nature reviews immunology

https://doi.org/10.1038/s41577-024-01104-7

Review article

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# Neuroinflammation in Alzheimer disease

A list of authors and their affiliations appears at the end of the paper

## Abstract

Increasing evidence points to a pivotal role of immune processes in the pathogenesis of Alzheimer disease, which is the most prevalent neurodegenerative and dementia-causing disease of our time. Multiple lines of information provided by experimental, epidemiological, neuropathological and genetic studies suggest a pathological role for innate and adaptive immune activation in this disease. Here, we review the cell types and pathological mechanisms involved in disease development as well as the influence of genetics and lifestyle factors. Given the decade-long preclinical stage of Alzheimer disease, these mechanisms and their interactions are driving forces behind the spread and progression of the disease. The identification of treatment opportunities will require a precise understanding of the cells and mechanisms involved as well as a clear definition of their temporal and topographical nature. We will also discuss new therapeutic strategies for targeting neuroinflammation, which are now entering the clinic and showing promise for patients.

## Sections



e-mail: michael.heneka@uni.lu

## Key points

- There is strong evidence for an inflammatory component of Alzheimer disease.
- Extrinsic factors, such as brain trauma, diet, systemic and local infections, and the gut microbiota, have an impact on the inflammatory component of Alzheimer disease.
- Factors intrinsic to the host, including microglial phagocytosis, barrier function in the brain, cellular metabolism and cell senescence, also have a central role in neuroinflammation in Alzheimer disease.
- Astrocytes, oligodendrocytes, lymphocytes and peripheral myeloid cells contribute to neuroinflammation in Alzheimer disease.
- Vascular cells become activated in Alzheimer disease and a leakiness of the blood–brain barrier is observed. A contributing role of the glymphatic system has also been described.
- New therapeutic approaches based on targeting the inflammatory component of Alzheimer disease are currently being tested in clinical trials. Future trials are also being designed to target these pathways.

## Introduction

Alzheimer disease (AD) represents the most common cause of dementia, accounting for roughly 70% of all cases, and given its high care burden, the disease is a major health care challenge. Neuropathologically, AD is characterized by extracellular deposition of misfolded and aggregated amyloid-β (Aβ) peptides as well as by the formation of intraneuronal neurofibrillary tangles made of hyperphosphorylated tau (p-tau). Although Alois Alzheimer described histological abnormalities in astroglia and microglia, the changes seen in these cells were long regarded as an irrelevant bystander effect. More recent studies have challenged and substantially changed this view, and immune-mediated disease mechanisms have become a field of intense research and drug development in AD. Consequently, one must consider which immunological process at which time point can be harnessed for therapeutic intervention. While, in general, such immune modulation may include preventive, disease-modifying or even acute therapeutic strategies, it is commonly accepted that clinically silent or even inapparent disease stages may hold the greatest potential for such interventions. Identification and definition of pre-dementia stages of AD, such as subjective cognitive impairment and mild cognitive impairment, together with biomarker discovery may allow delineation of the time, duration and sites where immune interventions will successfully interfere with disease pathogenesis and progression. In this Review, we summarize and weigh the current knowledge on immune processes in AD. Starting with a review of human evidence for an inflammatory component in AD, we then describe the individual cellular compartments and specific immune mechanisms that contribute to disease pathogenesis. Several of these mechanistic studies have been performed in animal models displaying a specific pathology, for instance, deposition of tau. While the detailed phenotypes, advantages and limitations of these animal models of AD are reviewed elsewhere[1–3], we focus here on the specific immunological aspects of these models and relate these to the human disease.

## Evidence for an inflammatory component in AD

### Brain pathology and microglial changes in AD

The term 'plaques' was introduced in 1898 — almost 7 years before Alois Alzheimer described AD — for structures that are today known as Aβ plaques in the AD brain[4,5]. Glial cells surrounding these plaques had already been described and it was speculated that these plaques were of glial origin[4,5]. It is now clear that microglia are reactive and increased in number in the AD brain as well as being associated with Aβ plaques[6–9], neurofibrillary tangles[10] and complement factors[6] (Fig. 1). These microglia generate immune mediators, such as cytokines, chemokines, inflammasomes and reactive oxygen species (ROS)[6,7,11–16], and contribute to both the asymptomatic and symptomatic disease stages[17,18]. Microglia are also likely to influence the clinical and pathological disease phenotype[19]. In humans, topographical associations have been reported for microglia with Aβ and p-tau but not between Aβ and p-tau, which is consistent with microglia playing a pivotal role in AD pathogenesis[20]. Diffuse Aβ plaques are present in the brains of middle-aged and older individuals who are cognitively normal[21], and markers of homeostatic microglia (such as ionized calcium-binding adaptor molecule 1 (IBA1), purinergic receptor P2Y12R and transmembrane protein 119 (TMEM119)) are downregulated following the appearance of Aβ[22]. While neuritic plaques are defined by the presence of Aβ, the presence of p-tau and activated microglia are additional features of AD[23], with these microglia expressing the phagocytic markers CD68 and macrophage scavenger receptor A (MSRA)[24]. Of note, there is wide variation in Aβ deposits with different involvement of microglia seen in the brains of patients with AD[25]. Aβ in neuritic plaques tends to be more fibrillar, with dense cores, and has a more varied composition with the presence of the 40-residue isoform $Aβ_{40}$, the 42-residue isoform $Aβ_{42}$, the 43-residue isoform $Aβ_{43}$, N-terminally truncated Aβ and other post-translationally modified forms of Aβ[26–28]. AD cases with an atypical clinical presentation show a different spreading and morphology of pathological hallmarks, associated with different levels and spatial localization of microglial activity[19,29]. This supports the hypothesis that the spatial activation of microglia is involved in both the clinical and pathological presentation of the disease. In conclusion, microglial activation is an early event in AD that is instrumental for the morphology of Aβ deposits, the spreading of pathology and the clinical presentation of patients with AD[23].

### Biofluid biomarkers of inflammation

Evidence for an ongoing chronic inflammatory disease component in AD has been further substantiated by probing inflammatory biomarkers in cerebrospinal fluid (CSF) or in blood samples and by the development of microglial positron-emission tomography (PET) tracers such as translocator protein (TSPO) ligands. Although the first studies on biofluid-based biomarkers for inflammation — primarily involving CSF or blood-based protein markers — date back nearly 30 years[30], there remains an unmet demand for reliable biomarkers that monitor the various aspects of AD neuroinflammation. Studies on 'classical' inflammation markers, like C-reactive protein (CRP) or pro-inflammatory cytokines, are large in number but have shown limited consistency in meta-analyses[31,32]. Quantitation of inflammatory mediators, such as cytokines in CSF, can be hampered by the sensitivity of detection technologies[33], but novel ultra-sensitive immunoassays, including single-molecule array, proximity extension assay and nucleic acid-linked immuno-sandwich assay, or measurement of brain-derived exosomes might overcome such limitations[34–36].

For CSF, a few proteins have emerged as robust markers to monitor neuroinflammation in AD due to their reproducible relationship to pathological features of the disease. These proteins are soluble triggering receptor expressed on myeloid cells 2 (TREM2), which is a marker of microglial activation; YKL-40, which is an astroglial inflammation marker; and glial fibrillary acidic protein (GFAP), which serves as a marker of astrocyte reactivity[37–39], although its appropriateness as a standalone marker is still under debate. Interestingly, the CSF GFAP signal in AD is robustly replicated in serum and plasma, with increases in plasma and serum GFAP concentrations closely associated with the onset of cerebral Aβ pathology[40], which likely reflects astrocytic reactivity in response to pathology[41]. Extensive proteomic studies that include validation in biofluids have described several other inflammatory messengers within sets of proteins affected by AD pathology[42]. Furthermore, novel immunoassays might enable the detection of inflammasome components, such as NACHT, LRR and PYD domains-containing protein 3 (NLRP3) and apoptosis-associated speck-like protein containing a CARD (ASC), as biomarkers of inflammasome activation in AD[43,44], with these being therapeutic targets that are soon to be clinically tested in neurodegenerative disease[45]. There is also growing interest in the detailed analysis of CSF leukocyte gene expression patterns. By their nature, CSF or blood-based fluid biomarkers do not help with ascribing inflammatory processes to specific brain areas and cannot be used to assess the spatial and temporal spread of inflammation over the entire disease trajectory. Nevertheless, they will likely be instrumental in detecting overall changes occurring in brain homeostasis and neurodegeneration, thereby helping to identify individuals at risk for disease who can then undergo more detailed investigations.

### Molecular imaging and PET

Changes in regional brain pathology can be partly determined by molecular imaging techniques, including PET, that allow for temporal and spatial analysis of the living human brain. To visualize microglial reactivity by molecular imaging in human brain, radiopharmaceuticals have been developed that target TSPO, which is an 18-kD protein found within the outer mitochondrial membrane[46]. Although TSPO is expressed by microglia, astrocytes and endothelial cells, its upregulation in response to activation is particularly prominent in microglia[47]. Current research aims to develop radiotracers that target receptors more specific to microglia (for example, P2X7R, P2Y12R and $CX_3C$-chemokine receptor 1 ($CX_3CR1$)) in order to visualize changes in these cells[48,49]. Of the second-generation TSPO tracers, two radiotracers (DPA-714 and PBR28) have shown higher binding potential (twofold to threefold) and reduced background activity in comparison to PK11195, a first-generation TSPO tracer[50]. In patients with AD, increased PBR28 binding (to temporal and parietal brain regions) correlates to higher levels of cognitive impairment and atrophy[51] as well as greater regional tau and Aβ deposition[52]. In a longitudinal study (2.7 years), patients positive for Aβ had a greater increase in TSPO binding in several brain regions compared to controls, and changes in TSPO binding correlated well with cognitive decline[53]. These results indicate that TSPO could serve as a biomarker of AD progression in patients and be used to measure the response to anti-inflammatory therapies[53].

By contrast, in prodromal AD, increased TSPO binding (as measured with DPA-714) in the temporoparietal cortex positively correlated with improved Mini-Mental State Examination (MMSE) scores and grey matter volume and slowed cognitive decline[54]. In this study, 30 patients with AD were stratified into slow or fast decliners after 2 years of follow-up. Excitingly, slow decliners showed higher TSPO binding than fast decliners[54]. These results demonstrate that reactive microgliosis occurs during the prodromal and preclinical stages of AD, and that it may even play a protective role at the very early stages of disease[54,55]. Moreover, in patients with clinical AD, an increase of DPA-714 binding was observed at follow-up. The correlation between increasing DPA-714 binding and poorer clinical outcome measures (for example, clinical dementia rating, MMSE, hippocampal atrophy) suggests a detrimental effect of increasing levels of neuroinflammation on clinical AD progression once the disease has developed[56]. In contrast, high initial DPA-714 binding was correlated with a low dynamic increase of microglial reactivity and a favourable clinical course. Another study has proposed an early and late peak of reactive microgliosis in AD trajectory[57]. Together, PET-based microglial imaging can decipher several microglial phenotypes at various disease stages and represents a non-invasive biomarker that may be used to assess future immune-modulating therapies in AD.

### Immune-related genetics

Strong support for the inflammatory hypothesis in AD has come from genome-wide association studies (GWAS). GWAS have not only unravelled a direct genetic connection of inflammation to disease pathogenesis but also hold promise for the identification of inflammation-related therapeutic targets. In total, the percentage of disease risk for AD that can be attributed to inheritable genetic factors has been estimated to be between 56% and 79% in twin studies[58,59]. The development of high-throughput genomic approaches over the

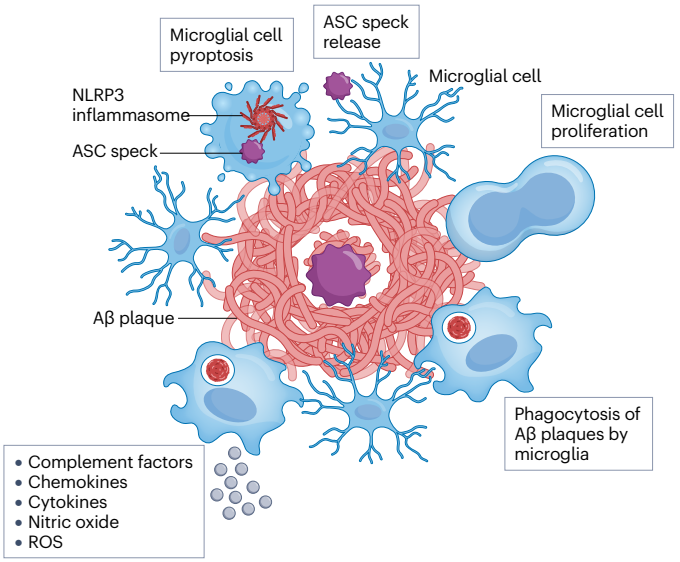


**Fig. 1 | Microglial cell responses at sites of Aβ deposition.** Oligomeric or fibrillar amyloid-β (Aβ) acts as a danger-associated molecular pattern to activate surrounding microglial cells. The microglia release immune mediators, including complement factors, chemokines and cytokines, as well as reactive oxygen species (ROS) and nitric oxide. Microglia attempt to phagocytose Aβ at the site of deposition and can proliferate. Finally, microglia also undergo cell death at sites of Aβ deposition. Activation of the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome can drive an inflammatory form of cell death, namely pyroptosis, which is associated with the release of apoptosis-associated speck-like protein containing a CARD (ASC) specks that can promote further tissue inflammation.

