodríguez, P., Sullivan, P. F., Hardy, J., Fu, A. K. Y., Li, Y., & Ip, N. Y. (2019). Non-coding variability at the APOE locus contributes to the Alzheimer's risk. *Nature Communications*, *10*, 10. https://doi.org/10.1038/s41467-019-10945-z

Zhou, Y., Song, W. M., Andhey, P. S., Swain, A., Levy, T., Miller, K. R., Poliani, P. L., Cominelli, M., Grover, S., Gilfillan, S., Cella, M., Ulland, T. K., Zaitsev, K., Miyashita, A., Ikeuchi, T., Sainouchi, M., Kakita, A., Bennett, D. A., Schneider, J. A., … Colonna, M. (2020). Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease. *Nature Medicine*, *26*, 131–142. https://doi.org/10.1038/s41591-019-0695-9

How to cite this article: Lau, S.-F., Fu, A. K. Y., & Ip, N. Y. (2023). Receptor–ligand interaction controls microglial chemotaxis and amelioration of Alzheimer's disease pathology. *Journal of Neurochemistry*, *166*, 891–903. https://doi.org/10.1111/jnc.15933