**Table 1 | A non-exhaustive list of the most relevant genes with risk variants for AD**

| AD-related risk factor | Description | Suggested role in AD |
|---|---|---|
| *ABCA7* | A member of the superfamily of ABC transporters | Genome-wide association study-identified risk factor for early-onset and late-onset AD. Has a role in lipid homeostasis and transport in the brain and plays a role in phagocytosis of microglia. Defects repress Aβ clearance |
| *ABI3* | Member of an adaptor protein family that regulates actin polymerization | Highly expressed in microglia and relevant for Aβ plaque-mediated microglial activation. Loss of its activity leads to increased cytokine levels, neuroinflammation and Aβ plaque accumulation. Defects lead to a decrease in microglia number and mobility in the brain |
| *ACE2* | Enzyme cleaves angiotensin I and angiotensin II and is involved in regulating intestinal amino acid homeostasis, expression of antimicrobial peptides and the ecology of the gut microbiome | Its activity is reduced in AD brains, which correlates with increased neuroinflammation and oxidative stress. In the brain, ACE2 converts angiotensin II into angiotensin-(1-7), which protects from inflammation and oxidative stress |
| *ADAM10* | Transmembrane metalloproteinase that cleaves the ectodomain of transmembrane proteins, including adhesion proteins, growth factor precursors and cytokines | The α-secretase cleaves APP within the Aβ sequence, reducing Aβ production. Defects increase extracellular Aβ plaque formation. It is also relevant for keeping normal synapse functions. Relevant for hippocampal neurogenesis. It may influence tau pathology |
| *APH1B* | Functional component of the γ-secretase complex, which enables the intramembrane cleavage of integral proteins including APP | Variants are associated with increased AD risk. Component of the γ-secretase complex. Involved in intramembrane cleavage of APP, producing Aβ. Dysregulated expression increases Aβ plaque formation |
| *APOE* | A core component of plasma lipoproteins that is involved in their production, conversion and clearance | The ε4 allele of this risk factor is related to sporadic AD, whereas the ε2 allele is protective. It has a role in lipid transport and metabolism as well as in membrane integrity and repair. Role for metabolism and clearance of Aβ. Accumulation of more Aβ plaques in the presence of an ε4 variant. The ε4 variant drives earlier and more abundant Aβ deposits and also leads to a stronger tau aggregation and spreading. The neuronal ε4 variant promotes tau phosphorylation and leads to increased neuroinflammation and cell death |
| *BIN1* | Involved in synaptic vesicle endocytosis and may interact with dynamin, synaptojanin, endophilin and clathrin | Risk factor for late-onset AD, relevant for Aβ production and clearance and involved in tau pathology. It is involved in neuronal synapse transmission and also expressed in microglia, where it is important for their activation and their role in neuroinflammation. Defects lead to an accumulation of enlarged early endosomal vesicles and neurodegeneration as well as activation of pro-inflammatory and disease-associated responses of microglia |
| *CD2AP* | Scaffolding molecule that regulates the actin cytoskeleton | Variants of this risk factor affect its protein function and increase susceptibility for AD. Defects lead to increased Aβ production and plaque formation as well as to tau fibrillar tangle accumulation. CD2AP contributes to maintaining blood–brain barrier integrity. It is involved in synaptic plasticity and structure especially in pre-synapses. Also important for dendrite branching and spine density |
| *CR1* | Member of the receptors of complement activation family | This risk factor for late-onset AD plays a role in phagocytosis of Aβ, and complement receptor 1 variants lead to the accumulation of Aβ plaques and to increased neuroinflammation. It is a receptor for components of the complement system of the immune system, which is relevant in regulating clearance of cell debris and pathogens |
| *ECHDC3* | Enoyl-CoA hydratase domain-containing 3, mitochondrial | Modulates neuroinflammation and has a role in lipid metabolism and endolysosomal membrane trafficking |
| *FERMT2* | Scaffolding protein that enhances integrin activation mediated by TLN1 and/or TLN2 but activates integrins only weakly by itself | Relevant for APP metabolism, it modulates APP processing by direct interaction with APP and by processing it to Aβ. Defects promote Aβ production; it affects synaptic plasticity and connectivity as well as axonal growth and guidance. Low expression of *FERMT2* has negative effects on neuronal health, axonal growth and synaptic function |
| *HS3ST1* | Member of the heparan sulfate biosynthetic enzyme family | Relevant for sulfation of heparan sulfate, which affects Aβ aggregation, plaque formation and its clearance as well as tau aggregation speed and aggregate internalization. 3-O-sulfated heparan sulfate can be identified in AD brains. Sulfated heparan sulfate interacts with various receptors and proteins involved in inflammation, possibly impacting neuroinflammation |
| *IL34* | Cytokine that promotes the differentiation and viability of monocytes and macrophages through the CSF1R | Involved in monocyte differentiation. Highly relevant for development, survival and function of microglia. Binds to CSF1R to promote microglial cell proliferation and survival. Relevant for Aβ clearance |
| *MINK1* | Serine–threonine kinase that acts as a negative regulator of Ras-related Rap2-mediated signal transduction to control neuronal structure and AMPA receptor trafficking | Associated with increased AD risk. Involved in various phosphorylation pathways and associated with inflammation in the brain. Required for keeping synaptic integrity and function, thereby important for cognition and memory |
| *PLCG2* | Transmembrane signalling enzyme that catalyses the conversion of 1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate to 1D-myo-inositol 1,4,5-trisphosphate and diacylglycerol using calcium as a cofactor | Gene variants modify AD risk. Expressed by microglia regulating their activity, including response to Aβ deposition. Its increased activity improves microglia functions such as phagocytosis. Associated with the inflammatory response via signalling pathways that regulate production of inflammatory cytokines and chemokines |

**Table 1 (continued) | A non-exhaustive list of the most relevant genes with risk variants for AD**

| AD-related risk factor | Description | Suggested role in AD |
|---|---|---|
| *PLD3* | Member of the phospholipase D family of enzymes that catalyse the hydrolysis of membrane phospholipids | Linked to increased risk for AD. Negative regulator of Aβ production and reduced expression correlates with higher Aβ plaque loads, whereas higher expression levels correlate to attenuated cognitive decline and lower Aβ loads in patients with AD. Positively linked to the number and size of endolysosomal vesicles in neurons as well as to Aβ metabolism |
| *PRKD3* | Serine–threonine protein kinase D family member. Converts transient diacylglycerol signals into prolonged physiological effects, downstream of PKC. Involved in resistance to oxidative stress | Associated with increased AD risk. May affect the production and clearance of Aβ; potentially involved in vesicle trafficking. Plays a role in different signalling pathways regulating neuronal differentiation, survival and apoptosis. Potential role in inflammatory responses in the brain |
| *PTK2B* | Protein tyrosine kinase that is involved in calcium-induced regulation of ion channels and activation of the MAP kinase signalling pathway | Associated with late-onset AD, interacting with Aβ as well as with tau pathology. Modulates Aβ toxicity and colocalizes with p-tau in AD. Relevant for regulating neuroinflammation by affecting microglia activity. Defects lead to increased neuroinflammation. Highly expressed in neurons, affecting synaptic plasticity and signalling. Involved in tau phosphorylation by regulating several tau-modifying kinases |
| *SCIMP* | Scaffold protein, expressed by antigen-presenting cells and is localized in the immunological synapse | Variants increase AD risk. Regulates immune responses in microglia upon Aβ exposure. Relevant for neuroinflammation as its dysregulation causes cerebral inflammation. Involved in pro-inflammatory signalling in Toll-like receptor-activated macrophages. Upregulated in microglia in mouse models of AD |
| *SHARPIN* | Involved in protein linear polyubiquitination and regulation of signal transduction | Related to late-onset AD. Its expression is enhanced by Aβ-induced oxidative stress. Relevant for the regulation of Aβ phagocytosis in peripherial macrophages. Enhances Aβ clearance and reduces Aβ plaque load. It has a role in regulating inflammatory responses in the brain by activation of the NF-κB pathway |
| *SLC2A4* | Protein that functions as an insulin-regulated facilitative glucose transporter | Insulin-regulated glucose transporter. Defects or dysfunction contribute to insulin resistance and metabolic deficits in AD, which can increase oxidative stress and neuroinflammation. Upregulated in AD temporal cortex microglia and involved in fuelling active synapses in neurons |
| *SORL1* | Sortilin-related receptor. Sorting receptor for several cellular proteins, including APP | Associated with AD risk and relevant for processing and trafficking of APP away from sites producing Aβ. It interacts with APOE and tau and may affect tau aggregation and spreading. Involved in Aβ clearance |
| *TREM2* | Triggering receptor expressed on myeloid cells 2. Forms a receptor signalling complex with TYROBP to mediate cell activation. Can bind APP cleavage products | Associated with late-onset AD affecting Aβ clearance and tau expression, aggregation, spreading, and its phosphorylation. Primarily expressed by microglia and relevant for their survival, proliferation and function. Modulates inflammatory responses via galectin 3 and is involved in regulating the production of cytokines and chemokines |
| *UNC5C* | Belongs to the UNC5 family of netrin receptors. Receptor for netrin required for axon guidance | Associated with developing AD and late-onset AD. Enhances neuronal susceptibility to Aβ toxicity and promotes cell death via apoptosis, in particular in the absence of netrin 1. Relevant in DAPK1-mediated tau hyperphosphorylation and neuronal apoptosis in relation to Aβ accumulation and tau pathology. Related to changes in brain structure and atrophy rates in the hippocampus and precuneus |

Aβ, amyloid-β; AD, Alzheimer disease; APOE, apolipoprotein E; APP, Aβ precursor protein; CSF1R, colony-stimulating factor 1 receptor.

past 15 years majorly improved our knowledge of AD genetics[60], and GWAS and next-generation sequencing approaches have now identified more than 80 independent genetic loci that modulate the risk of AD[61,62] (Table 1). Pathway analysis using these genetic findings has identified both innate and adaptive immune responses as key contributing pathways for AD pathogenesis[63,64]. It has also been shown that many AD risk alleles specifically activate enhancers in microglia[65]. In fact, close to 25% of the identified potential AD genetic risk factors could be highly or exclusively expressed by microglia and/or linked to immune-related function[66]. Several of these genes encode mediators that are involved in microglial responses, including factors that activate microglia (such as IL-34 and apolipoprotein E (APOE)), immune receptors (TREM2, transcription factor PU.1 (encoded by *SPI1*), membrane-spanning 4-domains subfamily A member 4A (MS4A4A), MS4A6A, HLA-DQA1 and CD33)[67], signalling intermediates (phospholipase Cγ2 (PLCG2), protein tyrosine kinase 2β (PTK2B) and phosphatidylinositol 3,4,5-trisphosphate 5-phosphatase 1 (INPP5D)) and molecules linked with the cytoskeletal machinery (ABI3 and EPHA1). Other genes encode molecules linked to additional immune-related responses such as complement regulation (complement receptor 1 (CR1) and clusterin (CLU))[66].

Recently, a large meta-GWAS by the European Alzheimer and Dementia Biobank reaffirmed most previously detected immunological loci. Crucially, it also provided genetic evidence linking the linear ubiquitin chain assembly complex (LUBAC) to AD[64]. Comprising SHARPIN, RBCK1 and OTULIN, LUBAC is a high-confidence AD risk factor, unique in forming linear ubiquitin chains and pivotal in inflammation and immunity research. LUBAC is integral to NLRP3 inflammasome activation, impacting innate immune responses and Aβ pathology in AD. It is also involved in autophagy, specifically in modifying TAR DNA-binding protein 43 (TDP43)-positive neuronal inclusions, potentially triggering autophagic clearance. Importantly, the same GWAS study also supported the significance of the TNF signalling pathway in AD. Genetic loci, such as *ADAM17*, which encodes a metalloproteinase crucial for the activation of TNF signalling[68], and *TNIP1*, which encodes a factor that inhibits the TNF pathway[69], were identified. Other relevant factors include SPPL2A, which has a role

in non-canonical TNF shedding[70], and progranulin (PGRN, encoded by *GRN*), which functions as a TNF receptor ligand and antagonist[71].

Genetics studies also suggest a role for adaptive immune responses mediated by HLA-DRB1 (and more specifically a protective role of the *HLA-DRB1*04* subtype), potentially by enabling immune targeting of tau, especially the K311-acetylated form of tau[72] that potentiates aggregation of the tau PHF6 fragment[73]. Importantly, AD research has also shown that tau pathology depends on Aβ42-evoked neuroinflammation and may be linked to microglia connecting both major pathological hallmarks of AD[74–76]. Functional genomics will now be the focus of ongoing work to enable the translation of genetic risk factors to therapeutics.

### Epigenetics

Emerging evidence points to an important role of epigenetics in the regulation of microglia during AD pathogenesis[77–80]. Microglia, as well as other tissue-resident macrophages, show a high degree of epigenetic heterogeneity between tissues and disease states[81]. They also display lineage-specific characteristics and epigenetically primed responses according to the context and previous events[82,83]. Chromatin compaction[84], DNA methylation[85,86], and histone acetylation[83,87], methylation[83,88,89], phosphorylation[84,90] or lactylation[91] are modified in microglia in response to different stimuli. Additionally, microglia are also regulated by non-coding RNAs, among which microRNAs (miRNAs) seem to play a prominent role in controlling microglia-specific gene expression and proteostasis. Changes in microglia-specific miRNAs are observed in liquid biopsies from patients with early AD and can predict disease progression[92,93]. While such epigenetic alterations can persist and may even transmit across generations, they are also reversible[94]. Interventions targeting epigenetic mechanisms, including treatment with DNA methylation[95] and histone deacetylase (HDAC)[96] inhibitors, RNA therapeutics[93,97], and depletion of key components of the epigenetic machinery such as DNA methyltransferase 1 (DNMT1)[98], ten-eleven translocation methylcytosine dioxygenase 2 (TET2)[99], HDAC1 and HDAC2 (refs. 83,100), sirtuin 1 (SIRT1)[101], polycomb protein embryonic ectoderm development[88,102], and Jumonji domain-containing protein 3 (JMJD3)[89], can modify microglial cell responses. Intriguingly, these effects can differ based on contextual factors and the brain's prior state, leading to contrasting outcomes during brain development, homeostasis and disease[81,100,103,104]. In conclusion, epigenetic processes help to shape microglia dynamics and responses to future events[83,105–107], making the epigenome an attractive drug target. Whether this hypothesis will withstand causal validation with epigenetic editing tools remains to be determined but, currently, it provides an exciting framework for future work.

## The exposome — can lifestyle factors modulate inflammation?

While genetic and epigenetic influences may still be viewed as 'given' and 'unchangeable', several lifestyle behaviours and environmental factors, which are collectively described as the exposome, modify the risk of developing AD. Several of these factors are directly or indirectly linked to the immune system, as we summarize below.

### Brain trauma

Traumatic brain injury (TBI) is one of the most important non-genetic, non-age-related risk factors for developing dementia, which correlates consistently with the number and severity of TBIs[108–110]. An association between a single moderate-to-severe TBI and AD neuropathology is less clear, with multiple studies showing no association[111,112]; however, other studies have found an association between TBI with a loss of consciousness and increased Aβ plaque burden, suggesting that the severity of TBI relates to Aβ deposition[113,114]. Notably, exposure to years of repetitive mild TBIs (such as those that occur in contact and collision sports as well as in military soldiers exposed to multiple mild concussive events) is a risk factor for developing chronic traumatic encephalopathy, a neurodegenerative disease characterized by tau pathology in the cortical sulci and around blood vessels[115,116]. Both a single moderate-to-severe TBI and repetitive mild TBIs are associated with chronic vascular injury and blood–brain barrier (BBB) disruption[117,118] as well as with persistent microgliosis[119,120]. Additionally, Aβ precursor protein (APP) is accumulated in axons with diffuse injury after TBI, increasing the risk for Aβ accumulation[121]. Due to the elevated levels of neuroinflammation common to TBI and AD, it is hypothesized that immune responses that occur after TBI accelerate or even trigger AD-prone neuropathological cascades during normal ageing or in individuals with a specific genetic predisposition. Even after a mild TBI, microglia and astrocytes remain persistently reactive[122], secreting inflammatory mediators, such as IL-1β, IL-6, TNF and ASC, that contribute to neurodegeneration post-injury through increased APP transcription[123], γ-secretase expression[124], reduced microglial phagocytosis[125], and pathological post-translational modifications of tau such as hyperphosphorylation[74] and acetylation[126]. Furthermore, in a vicious cycle, the accumulation of toxic peptides and proteins associated with neurodegenerative disorders may also enhance and perpetuate glial responses to traumatic injury, leading to significantly higher secondary damage and accelerated neurodegeneration[127]. Persistent neuroinflammation following TBI may also mediate the increased risk for other neurodegenerative diseases such as Lewy body disease[111,128] and TDP43 disease[129].

### Diet and exercise

Several lifestyle factors influence dementia risk via neuroinflammatory processes[130,131]. Higher physical activity[132,133] is associated with reduced dementia risk and lower inflammatory markers in human blood[134,135]. The association with cognitive performance is largely mediated by the amount of activated microglia[136]. In animal models, increased physical activity as well as an enriched environment attenuate the neuroinflammatory response to Aβ pathology, resulting in reduced cytokine release[134,137–141], altered microglial phagocytic activity[141–143] and improved cognition[137,138,140,142,143]. By contrast, a sedentary lifestyle combined with lack of a balanced diet increases the risk for midlife obesity, midlife hypertension and diabetes[144,145], which are established risk factors for dementia[131]. These processes can induce wide-ranging metabolic changes and systemic chronic inflammation[146,147]. Systemic inflammation and innate immune memory can, in turn, affect neuroinflammatory and neurodegenerative processes in the brain[83,148,149]. Accordingly, pro-inflammatory dietary patterns associate with cognitive decline-related blood-proteome changes[150], high risk for dementia[151] and reduced brain volume[152], while opposite association patterns are observed for a balanced, Mediterranean diet[153–157]. Promoting an active, stimulating lifestyle and a balanced diet (for example, by multi-domain behavioural interventions[158]) therefore holds promise in preventing dementia and reducing neuroinflammation in AD.

### Systemic infection and inflammation

It is generally accepted that peripheral inflammation impacts dementia. For example, enhanced cognitive decline was consistently found in patients with existing AD pathology who additionally experienced

peripheral infections (for a review see Bettcher et al.[159]). Many infections are linked with a significantly increased risk for developing AD and vascular dementia, and increasing numbers of infections increase risk in a cumulative fashion[160]. In mice, it has been shown that systemic inflammation induced by exposure to bacterial lipopolysaccharide (LPS) exacerbated Aβ and tau pathology, for example, through enhanced inflammatory activation and reduced clearance of Aβ and tau[148,161,162]. Interestingly, not only external bacterial challenges but also sterile inflammatory, autoimmune and allergic responses affect brain inflammation[163]. In humans, elevated levels of TNF and acute systemic inflammatory events were associated with more rapid cognitive decline over a 6-month period[160]. Exacerbated pathology is often due to enhanced inflammatory responses in the brain of patients, and this is also seen in animal models.

Mechanistically, inflammation causes 'priming' of microglia that leads to a severe inflammatory response in the pathologically altered brain and, in turn, drives further functional deterioration[164,165]. Interestingly, epidemiological studies have also provided strong evidence that peripheral inflammation increases dementia risk when the inflammatory insult occurs up to two decades earlier[166]. The mechanisms of these long-term effects are much less clear but may involve epigenetic reprogramming of microglia, leading to long-lasting innate immune memory (or 'trained immunity') in the brain that is sufficient to alter AD pathology in mouse models[83]. Such epigenetically driven changes have been described in peripheral macrophages[165,167], but whether microglial innate immune memory also exists in the human brain requires further investigation. Trained immunity may have beneficial functions in the periphery, such as enhanced pathogen clearance, but it may drive hyperinflammation in the brain, thereby exacerbating pathology. There is some evidence that patients with AD who died with infection show higher levels of brain IL-1β than those who died without infection[168] and LPS-induced systemic inflammation is known to potentiate IL-1β activity, driving further inflammasome activation and exacerbating both Aβ and tau pathology. Conversely, while immune tolerance may lead to immune paralysis in the periphery, increasing the risk for secondary infections, it may be beneficial in the brain by inhibiting detrimental microglial reactivity[83,167].

### Poor oral health and periodontitis

Periodontal disease represents a subtle and chronic form of peripheral inflammation. Support for an influencing role of oral hygiene comes from works linking microbiome dysbiosis to the development of dementia in later life[169,170]. LPS from the outer surface membrane of Gram-negative bacteria is a strong immune system activator[171]. The Gram-negative anaerobe *Porphyromonas gingivalis* is considered a keystone bacterium[172] in generalized periodontitis[173]. This bacterium and its virulence factors are found in autopsied AD brains[174–176]. The infection is responsible for causing extensive oxidative damage in a genetically modified ApoE knockout ($ApoE^{-/-}$) mouse model orally infected with *P. gingivalis* to initiate experimental periodontitis[177]. *P. gingivalis* infection and *P. gingivalis*–LPS-induced neuroinflammation were studied in mouse models[178–181] and it was reported that *P. gingivalis* induced classical complement pathway activation following oral infections. A subsequent report demonstrated release of pro-inflammatory cytokines, such as TNF, IL-6 and IL-1β, in the brains of middle-aged mice and also highlighted the involvement of the TLR4–NF-κB signalling pathway[181]. Another study found several types of microglial reactivity states[182] similar to those that account for cytokine secretion in the human brain[183]. Taken together, there are multiple hints that oral health my influence the risk and course of AD. Further clinical and experimental data have to identify the precise mechanisms and time at which oral health interacts with disease pathogenesis.

### Gut microbiome

In addition to the oral microbiome, the gut microbiome may influence immune processes in the brain. It was shown in mice that the gut microbiome essentially educates and shapes microglia responses to pathological insults. Strikingly, rats receiving faecal transplantation from patients with AD develop AD-like symptoms[184]. Conversely, faecal transplantation from healthy mice to AD model animals reduces disease pathology[185,186]. Disease microbiomes can be modified, for example, the traditional Indian medicine Triphala was shown to positively affect cognitive parameters in mice with AD and reduce serum Aβ levels by shifting the microbiome to *Bacteriodetes* and *Verrucomicrobiota* phyla with a reduction of *Cyanobacteria*[187].

There are several routes of communication between the gut microbiome and the brain, including the vagus nerve, the stress-associated hypothalamic–pituitary–adrenal axis, direct or indirect modulation of neurotransmitters and short-chain fatty acids (SCFAs) and other metabolites (reviewed in refs. 188,189). The BBB controls brain entry of peripheral immune cells and immune mediators. Microbiome-originated LPS and SCFAs may impair the permeability of the BBB[190–192] and affect homeostasis, maturation and reactive microgliosis, for example, by SCFA binding to free fatty acid receptor 2 or TLR4 (refs. 193,194). In germ-free[195] mice, the BBB has a higher permeability[192]. The BBB permeability in germ-free mice is rescued by mono-colonization with SCFA-producing bacterial strains[192].

In germ-free mice, there are global defects in microglia morphology and maturity. Temporal eradication of the microbiome subsequently leads to severe changes in microglial properties[193]. Microglia in germ-free animals have enhanced Aβ uptake at early disease stages[196] and protect against tau-related neurodegeneration[197]. Antibiotic-induced microbiome depletion disrupts the BBB in adult mice[198] and may allow peripheral immune cells to enter the brain[199]. Therapy with *Bifidobacterium* and *Lactobacillus* species-based probiotics after antibiotic administration improves BBB integrity and memory deficits in mouse models of AD[187,200]. In addition, microbially derived metabolites from tryptophan and indole that access the brain[201] have an anti-inflammatory effect on microglia and astrocytes. These metabolites bind the aryl hydrocarbon receptor, which then inhibits NF-κB-mediated pro-inflammatory pathways[202–204]. Primary and secondary bile acids that cross the BBB bind to microglial Takeda G protein-coupled receptor 5 (TGR5) and induce an anti-inflammatory phenotype[205] by inhibiting the pro-inflammatory NF-κB pathway via protein kinase A[206,207], therefore also blocking activation of the NLRP3 inflammasome[208]. The conjugated bile acid tauroursodeoxycholic acid reduces gliosis in the context of AD, resulting in reduced Aβ plaque formation and cognitive decline[209]. Despite these various lines of evidence for a disease-modulating role, the precise mechanisms through which microbiome alterations interfere with disease progression need to be better understood.

Additional environmental or personal lifestyle factors may contribute to AD pathogenesis by stimulating, aggravating or accelerating neuroinflammation but such an influence may depend on the genetic background of each individual. Studying gene–exposome interactions may therefore be important to pinpoint which genetic backgrounds and lifestyle factors combine to mediate detrimental as well as protective effects in AD.

## Box 1 | CNS-associated macrophages: an overview

For many years, the ontogeny of central nervous system (CNS)-associated macrophages was unclear and they were thought to originate from bone marrow-derived monocytes[589]. However, elegant fate-mapping experiments have proven their prenatal origin from distinct yolk sac progenitors described as c-KIT$^+$ non-committed erythromyeloid progenitors[590,591]. These progenitors engraft via the CNS surface to the embryonic mouse brain parenchyma at embryonic day 9.5 where they locally migrate, expand and finally gain their typical arborized morphology. Microglia are relatively long-lived cells with a lifespan of several years, and they divide very slowly at estimated rates of about 0.5% with considerable differences in various CNS regions in mouse and human[592–594]. Microglial cells in the steady-state CNS undergo self-renewal without any input from circulating haematopoietic cells, which are excluded by the tight blood–brain barrier[595,596]. As typical tissue macrophages, microglial cells are thought to be extremely sensitive to even minute changes in their microenvironment. As such, they are considered to be tremendously plastic cells that can quickly adopt multiple functional and morphological phenotypes, influenced by environmental cues. The recent advent of several novel single-cell technologies and innovative fate-mapping studies have shed new light on the transcriptional and cellular heterogeneity of microglia in mouse and human[597]. Microglial cells are characterized by distinct transcriptional, epigenetic, proteomic and functional profiles during development, homeostasis and perturbation[214,598]. During pathology, several microglial states have been defined leading to a perplexing nomenclature of context-associated microglial signatures[214,217,221,281,599–601]. Whether this endless description of putative novel microglial clusters or even subsets is meaningful and whether these reflect real distinct biological conditions remains to be determined.

## Microglia and pathophysiological processes in AD

### Microglial cell transcriptomes and differences between murine and human microglia

In the central nervous system (CNS), local macrophages exist in two distinct flavours: either as juxta-neuronal macrophages in the parenchyma — where they are traditionally called microglia — or as resident macrophages at CNS interfaces such as the leptomeninges, the perivascular space and choroid plexus[210–212]. These border macrophages comprise the CNS-associated macrophages (CAMs) (Box 1). CAMs are positioned at strategically important CNS boundaries but their functions are not yet fully understood as was recently discussed[96,213–215].

Nevertheless, the identification of microglial phenotypes that are associated with neurodegeneration[216] in mouse models of AD[217] has sparked considerable interest in these cells. However, mouse models of AD only partially recapitulate the complex brain environment encountered in patients with AD. Human microglia respond to a plethora of environmental signals in the AD brain and genetic variations can also affect microglial function. Bulk analysis of microglia isolated from the brain tissue of children or adults who were cognitively healthy led to the identification of a homeostatic microglial cell gene expression signature[218,219]. Homeostatic microglial marker genes include genes encoding microglia-enriched surface receptors such as $CX_3CR1$, P2RY12 and TMEM119. The generation of single-cell and single-nuclei transcriptomic data from isolated human microglia has revealed multiple, small subclusters — microglial states — that differ from homeostatic microglia and are characterized by the upregulation of distinct marker genes[220,221]. In neurotypical brains, the upregulation of genes encoding MHC class II-associated molecules, such as CD74 and HLA-DRA, by microglia suggests that they can participate in antigen presentation in the brain. Other microglial cell activation states include interferon-responsive microglia (expressing, for example, interferon-induced transmembrane protein 3 (IFITM3), interferon-induced protein with tetratricopeptide repeats 1 (IFIT1), IFIT3 and ubiquitin-like protein ISG15), inflammatory microglia (expressing, for example, CC-chemokine ligand 2 (CCL2), CCL3 and CCL4), proliferative microglia (expressing, for example, MKI67 and PCNA), and a small subset reminiscent of mouse disease-associated microglia (DAM) that expresses APOE and lipoprotein lipase[221].

However, data on gene expression profiles of human microglia states in AD is still limited. Compared to microglia from mouse models, human AD-associated microglia show a higher degree of variation. This is probably due to manifold environmental and genetic differences but also may arise due to technical reasons (for example, differences in microglia isolation and sequencing technologies). Nevertheless, isolation of microglial cells from AD brains and subsequent analysis of the transcriptome has provided important insights into microglial cell activation states[220,222]. Reflecting the complex environmental changes in AD, signature genes for DAM were found across several microglial cell clusters, whereas numbers of MHC class II-positive microglia were reduced[220]. Comparison with mouse microglia isolated from an Aβ mutant mouse model showed only a partial overlap between mouse and human DAM signatures, with the common denominator being genes associated with lipid metabolism and lysosomal function[223]. Regressing microglia gene expression against Aβ and p-tau load revealed that these pathologies are characterized by distinct gene expression responses in microglia[222]. As mentioned above, the gene expression profile of mouse microglia substantially differs from human microglia already under homeostatic conditions. One strategy that can measure the impact of different environmental stimuli on human microglia is the transplantation of human induced pluripotent stem (iPS) cell-derived haematopoietic progenitor cells (HPCs) into the brain of immunodeficient mice[224] that overexpress human colony-stimulating factor 1 (CSF1), which supports human microglia survival[225,226]. The presence of Aβ resulted in the transition of iPS cell-derived HPCs to DAM that, again, showed only a partial overlap in gene expression when compared to the murine DAM signature. An advantage of such chimeric mouse models is the possibility to investigate the response of human microglia to microglial cell-autonomous genetic perturbations such as the loss of *TREM2*. Deletion of *TREM2* in human microglia resulted in the loss of the DAM response in AD-like chimeric mouse models and changed microglia function as evidenced by impaired phagocytosis and chemotaxis[227]. Single-cell RNA sequencing of xenografted iPS cell-derived HPCs with the *TREM2* R47H loss-of-function variant identified a cluster that resembled foam cells seen in atherosclerosis[228]. Collectively, these transplantation studies may help to provide more biological and mechanistic insights into the varying microglial cell states in the context of different environmental stimuli. However, limitations of the chimeric models include the murine and immunocompromised background.

Although we have gained substantial insights into various microglial cell states and their underlying gene expression profiles

in recent years, the transcriptional mechanisms by which different environmental cues in AD drive these distinct phenotypes are largely unknown. Recent advances in sequencing technologies, including ATAC-Seq and ChIP-Seq scRNA, may help us to infer key transcription factors responsible for context-dependent gene expression in microglia. Transfer of human microglia from the brain into a culture environment results in rapid chromatin remodelling with alterations in chromatin accessibility and active gene regulatory elements, mainly enhancers[219]. A multi-omics study assessing microglia chromatin accessibility and gene expression in AD brains identified *SPI1* (which encodes PU.1) as a key regulator of microglia in AD[79]. Other transcription factors of interest include members of the MAF, AP-1 and microphthalmia (MIT/TFE) families, which were shown to be upregulated in microglia isolated from AD brains[222]. Clarification of the key transcriptional regulators of microglial states may lead to the development of novel strategies for selectively targeting microglia phenotypes.

### Microglial phagocytosis in AD

Phagocytosis may be influenced by many of the genes associated with AD that are expressed by microglia, including *TREM2*, *PLCG2*, *ABI3*, *CD33*, *PILRA* (encoding paired immunoglobulin-like type 2 receptor-α), *SIGLEC11* (encoding sialic acid-binding immunoglobulin-like lectin 11), *ABCA1* and *ABCA7* (encoding phospholipid-transporting ATPase ABCA1 and ABCA7, respectively), *CR1* (encoding CR1), *GRN*, *CLU* and *APOE*[229]. APOE can opsonize Aβ plaques, synapses or neurons, and then consecutively activate TREM2, PLCG2 and ABI3 to induce microglial phagocytosis; this pathway is potentially inhibited by CD33, PILRα and SIGLEC11 (ref. 229). Thus, most of the known genetic AD risk variants are potentially linked to microglial phagocytosis, but it remains unclear whether this concerns the phagocytosis of soluble Aβ, Aβ plaques, dead cells and debris, myelin debris, live synapses, or even whole neurons. Aβ plaque-associated microglia show increased expression of TREM2, which can bind Aβ, inducing phagocytosis of Aβ, causing compaction of Aβ plaques, and reducing Aβ seeding of new plaques[216,217,230,231]. Accordingly, antibodies that increased TREM2 expression and signalling reduced Aβ plaque burden in a mouse model of amyloidosis[102]. Activation of TREM2 can induce a DAM expression profile in microglia, including increased expression of the phagocytic receptors Axl and Mer[217], which also have increased expression in Aβ plaque-associated microglia[232]. Knockout of *Axl* and *Mer* in a mouse Aβ model lowered Aβ phagocytosis by tenfold and led to a surprising and selective reduction in the number of dense-core Aβ plaques. This suggests that microglial phagocytosis of Aβ via this class of receptors leads to the formation of dense-core plaques by microglia, which is arguably a protective confinement mechanism to prevent the release of toxic Aβ species[232].

Fc receptors have also been shown to mediate microglial phagocytosis of Aβ species bound to immune complexes[233]. This is presumed to be one of the mechanisms underlying the Aβ-clearing effects of the anti-Aβ antibodies aducanumab and lecanemab, which were recently approved by the FDA for AD. Although there are still considerable concerns associated with the use of these anti-Aβ antibodies, they clearly highlight and validate the potential of Aβ clearance by microglia as a promising therapeutic avenue (Box 2).

Nonetheless, in later stages of AD pathology, microglial phagocytosis may contribute to synapse loss (see synapse section below) and neuronal loss. TREM2 can mediate microglial phagocytosis of synapses in Aβ or tau models of AD[234–236]. Mer can mediate microglial phagocytosis of newborn neurons in Aβ mouse models, limiting neurogenesis and seizures[237]. Aggregated and oligomeric tau can induce microglial phagocytosis of live neurons in vitro or in vivo, and this neuronal loss can be prevented by blocking microglial phagocytosis, which also prevented memory loss in mice[238–240]. Thus, microglial phagocytosis of Aβ, synapses and neurons may affect AD onset and progression, and interventions need to focus on the specific phagocytic receptors involved at different stages of disease.

### Microglial barrier function

Beyond these clearance functions, microglia also form a barrier around sites of degeneration and injury. In AD, microglia cluster around Aβ plaques, wrapping their processes tightly around the plaque surface. This encapsulation creates a physical barrier that limits Aβ plaque expansion and leads to a more compact conformation of the Aβ deposit[241,242]. Surrounding each Aβ plaque are hundreds of neurites with spheroid enlargements[243] that disrupt electrical conduction and neural circuit function[244]. Microglia encapsulation of plaques plays a crucial role in protecting axons by limiting their exposure to toxic protofibrillar Aβ[242].

## Box 2 | Anti-Aβ immunotherapies for AD

Although there are multiple mechanisms to explain the efficacy of anti-amyloid-β (Aβ) immunotherapies, data from both successful and failed human Alzheimer disease (AD) clinical trials support the concept that preferential targeting of deposited Aβ and subsequent microglial reactivity underlies efficacy. Thus, these interventions represent a major translational success for the field, as the proof of concept and mechanism of action was first obtained in Aβ-depositing mouse models. Additional immune therapies are now being evaluated both in preclinical studies and in human clinical trials. However, there is little consensus regarding how to best evaluate these novel therapies in preclinical models and which models should be used. As the balance of positive (for example, Aβ and/or tau reduction, synaptic integrity) and negative effects (for example, excessive synaptic pruning, overt toxicities, impacts on peripheral immune status) of any manipulation may limit therapeutic benefit, the field would be well-served to utilize a rigorous and systematic approach to evaluate these therapies in models before human trials.

Indeed, the examples of immune modulation that have opposing effects on Aβ and tau pathologies in mice illustrate why we should insist on a more rigorous and systematic approach to testing these novel therapies before moving them into human trials. Few in the field would be comfortable with advancing a therapy for AD that had opposing effects on the classic core pathologies. Yet, most immune interventions are advanced to the clinic without rigorous testing in both models and with only limited study of impacts on the peripheral immune system. To increase the probability of translational success and reduce the potential for doing harm we might consider using systems-level omics studies both at a cellular and multiorgan level to assess potential benefits and liabilities of novel immune therapies. Indeed, immune manipulation in a population of older individuals with AD or at high risk for developing AD raises many safety concerns, and we should try to de-risk these interventions as much as possible.

Microglia Aβ plaque sensing and encapsulation are disrupted in ageing[242] and with hypomorphic TREM2 human variants[245] as well as by deletion of *Trem2* (refs. 245,246) or disruption of downstream DAP12 and SYK signalling[247,248] in mice. Additional receptors, including the receptor tyrosine kinase MERTK[232] and PIEZO1 (the pore-forming subunit of the mechanosensitive Piezo channel)[249], may also mediate microglial cell plaque sensing and barrier formation. Disruption of these signals is associated with more diffuse Aβ plaques and greater axonal spheroid formation[245,246] and neuritic tau hyperphosphorylation[250]. In contrast, overexpression of *Trem2* (ref. 251) or treatment with activating TREM2 antibodies[252] enhances microglia encapsulation and reduces plaque-associated axonal pathology in mouse models of cerebral Aβ deposition. Astrocytes intermingle with microglia at the plaque interface, suggesting a coordinated interaction during barrier formation[253], which may be mediated through TREM2 and APOE signalling[254]. Overall, the evidence suggests that targeting microglia and astroglial cells in AD to enhance the formation of neuroprotective barriers could yield beneficial therapeutic effects.

### Microglial cell proliferation

Microgliosis due to increased microglial cell proliferation represents another key feature of AD (Fig. 1) and predicts the onset of cognitive decline[255]. An increase in the proliferation of microglia is observed in post-mortem samples from patients with AD in association with upregulation of the CSF1 receptor (CSF1R) pathway[256–258]. *CSF1R* gene variants may associate with the risk of developing AD[259], although this has not yet been confirmed by meta-GWAS analyses. However, studies using mouse models of cerebral Aβ pathology have helped to elucidate the timing and consequences of microglial proliferation. An accepted mechanistic model suggests that there is an early microglial response to nascent Aβ pathology that triggers microglial proliferation, and this has been observed using in vivo imaging in mice[242]. Microglial proliferation increases progressively in proximity to Aβ plaques in a CSF1R-dependent manner[258]. Prevention of microglial proliferation via inhibition of the tyrosine kinase activity of CSF1R impedes the degeneration of synapses, ameliorating cognition deficits without modifying the levels of Aβ in the APP/PS1 model[258], the 3xTg model[260] and 5xFAD mouse model[261,262] of cerebral Aβ pathology. Microglial proliferation can be prevented using alternative agents, such as the antibiotic minocycline, rendering similar beneficial effects over AD-like pathology[263]. The inhibition of CSF1R is also a disease-modifying mechanism in a model of tauopathy, leading to reduced neurodegeneration and an improvement in behavioural performance. Functionally, prevention of microglial proliferation induces a return of microglia to a homeostatic phenotype[258,264]. Interestingly, inhibition of microglial proliferation is linked to prevention of the onset of replicative senescence in microglia associated with specification of the DAM phenotype[265]. Collectively, these studies point to microglial proliferation as a mechanism underpinning the contribution of microglia to disease pathology and identify CSF1R as a possible therapeutic target. This body of evidence has led to promising drug discovery programmes[266] and, in coming years, the field will collect valuable clinical information about their potential efficacy in AD.

### Microglial energy metabolism

Metabolically, the brain is a highly active organ and its energy demand is predominantly fuelled by glucose. Glycolytic signalling can power inflammatory activity in macrophages and peripheral immune cells, yet we are still uncovering the extent to which such signalling impacts microglia. In primary microglia, Aβ can increase glycolysis with a corresponding reduction in oxidative phosphorylation[267]. This switch to glycolysis activates the mTOR–HIF1α pathway, which in turn directly regulates the production of inflammatory cytokines, including IL-1β[267]. Similar effects have been found in murine models of AD, where microglia from APP/PS1 mice show increased glycolytic activity[268]. This was recently shown to be sex-dependent as microglia from aged female APP/PS1 mice are more glycolytic and inflammatory than those from their male counterparts, with a corresponding reduction in phagocytic ability[269]. Whether this finding relates to sex differences in AD remains to be further investigated. Interestingly, microglia are metabolically flexible and not solely reliant on glucose. Instead, they can also use amino acids, such as glutamine, or fatty acid oxidation to fuel important surveillance and migratory activities[270]. Recent studies indicate that, in microglia and macrophages, glycolysis and mitochondrial function decline significantly with ageing, leading to an energy-depleted state that disrupts homeostatic cell responses such as phagocytosis and inflammation resolution. Several mechanisms have been identified that contribute to this change. With age and immune stimulation, myeloid cells lose their capacity for de novo $NAD^+$ biosynthesis because of a distal breakdown in tryptophan metabolism[271]. Moreover, with ageing, glucose is shunted away from glycolysis and towards the production of glycogen, an effect driven by increased signalling by the immune modulator prostaglandin $E_2$ via its EP2 receptor[272]. EP2 signalling also disrupts glutaminolysis in ageing myeloid cells, an alternative source of energy that fuels the tricarboxylic acid cycle and mitochondrial respiration via anapleurosis. Inhibition of EP2 signalling genetically and pharmacologically restores bioenergetics and homeostatic immune responses in microglia and macrophages and reverses age-associated cognitive decline. Recent studies also identified TREM1 as a disruptor of homeostatic myeloid glucose metabolism that contributes to cognitive decline in ageing and in models of amyloidosis. Thus, myeloid metabolism directs immune responses in microglia and macrophages, which in turn regulate cognitive function in ageing and models of neurodegeneration.

### Microglial lipid metabolism

The majority of the brain dry mass comprises lipids (in white matter, lipids constitute 49–66% of the dry mass; in grey matter, this figure is 36–40%)[273]. In recent years, lipid metabolism and membrane transport have been shown to have important roles in AD neuropathogenesis[274–276]. It became clear that, due to ROS production in AD, lipids containing polyunsaturated fatty acids are peroxidized, leading to the formation of toxic lipid peroxidation byproducts that can crosslink with DNA and amino acids in proteins[277,278]. It seems that ROS induces lipid synthesis in neurons and storage of peroxidized lipids in lipid droplets, which are then transferred via APOD or APOE to glial cells as a neuroprotective measure[279]. The CMS121 inhibitor of fatty acid synthase reduces lipid peroxidation and inflammation in AD[280]. In ageing and neurodegeneration, accumulation of lipid droplets can be observed in microglia, which leads to a pro-inflammatory cell phenotype[228,281]. Phosphatidylinositol-binding clathrin assembly protein (PICALM) and homozygosity for the APOEε4 allele are also linked to microglial lipid droplet formation in AD[282,283] and raised total cholesterol levels[284] that, in turn, cause problems in neurons[285]. Lipid droplet accumulation in microglia in the context of tauopathies is regulated by AMPK[286]. The accumulation of these lipid droplets reduces microglial cell abilities to phagocytose and clear aggregates[287,288]. In addition, it has been shown that a loss-of-function mutation in the innate immune receptor

TREM2 leads to lysosomal defects as well as to a downregulation of cholesterol synthesis and lipid droplet formation in microglia[289]. Furthermore, Aβ aggregation takes place at neutral membranes and is dependent on membrane composition[290]. Microglial cell-mediated Aβ monomer degradation accelerates upon APOE-mediated efflux of cholesterol from the cell[291]. Long-term exposure to a high-fat diet[292] as well as several regulators of lipid metabolism, such as cholesterol 25-hydroxylase (CH25H)[293], INPP5D[294], the transcriptional repressors BHLHE40 and BHLHE41 (ref. 295), MS4A4A[296], transient receptor potential cation channel subfamily V member 1 (TRPV1)[297] and hexokinase 2 (HK2)[298], have also been linked to inflammation in the setting of tauopathies. Strategies that target microglial function in the context of lipid metabolism have emerged as novel therapeutics[276].

### Microglial senescence

Cellular senescence is a hallmark of ageing and age-associated diseases, including AD. Senescent cells are characterized by an irreversible proliferation arrest and profound changes in their metabolism and behaviour, preventing them from executing their physiological function. In addition, senescent cells frequently display a senescence-associated secretory phenotype (SASP) that is characterized by the release of various pro-inflammatory factors[299]. SASP factors were detected in the brain, CSF and serum of patients with AD[300–303], and these factors are associated with aged and potentially senescent microglia[304]. Interestingly, microglial cell-mediated inflammation, especially that driven by the SASP factor IL-1β, was shown to contribute to tau spreading and tau-mediated neurodegeneration[74,161,305,306]. In line with this, microglia have been identified as a putative senescent population in tauopathies, including AD[265,302,307,308]. Senescent microglia developed before the onset of neurofibrillary tangle deposition in human P301S *tau*-transgenic mice (PS19 mice); using single-cell RNA sequencing, these microglia were found to represent a subset of DAM[309]. Remarkably, removal of senescent cells, either genetically or with senescence-targeting pharmacological means, alleviated tau pathology, tau-mediated neurodegeneration and cognitive deficits in this model[307], suggesting that senescent microglia contribute to disease progression. Cellular senescence can be induced via multiple pathways. The sustained proliferation of microglia in Aβ-depositing APP/PS1 mice promoted replicative senescence, ultimately fuelling Aβ accumulation and synaptic defects[265]. Furthermore, microglia internalizing tau aggregate-bearing neurons or monomeric tau from the extracellular space enter a senescent state and present with a SASP[310,311] that might modulate AD pathology, neuronal function and neurodegeneration. While senescent glial cells seem to be involved in AD pathogenesis as outlined above, a unifying set of markers for microglial senescence and the SASP has not yet been defined. Further studies will have to detail markers of senescence and assess their occurrence over the course of AD longitudinally, both in the brains of patients with AD and in related mouse models.

## Which other cells drive neuroinflammation in AD?

### Astrocytes

Astrocytes support the normal development and maintenance of the CNS and are vital for neuronal health and function[312,313]. The response of astrocytes during acute infection or brain injury and in chronic disease states is referred to as astrocyte reactivity. Any one particular reactive response may include several heterogeneous reactive 'sub-states' — each with distinct transcriptomic profiles and possible functional outcomes[312,314]. The response of astrocytes to neurodegenerative diseases like AD has been linked to inflammatory responses of microglia and peripheral immune cells, pathological proteins like Aβ and tau, barrier leakage, and many other pathological indications[315].

While there are many initiators of astrocyte reactive states in AD, the main hallmarks are hypertrophy of astrocytic processes, upregulation of cytoskeletal proteins (like GFAP and vimentin), increased expression of innate immune-related genes (such as *LCND2* (encoding lipocalin 2) and *SERPINA3N* (encoding the protease inhibitor α1-antichymotrypsin)) and many components of the cholesterol synthesis pathway[316]. These transcriptomic and morphological changes often occur long before cognitive deficits. Reactive astrocytes are associated with senile plaques and, while there is restructuring of astrocyte gross morphology, their domain architecture is preserved, indicative of isomorphic, non-proliferative astrogliosis[317]. Proliferation or scar formation is uncommon, although reactive astrocytes are accumulated around senile plaques. Other reported altered functional changes in reactive astrocytes include decreased phagocytosis, decreased glutamate uptake, loss of endfeet polarization and expression of AQP4 water channels, and secretion of neurotoxic compounds[318]. In particular, astrocytes in AD upregulate expression of monoaminoxidase-B, which translates to increased synthesis of GABA (thus increasing tonic inhibition, counteracting neuronal hyperexcitability and causing cognitive impairment) and increased production of $H_2O_2$. Similarly, $H_2O_2$ is produced by increased activity of the urea cycle, implemented in detoxification of ammonia and utilization of Aβ[319,320]. Oxidative stress is further augmented by age-dependent decline in astrocyte anti-oxidative systems[317], thus precipitating direct neuronal injury. In addition, astrocytes can secrete cytokines[321], thus contributing to the regulation of inflammation. Single-cell RNA sequencing revealed substantial changes in expression of immune response genes, genes associated with Aβ clearance and CD74 (which is involved in antigen presentation) in post-mortem samples from patients who had AD[322]. A substantial subpopulation of astrocytes in AD demonstrates atrophy and loss of homeostatic support, further aggravating neuronal damage[323].

Given that each astrocyte interacts with up to 2 million synapses in the human brain[324], changes in synapse-forming functions likely have major contributing roles to cognitive decline. Synaptic uncoupling of neurons projecting between brain regions, particularly in the hippocampus, likely decreases memory function. The neurotoxic reactive astrocyte sub-state is also likely to contribute to the degeneration of neurons and synapses[318], for example, by secretion of toxic saturated lipids contained in lipoparticles[325]. Other putatively protective reactive astrocytes seem more prevalent in the early stages of AD and may help maintain CNS integrity by limiting the infiltration of peripheral immune cells[314]. How astrocytes respond directly to Aβ deposits remains under investigation, but decreased astrocyte AQP4 levels could slow the clearance of pathogenic proteins through the glymphatic system, which resides between the blood vessel endothelium and astrocyte endfeet.

Loss of cholesterol synthesis machinery is also important for understanding modulation of neuroinflammation in the context of AD. As almost sole producers of cholesterol in the CNS, astrocytes are integral for the biosynthesis of cell membranes in the brain and spinal cord. Astrocyte-derived cholesterol has also been reported to support the survival of oligodendrocytes and remyelination[326], which may add to neuroprotection in the context of AD. Cholesterol is also an important trophic molecule for microglia, and evidence suggests that astrocytes expressing the AD-associated APOE4 allele are less

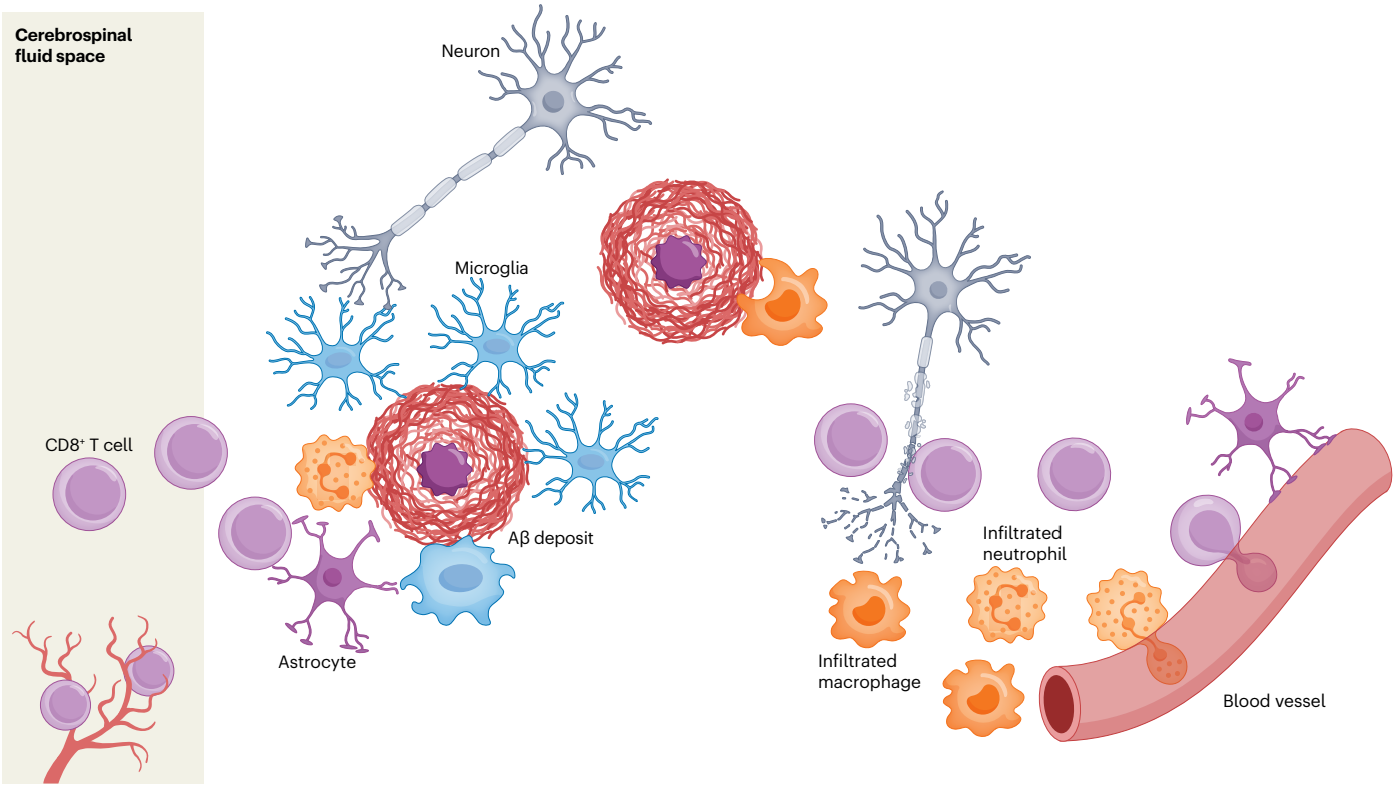


**Fig. 2 | Contribution of peripheral immune cells to Alzheimer disease.** Neutrophils and CD8⁺ T effector memory CD45RA⁺ cells may infiltrate the brain parenchyma in Alzheimer disease by leaving either the cerebral vasculature or the cerebrospinal fluid compartment. T cells can proliferate and might promote neuronal damage either through the release of inflammatory and cytotoxic molecules or by physically interacting with neuronal processes, causing the formation of structures called spheroids that indicate restricted or blocked axonal transport. Aβ, amyloid-β.

competent at producing and secreting cholesterol. This could initiate a feedback loop between decreased cholesterol driving microglial reactive states, which in turn feed back to drive reactivity in astrocytes[327]. Indeed, this astrocyte–microglial cell crosstalk is important for the maintenance of many physiological microglial functions, including synapse pruning and debris clearance.

### Oligodendroglia

In models of AD, oligodendrocytes undergo marked transcriptional changes, transforming into what are termed disease-associated oligodendrocytes[328–330]. Spatial transcriptomics has identified alterations in oligodendrocytes located near Aβ plaques[316,331,332]. Like DAM, this state is not confined to a specific brain pathology but is seen in various models of brain injury and disease. While pathway analyses indicate that the primary disease-associated oligodendrocyte state may have immunemodulatory functions, our understanding of their role in the diseased or ageing brain remains limited. Independent lines of evidence suggest causal links between oligodendrocytes in the ageing brain, secondary neuroinflammation and AD neuropathology. Oligodendrocytes make myelin for rapid impulse propagation and provide metabolic support to myelinated axons[333], extending beyond white matter tracts. Notably, there is extensive intracortical myelination of projection neurons and interneurons[334], persisting well into the second and third decade of human life. Importantly, with advancing age, cortical myelin decreases in abundance, showing an inverse correlation with the onset of pathologies that become the hallmark of AD[335]. Specifically, the late and thinly myelinated regions of the human brain appear to be the first to develop AD pathology[336]. Underlying myelin loss is a gradual deterioration of myelin integrity, initially documented by electron microscopy in ageing primate brains[337]. This degeneration affects the cytoplasmic channels within myelin[338] that are required for the delivery of metabolic support to the encapsulated axon[339,340]. Thus, advanced ageing of the cortex is associated with axonal perturbation, myelin degeneration and secondary inflammation[341,342], the latter triggered by axon loss and the ingestion of myelin debris by microglia contributing to their pro-inflammatory activation[330,343,344]. Combining mouse models of AD with oligodendrocyte-specific defects that cause a premature white matter ageing phenotype demonstrated that myelin dysfunction drives amyloidosis and Aβ plaque formation[345]. Interestingly, increased brain Aβ load is a consequence of both more Aβ processing in affected nerve fibres and a distinct molecular phenotype of DAM; the latter become visibly recruited away from Aβ plaques by dysfunctional myelin, leading to less efficient clearance of Aβ from the brain parenchyma.

### Lymphocytes in AD

The adaptive immune system is increasingly recognized as being involved in the pathogenesis of AD. Disruption of the BBB in AD[346] creates the possibility for peripheral lymphocytes, including B cells and T cells, to enter the brain parenchyma (Fig. 2). Indeed, pathology

in transgenic mouse models of AD is associated with infiltration of B cells into the brain parenchyma and with immunoglobulin deposition at Aβ plaques[347]. Furthermore, in the absence of B cells, Aβ plaque burden was reduced, suggesting that B cells might contribute to AD pathogenesis. Importantly, the absence of B cells reversed behavioural and memory deficits, suggesting these cells as promising targets for AD therapy.

One of the most remarkable changes that accompany immune system ageing relates to the function and maintenance of T cell populations. Whereas the naive T cell population shrinks with age, central memory T cell, effector memory T cell and exhausted T cell populations accumulate with age and often show dysregulated properties[348–350]. Low-grade chronic systemic inflammation, which accompanies and/or is caused by processes such as tissue senescence and altered metabolism[351], acts as an additional component that contributes to T cell dysfunction in ageing. A compelling question is whether the emergence of dysregulated T cell subsets prepares the ground for the development of AD[352]. Support for this was evident in a recent study in humans, which found increased frequencies of pro-inflammatory $CD8^+$ T effector memory $CD45RA^+$ cells in the peripheral blood of individuals with mild cognitive impairment and AD, as well as the clonal expansion of these cells in the CSF, suggesting antigen-specific reactivation[353]. $CD8^+$ T cells were also observed within the meningeal tissues and the brain parenchyma of people with AD[353] (Fig. 2).

Recent studies using mouse models of tau pathology also suggest an instrumental role of T cell infiltration in tau-related neurodegeneration, neuroinflammation and cognitive deficits[354,355]. Pathology was associated with the clonal expansion of selected T cell populations, although their antigen specificity remains unknown[354]. These observations are reminiscent of earlier reports showing increased frequencies of late-stage differentiated $CD4^+$ T effector memory $CD45RA^+$ cells in the blood[356] and clonal expansion of $CD4^+$ T cells in the CSF[357] of patients with AD compared to healthy controls, as well as of studies showing enhanced circulating Aβ-specific $CD4^+$ T cells in elderly individuals and in people with AD[358]. The precise role of these T cells in AD pathogenesis remains to be defined, but their identity as tissue-resident memory T cells has been confirmed through transcriptome analysis[359]. Moreover, the fact that the $CD8^+$ T cells within the brain parenchyma are in direct contact with microglia suggests a regulatory crosstalk between both cell types[360].

Such T cell–microglial cell crosstalk was illustrated in a recent study showing that the CXCL16–CXCR6 axis retains $CD8^+$ T cells in the brains of mice with AD-like pathology[361]. *Cxcr6* deficiency reduced the accumulation and clonal expansion of $CD8^+$ T cells in the brain, while ablation of $CD8^+$ T cells ultimately increased pro-inflammatory cytokine production from microglia. These findings suggest beneficial roles for brain $CD8^+$ T cells in protecting against AD pathogenesis. In contrast, the observed direct contact of the $CD8^+$ T cells with neurites argues for the possibility of a neurotoxic activity[353]; however, this requires further experimental evidence. Nevertheless, antibody-mediated depletion of $CD8^+$ T cells in a transgenic mouse model of AD resulted in changes in the expression of neuronal genes in the brain. Moreover, the infiltration of $CD8^+$ T cells into a 3D culture system resembling AD pathology led to an increase in neuroinflammation and neurodegeneration[362]. In summary, it is still unclear if $CD8^+$ T cells are friends or foes in AD pathology. Whether $CD8^+$ T cells play a protective or pathological role might ultimately depend, for example, on the precise time and stage of disease pathology.

The topic requires further investigation, in particular since immune therapeutics targeting $CD8^+$ T cells in other settings, such as cancer immunotherapy, could be repurposed for use in neurodegenerative diseases such as AD[363]. Clinical studies suggest that the homeostasis and suppressive functions of regulatory T ($T_{reg}$) cells are also altered in patients with AD[364,365]. $T_{reg}$ cells were shown to critically control anti-Aβ $CD4^+$ T cell responses[366], and the selective amplification of $T_{reg}$ cells via low-dose IL-2 treatment modulated reactive microgliosis and restored cognitive functions in a mouse model of AD-like Aβ pathology[367]. Recent reports showed that $T_{reg}$ cells also modulate and finetune the balance of reactive astrocyte subtypes in AD-like pathology[368]. Other $CD4^+$ T cell populations may also have protective roles in AD. Aβ-specific T helper 1 cells injected into the ventricles of 5xFAD mice migrated into the brain parenchyma and stimulated the expansion of MHC class II-positive microglial cells with improved capacity for Aβ uptake[369]. Genetic engineering of these T cells to overexpress brain-derived neurotrophic factor (BDNF) facilitated neuronal repair[370].

These studies together support intricate roles of T cells in the context of AD neuroinflammation. It is intriguing to speculate that the emergence of dysregulated T cells with ageing facilitates neuroinflammation and the progression of AD. Further characterization of immune senescence processes and defining the antigen specificity of disease-associated T cells could pave the way towards novel therapies for AD that target lymphocytes.

### Peripheral myeloid cells

Circulating myeloid cell populations, such as neutrophils and monocytes, can migrate into the brain during AD and may contribute to disease pathogenesis (Fig. 2). Neutrophils accumulate in the AD brain and the peak of neutrophil infiltration in mice with AD-like disease coincides with the onset of memory loss[371]. Transient neutrophil depletion during early disease in AD models reduces cognitive deficits and neuropathology, suggesting that these cells have a detrimental role[371,372]. Neutrophils adhere in brain vessels and migrate into the parenchyma but they also obstruct blood flow by plugging brain capillaries[371–373]. Soluble oligomeric $A\beta_{1-42}$ triggers the rapid activation of LFA1 integrin, leading to neutrophil adhesion, whereas Aβ deposits promote neutrophil arrest and spreading in brain venules but also determine the intraparenchymal localization of these cells[371]. In keeping with this, LFA1 integrin blockade has therapeutic effects in mouse AD models[371].

Neutrophils are highly reactive cells that release multiple cytotoxic molecules during AD, including myeloperoxidase, elastase and IL-17 (refs. 371,374,375). They also deploy neutrophil extracellular traps in the vasculature and inside the parenchyma, thus contributing to BBB dysfunction and neuronal damage[371]. Notably, circulating neutrophils have a hyperactivated phenotype in patients with AD compared to control individuals, and neutrophil abnormalities correlate with faster cognitive decline[376–379]. Neutrophil indicators could therefore be suitable as disease biomarkers and understanding the phenotype of neutrophils in AD may help to identify new therapeutic approaches. Monocytes have also been implicated in AD pathology. In mouse models of cerebral amyloidosis, circulating monocytes migrate into the brain via the CCR2–CCL2 axis and contribute to Aβ clearance[380,381]. However, a beneficial effect for monocyte infiltration has recently been challenged in the context of AD[382,383]. A dysfunctional monocyte compartment has been reported in patients with dementia, further highlighting that alterations in peripheral myeloid cells could drive pathology in AD[377,384].

## The blood and lymphatic vasculatures

### Vascular cells

Alzheimer himself described increased endothelial cell proliferation and growth in the first case of AD reported[4], suggesting that vascular cells become activated during the progression of the disease. Many reports have described vascular anomalies, including but not restricted to the existence of a major brain microvascular pathology[385,386], insufficient angiogenesis[387–390], deficient clearance of Aβ due to an altered BBB[391], and the accumulation of hypoxic markers in brains of patients with AD and in related animal models[392–397]. It has also been suggested that the vascular network associated with Aβ plaques is altered early both in patients with AD[398–401] and in mouse models[402–404], where vascular voids surrounded by hypervascularized areas were found to be associated with Aβ deposits. A recent multifactorial study found that vascular dysfunction is an early event in AD pathology[405], while small nuclear RNA-sequencing analyses identified specific changes in AD that are associated with endothelial cells and pericytes[406] and reported enriched expression of AD risk genes in vascular cells[406].

Mechanistically, vascular activation has been associated with (1) Aβ accumulation in the wall of brain vessels in the form of cerebral Aβ angiopathy[407]; (2) brain pericyte contraction[408]; (3) clotting of blood vessels by neutrophils[371,372]; (4) infiltration of peripheral immune cells in the brain parenchyma[409] in response to chemokines released during neuroinflammation[410,411]; and (5) a reduction in the number of vessels through non-productive angiogenesis, which activates microglia to disassemble blood vessels around Aβ plaques[392]. In addition, perivascular microglia, astrocytes and pericytes may also directly affect BBB patency in AD[412,413]. Importantly, the pathological leakage across the BBB induced by dysfunction of these cells may in turn also modulate innate immune cell function in the brain, indicating a vicious circle of vascular injury leading to perivascular inflammation and vice versa[414]. In addition to these cellular changes, cerebral vasculature functions, including neurovascular coupling, are also altered in patients and mouse models of AD[415]. In animal models, these detrimental effects are mediated by Aβ inducing the CD36-mediated generation of ROS in perivascular macrophages[416] as well as by p-tau disrupting the synthesis of the vasodilator nitric oxide (NO) evoked by synaptic activity[417]. These changes are exacerbated by additional vascular effects at the capillary level such as pericyte-mediated vasoconstriction[408].

### Glymphatic system

The role of the BBB in the removal of Aβ from the brain is well established[418]. However, this is not the sole route of Aβ removal. Typically, tissue metabolites are cleared through the lymphatic network that pervades most tissues. However, CNS parenchyma lacks this comprehensive lymphatic vasculature, leading many to presume for decades that the brain, due to its 'immune privileged' status, has no lymphatic connection to the peripheral immune system. This belief was disproved in 2015 when functional lymphatic vessels were redescribed just outside the parenchyma of the brain[419] and spinal cord[420], specifically in the outermost layer of their meningeal covering, the dura mater. While these vessels are outside the CNS parenchyma, they serve as a lymphatic conduit for the CNS, delivering brain and spinal cord-derived molecules to the draining lymph nodes[419]. To effectively drain CNS-derived molecules, including Aβ, these meningeal lymphatics must interact with the so-called glymphatic system, a conceptual model for understanding CSF flow through the brain[421]. Arterial pulsations drive CSF from peri-arterial to intraparenchymal spaces, and this CSF is then reabsorbed at the peri-venule spaces with the aid of the glial AQP4 molecule[422,423]. When the 'dirty' CSF, containing brain metabolites, such as Aβ, leaves the brain, it traverses the meningeal layers, a process observed in both mice[424] and humans[425]. However, the exact path that the CSF takes remains elusive. Upon reaching the dura mater, brain-derived molecules are sampled by dural antigen-presenting cells, and the remaining molecules are removed by the meningeal lymphatics[424,426]. Impairment of these meningeal lymphatics, either through pharmacological or genetic manipulation or complete ligation at the entry of the draining lymph node, results in increased deposition of Aβ plaques in the brain parenchyma and their occurrence in previously plaque-free meninges[427–431]. Moreover, malfunctioning lymphatics hinder the effectiveness of anti-Aβ antibodies in plaque clearance and lead to side effects, such as a compromised BBB and abnormally activated microglia, mirroring the microglia phenotype seen in humans with AD[432]. Given that the functionality of meningeal lymphatics declines with age[432], it is plausible that these lymphatics must be operational for patients to benefit from anti-Aβ drugs and possibly other therapies. Future therapies should aim to combine plaque removal with strategies that enhance the function of the meningeal lymphatics.

## Immune mediators in AD

In the sections above, we have highlighted the key cell types that are likely to contribute to AD development and progression. Below, we summarize the key immune mediators and receptors that have been linked to neuroinflammation in the context of AD (Table 2).

### Damage-associated molecular patterns

Damage-associated molecular patterns (DAMPs) accumulate in the brain in AD, contributing to several aspects of the pathology and accelerating disease progression[433]. The most relevant is Aβ, which can activate microglia via multiple surface receptors. Microglia can phagocytose Aβ through its binding to CD36, subsequently inducing the formation of TLR2–TLR6 heterodimers and NF-κB activation[434]. Further uptake mechanisms exist, including but not restricted to CD14 (which is a co-receptor of TLR4), TLR6, TLR9, α6β1 integrin and the scavenger receptor SCARA1 (refs. 433,435–437). Following TLR activation, Aβ initiates NLRP3 inflammasome activation, promoting the release of inflammatory cytokines[438]. Furthermore, Aβ can also activate NLRP1 expressed in neurons and oligodendrocytes through different mechanisms, including TLR4 binding[439]. Other DAMPs, including tau monomers and oligomers, HMGB1, chromogranin A, S100 proteins, circulating DNA, mitochondrial DNA, ceramides and ATP, also activate pattern recognition receptors to drive innate immune activation in the context of AD[439,440].

### TREM2 and APOE

APOE is the primary transporter of lipids and cholesterol in the brain; it also has immunomodulatory functions that are entwined with the microglial receptor TREM2. APOE is an activating ligand of TREM2 and, in turn, TREM2 signalling sustains microglial production of APOE in the brain. TREM2 directly binds numerous ligands, including lipidated as well as recombinant non-lipidated APOE[441–444]. Upon binding APOE, TREM2 transmits intracellular signals that promote reactive microgliosis. However, the *TREM2* R47H variant, which is associated with increased risk for AD, is unable to bind APOE[441–443]. Thus, direct APOE–TREM2 interactions may sustain microglial cell responses to AD pathology. Microglial cell transition from a homeostatic to an activated

**Table 2 | Mediators linked to Alzheimer disease**

| Alzheimer disease-associated mediators and factors | Specific examples linked to Alzheimer disease | Animal study data on examples? | | Clinical study data on examples? | |
|---|---|---|---|---|---|
| | | Yes | No | Yes[a] | No |
| Cytokines | IL-1α, IL-1β, IL-2, IL-6, IL-10, IL-12, IL-13, IL-17, IL-23, IL-33, IL-34, TNF, TGFβ, IFNγ, GM-CSF | IL-1α, IL-1β, IL-2, IL-6, IL-10, IL-12, IL-13, IL-17, IL-23, IL-33, IL-34, TNF, TGFβ, IFNγ, GM-CSF | – | IL-1α, IL-1β, IL-2[a], IL-6, IL-10, IL-12, IL-13, IL-17, TNF, TGFβ, IFNγ, GM-CSF[a] | IL-23, IL-33, IL-34 |
| Chemokines | CCL2, CXCL16 | CCL2, CXCL16 | – | CCL2 | CCL16 |
| Transcription factors | NF-κB | NF-κB | – | NF-κB | – |
| Inflammasomes | NLRP3 | NLRP3 | – | NLRP3 | – |
| Oxidative mediators | ROS, NO, $O_2^{\cdot}$ | ROS, NO, $O_2^{\cdot}$ | – | ROS, $O_2^{\cdot}$ | NO |
| Microglial-expressed inducible nitric oxide synthase | NOS2 | NOS2 | – | – | NOS2 |
| Apolipoproteins | APOE | APOE | – | APOE | – |
| Immune receptors | TREM2, SPI1, MS4A4A, MS4A6A, CD33 | TREM2, SPI1, MS4A6A, CD33 | MS4A4A | TREM2, CD33 | SPI1, MS4A4A, MS4A6A |
| MHC | HLA-DQA1, HLA-DRB1 | HLA-DQA1, HLA-DRB1 | – | – | HLA-DQA1, HLA-DRB1 |
| Signalling intermediates | PLCG2, PTK2B, INPP5D | PLCG2, PTK2B, INPP5D | – | – | PLCG2, PTK2B, INPP5D |
| Complement machinery | CR1, clusterin | CR1, clusterin | – | Clusterin[a] | CR1 |
| Cytoskeletal machinery | ABI3, EPHA1, FERMT2 | ABI3, EPHA1 | FERMT2 | – | ABI3, EPHA1, FERMT2 |
| Prostanoid enzymes | COX1, COX2 | COX1, COX2 | – | COX1[a], COX2[a] | – |
| Other immune and neuronal proteins | SPP1, NPTX2, SRPX2, CD47, SIRPα | SPP1, NPTX2, CD47, SIRPα | SRPX2 | NPTX2 | SPP1, SRPX2, CD47, SIRPα |
| DAMP receptors | TLRs, NLRs, AIM2-like receptors, RLRs, CTDRs | TLRs, NLRs, AIM2-like receptors | RLRs, CTDRs | TLRs[a], NLRs | AIM2-like receptors, RLRs, CTDRs |
| Regulators of APP processing | BACE1, γ-secretase, IFITM3, SMAD, PPARγ, STAT1, GSK3 | BACE1, γ-secretase, IFITM3, SMAD, PPARγ, STAT1, GSK3 | – | BACE1, γ-secretase[a], PPARγ[a], GSK3[a] | IFITM3, SMAD, STAT1 |
| Regulators of ubiquitination and other pathways | SHARPIN, RBCK1, OTULIN, LUBAC, ADAM17, TNIP1, SPPL2A, PGRN | SHARPIN, LUBAC, ADAM17, SPPL2A, PGRN | RBCK1, OTULIN, TNIP1 | – | SHARPIN, RBCK1, OTULIN, LUBAC, ADAM17, TNIP1, SPPL2A, PGRN |
| Epigenetic regulators | HDAC, DNMT1, TET2, SIRT1, JMJD3 | HDAC, DNMT1, TET2, SIRT1, JMJD3 | – | HDAC[a], SIRT1[a] | DNMT1, TET2, JMJD3 |
| Exposome factors | Brain trauma, midlife hypertension, diabetes, systemic inflammation, oral and gut microbiome dysbiosis | Brain trauma, midlife hypertension, diabetes, systemic inflammation, oral and gut microbiome dysbiosis | – | Diabetes[a], systemic inflammation, oral and gut microbiome dysbiosis[a] | Brain trauma, midlife hypertension |
| Cellular factors | Microglia, astrocytes, oligodendroglia, lymphocytes | Microglia, astrocytes, oligodendroglia, lymphocytes | – | Microglia[a], astrocytes[a], lymphocytes | Oligodendroglia |

APP, amyloid-β precursor protein; APOE, apolipoprotein E; BACE1, β-secretase 1; CDTRs, C-type lectin-like receptors; COX, cyclooxygenase; CR1, complement receptor 1; DAMP, damage-associated molecular patterns; DNMT1, DNA methyltransferase 1; EPHA1, ephrin type-A receptor 1; FERMT2, fermitin family homolog 2; GM-CSF, granulocyte–macrophage colony-stimulating factor; GSK3, glycogen synthase kinase 3; HDAC, histone deacetylase; IFITM3, interferon-induced transmembrane protein 3; INPP5D, phosphatidylinositol 3,4,5-trisphosphate 5-phosphatase 1; JMJD3, Jumonji domain-containing protein 3; MS4A4A, membrane-spanning 4-domains subfamily A member 4A; NLRs, NOD-like receptors; NLRP3, NACHT, LRR and PYD domains-containing protein 3; NO, nitric oxide; NOS2, nitric oxide synthase 2; NPTX2, neuronal pentraxin 2; PGRN, progranulin; PLCG2, phospholipase Cγ2; PTK2B, protein tyrosine kinase 2β; RLRs, RIG-I-like receptors; ROS, reactive oxygen species; SIRT1, sirtuin 1; TET2, ten-eleven translocation methylcytosine dioxygenase 2; TLRs, Toll-like receptors; TREM2, triggering receptor expressed on myeloid cells 2.
[a]Clinical study about the specific target; otherwise only measured in a drug testing study.

state in mouse models of Aβ accumulation is partially dependent on both TREM2 and APOE[231,445]. Interaction between TREM2 on microglia and APOE within Aβ plaques may be crucial for compaction: Aβ plaques in both APOE-deficient mice and in TREM2-deficient mice display filamentous morphology and are associated with axonal dystrophy[254]. Though TREM2 affinity for APOE isoforms may be similar[441,442], APOE variants are recognized and engulfed by TREM2 at varying rates, suggesting that APOE4 may have a more marked impact than other isoforms[227]. During homeostasis, APOE is mainly secreted by astrocytes. However, microglia, particularly those wrapped around Aβ plaques, secrete large amounts of APOE in AD and related mouse models[216,217,316,446]. This is largely dependent on TREM2: very little APOE is produced by microglia that express the *TREM2* R47H variant[228,447] or that lack a functional *Trem2* gene[217,231]. Thus, APOE–TREM2 interactions may constitute an autocrine circuit that sustains microglial cell responses to Aβ plaques.

### Complement factors

It has been known for over four decades that the complement components C1q and C3 are associated with pathological hallmarks of AD (plaques and tangles)[6,448,449]. More recent studies demonstrated increased expression of complement proteins (reviewed in ref. 450) and the generation of activated complement fragments in the brains of patients with AD brain and in mouse models of AD[451,452]. Excessive complement activation can lead to detrimental inflammation and neurotoxicity via the C5a and C3a fragments, which signal through their receptors and synergize with other innate immune signalling pathways such as TLRs and RAGE[453,454] as well as via the generation of the membrane attack complex (C5b-9), all of which are relevant to AD progression[455–457].

The role of C3 and the receptors for its diverse activation fragments in AD is clearly complex and regulated by time and location[458,459] (and reviewed in ref. 460). C3-deficient mice show protection from neurodegeneration[461], spine loss[452], and excessive microglial cell-mediated synapse loss[452] and C3aR is a modulator of microglial function[451,462]. C5ar1 expression is upregulated in AD brain[463,464]. In mouse models of AD, antibody to the pro-inflammatory complement activation fragment C5a, genetic ablation of C5aR1 or pharmacological antagonism of C5aR1 resulted in less inflammatory microglia and astrocytes, preservation of neuronal complexity, reduction of cognitive loss, and suppression of synapse engulfment by microglia[464–467]. In addition, classical complement activation (through C1, C2, C4 and C3) has a substantial role in synapse pruning during neural development and adult plasticity, but aberrant or unregulated activation leads to excessive synapse elimination in AD mouse models[234,468–470]. However, induction of C1q expression is an early response to injury prior to upregulation of other complement components in brain, and protective roles of C1q have been documented, including an enhancement of phagocytosis, suppression of microglial cell-mediated inflammation, and neuroprotection[471]. As a result, unintended immunocompromising consequences of targeting this component must be considered. Novel approaches to modulate neuronal activators of the complement cascade may be selective and effective for different subtypes of AD[472].

### Cytokines

In AD, cytokine production is initiated by DAMPs activating pattern recognition receptors and can be regulated at multiple steps, including cellular release. In the brain, cytokines are released by microglia, astrocytes, lymphocytes, pericytes, and other cells and act on neighbouring cells, including the releasing cells, to drive neuroinflammation. In microglia, activation of the NLRP3 inflammasome generated IL-1β, which reduced microglial clearance of Aβ and the release of Aβ-degrading enzymes (such as insulin-degrading enzyme and neprilysin) and stimulated the production of NO and subsequent immune cascades[438]. Neurons exposed to microglia-derived IL-1β show enhanced spine loss and reduced hippocampal long-term potentiation[438,473]. Reduced long-term potentiation has also been reported in hippocampal slice preparation experiments following exposure to IL-2, IL-6, TNF and other cytokines[474–477]. In animal models, IL-1β can cause neurofibrillary tangle formation and tau pathology through an IL-1 receptor-mediated calcium–calmodulin-dependent protein kinase IIα (CamKIIα)-dependent mechanism[74]. NLRP3 inflammasome activation can also result in microglial pyroptosis, release of ASC specks and further seeding of Aβ deposition[478] (Fig. 3).

More recently, the generation of type I interferons and other cytokines through the cGAS–STING pathway, which is activated by cytosolic DNA, has become a focus of intense research[479–481]. Type I interferons are elevated in AD, and genetic deficiency for the type I interferon receptor (IFNAR1) can be protective in some mouse models of AD[482]. IL-1α, type I interferon, IFNγ, GM-CSF, IL-10 and IL-13 are elevated in AD brains in association with neurofibrillary tangles[483]. T cell-derived IFNγ can increase reactive microgliosis and Aβ deposition in Aβ mouse models[484]. IL-10 is generally anti-inflammatory but knockout of the *Il10* gene in an Aβ mouse model reduced amyloidosis, synaptic loss and cognitive deficits, while increasing reactive microgliosis and phagocytosis[485]. IL-12 and IL-23 are elevated in AD, and depletion of their shared subunit (p40) reduced Aβ load and cognitive deficits in an AD mouse model[486]. In contrast, other cytokines may be protective in AD. For example, IL-33 is reduced in AD brains, and IL-33 deficiency resulted in increased tau pathology and neurodegeneration in mice[487]. Furthermore, IL-33 injection reduced microglial reactivity, Aβ plaques, synaptic loss and cognitive deficits in a mouse model of AD[488].

### Cyclooxygenases and prostanoids

Prostanoids were initially implicated in AD pathogenesis based on cross-sectional and longitudinal epidemiological studies showing reduced risk for AD in individuals taking non-steroidal anti-inflammatory drugs, which inhibit both cyclooxygenase 1 (COX1) and COX2 (refs. 489,490). Although clinical trials of non-steroidal anti-inflammatory drugs and COX2-selective inhibitors were abandoned due to lack of clear benefit and potential cardiovascular risks[491], continued preclinical work highlights unique roles for these enzymes in the context of AD. For example, COX1 is constitutively expressed by microglia[492], and its activity was associated with memory impairment and neuropathology in various models[493–495]. In addition, cyclooxygenases have been implicated in communication across the BBB[190,496], and might therefore link peripheral inflammation to dementia and AD progression[497]. Other data demonstrate unique roles for specific prostanoids and their G protein-coupled receptors. For instance, prostaglandin E2 acting on EP2 receptors reduced Aβ phagocytosis in several models[498,499] and worsened spatial memory performance in APP/PS1 and ageing mice[272,498], possibly by driving age-associated changes in myeloid cell inflammatory and metabolic states[272]. Moreover, EP1 receptors facilitate excitotoxic injury in ischaemic and AD models[500,501]. Such findings support interventional targets that are more specific than general COX inhibitors.

### iNOS and NO

One major hallmark of neuroinflammation is aberrant NO production by microglial cell-expressed inducible nitric oxide synthase (iNOS or NOS2), a factor held responsible for aggravating pathology. iNOS generates high levels of NO, with the stimulation of microglia by LPS and IFNγ[456] resulting in NO production at a rate of ~140 pmol per minute per million cells[502]. In the presence of ROS following NADPH oxidase activation, various reactive nitrogen species are generated, including the potent oxidant peroxynitrite, which enhances nitrosative stress and causes oxidative damage, nitration, and S-nitrosylation of proteins, lipids and DNA. Evidence suggests that iNOS expression is the major source for NO-mediated post-translational modifications likely rendering many target proteins dysfunctional in AD and other neurodegenerative disorders[503–506].

In AD, 3-nitration of γ-secretase, triosephosphate isomerase, tau or Aβ itself may aggravate pathology[507–511]. These modifications can induce a positive feedback loop by which chronic and uncontrolled neuroinflammation causes further excessive microglial reactivity,

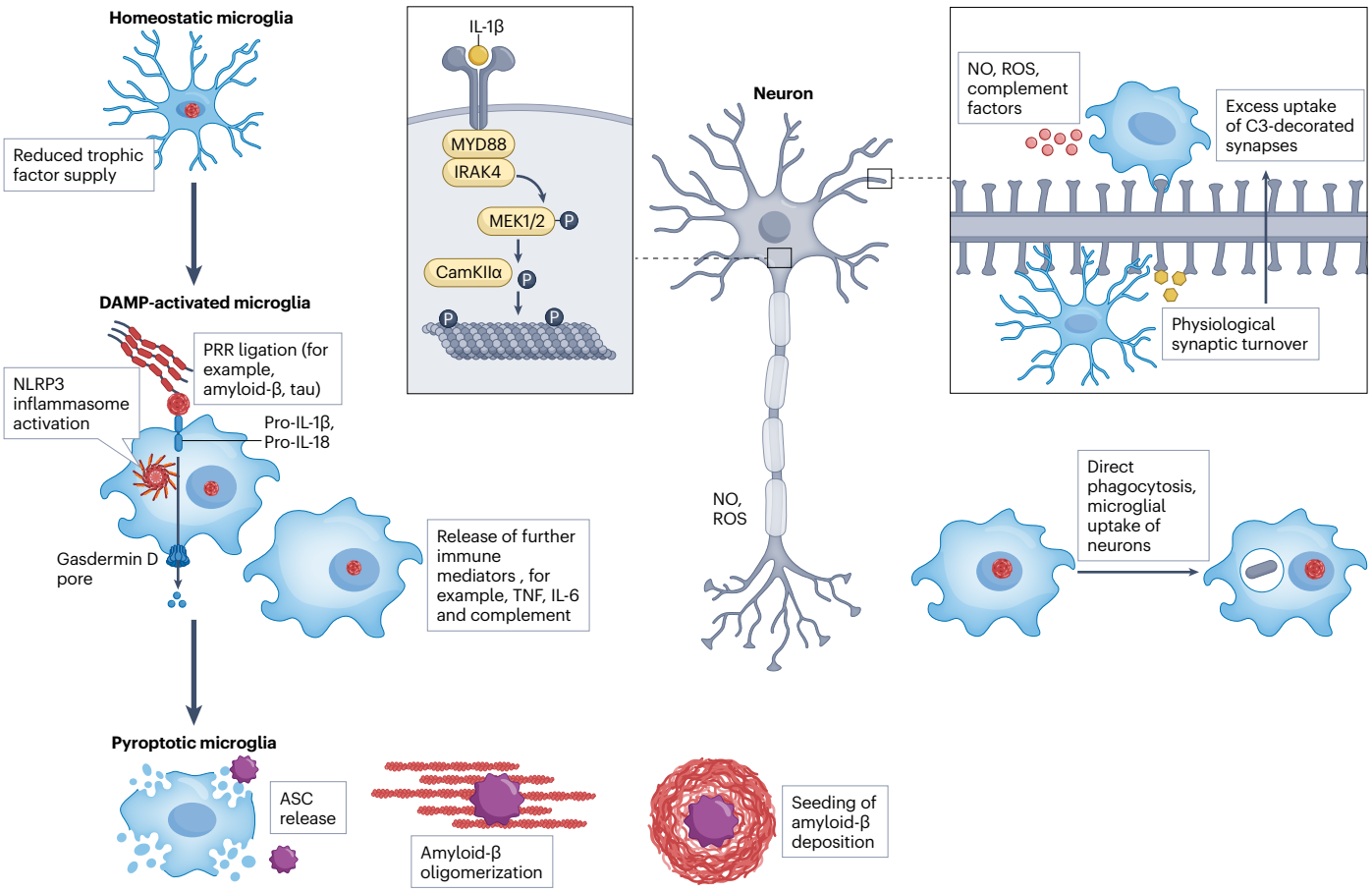


**Fig. 3 | Local neuronal and immune cell interactions in Alzheimer disease.** Homeostatic microglia are activated through pattern recognition receptor (PRR) ligation by neurodegeneration-associated proteins such as tau or amyloid-β. This results in NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome activation and subsequent release of IL-1β and IL-18 through a gasdermin D-formed pore complex. IL-1β can lead to the phosphorylation of tau and to subsequent formation of neurofibrillary tangles within neurons. Immune-activated neurons reduce their production of neurotrophic factors. Instead, they generate and release further immune factors such as TNF, IL-6, complement factors, nitric oxide (NO) and reactive oxygen species (ROS), which lead to neuronal damage and axon damage. Sustained inflammasome activation leads to pyroptosis (an inflammatory form of cell death) in microglia and subsequent release of the active inflammasome apoptosis-associated speck-like protein containing a CARD (ASC) speck, which contributes to further seeding of amyloid-β within the brain parenchyma. Excess decoration of synaptic structures with C3 results in an increased uptake of synapses, thus exceeding the physiological synaptic turnover by microglia. In addition, neurons that do display so-called 'don't eat me signals' can be entirely engulfed by microglial cell phagocytosis. CamKIIα, calcium–calmodulin-dependent protein kinase IIα; DAMP, damage-associated molecular pattern.

resulting in release of additional pro-inflammatory cytokines and chemokines and damage to the nervous system. In contrast to iNOS-derived NO, calcium-dependent neuronal NOS (nNOS) activity leads to NMDA-dependent peak NO production of ~2 fmol per second (~120 pmol per minute) in the entire hippocampus, which increases in aged 3xTg-AD mice due to higher nNOS protein expression[512]. This enhanced NO production was also seen in APP/PS1 mice due to increased interaction between C-terminal PDZ-ligand (CAPON) and nNOS[513], a mechanism that, when disrupted, prevented memory defects and dendritic loss in this model. Additional evidence suggests that tau nitrotyrosination is caused by the enhanced nNOS–CAPON interactions that occur in the *App*$^{NL-G-F}$ mouse model of AD[514]. These data confirm an NMDA receptor–nNOS-dependent route contributing to AD pathology, consistent with earlier studies and clinical trials, where application of the NMDA receptor antagonist memantine (an open-channel blocker) reduced excitotoxicity and ameliorated AD pathology[515].

There are various hypotheses as to where excitotoxicity and the associated and well-described neuroinflammation originate. Classically, accumulation of Aβ aggregates and cell debris are involved in a neuroinflammatory response and augmented NO production. Indeed, both fibrillary and oligomeric forms of Aβ directly activate microglial cells, including iNOS expression and NO production[516–518]. To target NO-mediated cytotoxicity in neurodegenerative conditions, one therapeutic approach is to suppress overall NO production, either pharmacologically or genetically. This method showed promising outcomes in a variety of model systems where NOS inhibition or iNOS deletion prevented or slowed disease progression[519,520]. However, clinical trials have not yet achieved any beneficial effects, although phase I and II trials (NCT02167256, NCT01864655) using Src family kinase inhibitors

(such as saracatinib) to suppress NF-κB[521], the transcription factor necessary for iNOS expression, were performed[522,523]. It seems obvious that there is a need to identify the optimal time window in which inhibition of NO production could exert the most clinical efficacy[524,525].

## Mutual interaction between immune mechanisms and neurodegeneration

### Inflammation regulates Aβ production

Inflammation can have detrimental effects in AD by exacerbating the generation of Aβ. It was proposed that pro-inflammatory cytokines could enhance the transcription of *APP* and affect Aβ aggregation and generation[526–528]. The expression of β-secretase 1 (BACE1) and APP increases upon incubation with pro-inflammatory mediators, such as cytokines and ROS[529–532], or in response to events leading to chronic gliosis such as TBI and stroke[533–536]. Other reports have suggested that inflammatory cytokines can regulate γ-secretase activity by inducing the expression of interferon-induced transmembrane protein 3 (IFITM3), which binds to γ-secretase, thereby increasing Aβ levels[537]. Interestingly, peripheral infection, including with a periodontal pathogen, can lead to an increase in APP and BACE1 expression[179]. In addition, studies in models of cerebral amyloidosis have revealed that low-grade peripheral inflammation induced by LPS injection exacerbates Aβ pathology by affecting Aβ clearance mechanisms[148,538,539] or Aβ generation[540,541]. However, other reports have shown the opposite effects, with a reduction in Aβ when LPS was injected intracranially[542,543] or when mice are primed with low doses of LPS before the onset of transgene-driven Aβ deposition[149]. The effect of inflammation on APP and BACE1 expression has been related to the presence of consensus binding sites for various transcription factors that are known to be regulated by inflammation (such as SMAD, NF-κB, PPARγ and STAT1) in the *BACE1* and *APP* promoters[529,544–546]. In addition, changes in inflammatory markers have been associated with alterations in epigenetic reprogramming[547], including the expression of miRNAs regulating the expression of genes (such as *BACE1* and *GSK3*) involved in Aβ generation and tau phosphorylation[535].

### Tau pathology

Tau pathology can spread from cell to cell by unknown mechanisms. Accordingly, tau can be found in the extracellular space and potentially enters cells trans-synaptically, a phenomenon thought to be involved in disease progression[548–550]. In tau-transgenic mouse models, tau pathology and tau spread were shown to be driven by activated microglia, potentially via the release of IL-1β[161,305] (Fig. 3). In line with this, depletion of microglia led to reduced tau transfer between neurons[551]. Tau was identified as an activator of the NLRP3 inflammasome, and NLRP3 inflammasome activation was detected in the brains and CSF[552] of patients with tauopathy. The loss of inflammasome function markedly reduced progression of tau pathology as well as tau seeding downstream of Aβ[74]. In another study, p-tau and misfolded tau activated NF-κB signalling and NLRP3 inflammasomes in microglia[552]. Notably, myeloid cell-restricted deletion of MYD88 or ASC rescued tau pathology and improved cognitive function in a mouse model. Importantly, suppression of tau via doxycycline or virus-like particle-based neutralization significantly reduced NLRP3 and ASC levels in the rTg4510 mouse model of tauopathy[552]. This suggests that neuronally derived tau can serve as a DAMP and trigger microglial cell immune responses. Strategies to block tau or tau–microglia cell interactions could be potential therapeutic strategies for tauopathies, including AD.

### Synapses and axons

It is becoming clear that microglia play crucial roles at the neuronal synapse (thus the term quadripartite synapse)[216,553]. Microglia constantly contact synapses and contribute to synaptic homeostasis and function throughout lifespan[553–555] (Fig. 3). One key microglial function during development is the coordination of synaptic pruning via the classical complement cascade[556,557]. Interestingly, this process becomes reactivated in a region-specific manner in various models of neurological disease, including in both Aβ-based[461,469] and tau-based[452,558] AD models. These studies have shown that complement components C1q and C3 are upregulated and localized to synapses, leading to aberrant elimination of the tagged synapses by microglia[469] (Fig. 3). This microglial response is suggested to mediate synapse loss and dysfunction in models of AD and of other neurological diseases[559–563] as well as in ageing[461,564] and across species[565].

Several immune and neuronal proteins have emerged as potential upstream regulators of microglial cell-mediated phagocytosis and production of C1q in AD models, including phosphatidylserine (PtdSer), SPP1, TREM2 and neuronal pentraxin 2 (NPTX2)[566–568]. Still, further investigations are necessary to determine how specific synapses are being targeted and eliminated while others remain intact[569]. This could include molecules that negatively regulate complement proteins, such as the newly identified complement inhibitor SRPX2, or molecules that negatively regulate microglial phagocytosis such as CD47 and SIRPα. Another important consideration is that microglial cell-mediated synapse elimination may not always be detrimental in neurodegeneration[570,571]. For example, it has recently been shown that microglial cell-mediated elimination of synapses can protect circuits from hyperexcitability in AD-related neurodegeneration. It is possible that synapse elimination early on in neurodegeneration could be beneficial as this might protect neurons from excitotoxicity and detrimental effects propagating in an uncontrolled manner, leading to cognitive decline. Thus, further elucidating the timing and circuit specificity of microglial cell-mediated and complement-mediated synapse elimination during neurodegeneration will improve our ability to therapeutically target these mechanisms in disease.

## Clinical trials and future therapeutic targets

The modern era of studying neuroinflammation in AD began in 1982 with the report from Eikelenboom and Stam of complement components decorating Aβ plaques[6,9]. These results were fortified by additional studies by McGeer et al.[11] and Rogers et al.[12] in the late 1980s. Given that the implication of inflammation in AD pathogenesis predates articulation of the Aβ hypothesis[572], and given an assumption that such inflammation must harm surrounding tissues, one may wonder why no agents have been approved for modification of AD pathogenesis by modulation of inflammation as well as why no such agents are presently in late-stage clinical trials. Clinical trials to date have resulted in null or, in some instances, negative (suggesting harm) findings (reviewed up to 2018 in ref. 573). These trials tested anti-inflammatory agents of different categories and, in some instances, employed strategies to avoid exposure at later stages of the disease process, enroling relatively 'young–elderly' cognitively normal individuals with a parental history of AD[574]. The most concerning result emerged from a trial that tested the ability of the discontinued COX2-selective agent rofecoxib to prevent 'conversion' of mild cognitive impairment to AD dementia, producing a statistically significant hazard ratio of 1.46 ($P = 0.011$) in favour of incident dementia. Such findings have likely discouraged more recent trial efforts, as a search for "neuroinflammation Alzheimer

## Glossary

### 3xTg model
Mouse model of Alzheimer disease (AD) carrying three mutations associated with familial AD (FAD): *APP* Swedish, *MAPT* P301L and *PSEN1* M146V.

### 5xFAD mouse model
Mouse model of AD that overexpresses both mutant human *APP* (encoding amyloid-β precursor protein 695) with the Swedish (K670N, M671L), Florida (I716V) and London (V717I) FAD mutations and a human *PSEN1* harbouring two mutations, M146L and L286V. Overexpression of these genes results in cerebral amyloidosis and behavioural changes in mice.

### β-Secretase 1
(BACE1). In the context of AD, BACE1 is the major β-secretase that generates Aβ in neurons by cleaving APP.

### Amyloid-β
(Aβ). An aggregation-prone peptide of 36–43 amino acids that originates from Aβ precursor protein (APP) after being processed by β-secretase and γ-secretase. Aβ is the main component of AD Aβ plaques.

### APP/PS1 model
Mouse model of AD expressing a chimeric mouse/human APP (Mo/HuAPP695swe) and a mutant human presenilin 1 (PSEN1-dE9), both directed to central nervous system (CNS) neurons. Other combinations of FAD-related gene variants exist.

### Blood–brain barrier
(BBB). A network of blood vessels and tissue that is made up of closely spaced cells and helps keep harmful substances from reaching the brain.

### Central memory T cell
Central memory T cells express CD45RO, CCR7 and L-selectin (CD62L). They are commonly found in the lymph nodes and in peripheral blood circulation.

### CNS-associated macrophages
(CAMs). Macrophages located at CNS interfaces, including the meninges, perivascular space and choroid plexus. CAMs are also referred to as BAMs or 'border-associated macrophages' in the literature.

### Damage-associated molecular patterns
(DAMPs). Also known as alarmins, these are molecules released by stressed cells undergoing cell death and act as endogenous danger signals to promote and exacerbate the inflammatory response.

### Disease-associated microglia
(DAM). A subset of brain-resident macrophages that can be found next to sites of neurodegeneration. DAM may have protective roles and might have a sensory mechanism to identify neurodegeneration-associated molecular patterns. DAM were first described in the 5xFAD mouse AD model in 2017 by Keren-Shaul et al.[217].

### Effector memory T cell
Effector memory T cells express CD45RO but lack expression of CCR7 and L-selectin. Because these memory T cells lack the CCR7 lymph node-homing receptor they are found in the peripheral circulation and tissues. They are important for the rapid response to previously experienced immune (pathogen) challenges.

### Exhausted T cell
A condition in which T cells lose their ability to kill certain cells, such as cancer cells or cells infected by a pathogen, mostly due to sustained overactivation in response to chronic immune challenges.

### Inflammasome
Cytosolic multi-protein complexes that enable the cell to initiate inflammatory responses following the sensing of DAMPs and pathogen-associated molecular patterns. They activate caspase 1-mediated cleavage of pro-inflammatory cytokines and can initiate pyroptosis, an inflammatory form of cell death.

### Innate immune memory
A type of epigenetically driven memory shown by myeloid cells and innate-like lymphocytes following exposure to pathogen-associated molecular patterns or DAMPs.

### Lewy body disease
A disease associated with abnormal deposits of a protein called α-synuclein in the brain. These deposits, called Lewy bodies, affect chemicals in the brain and can lead to problems with thinking, movement, behaviour and mood.

### Long-term potentiation
A form of activity-dependent plasticity that results in a persistent enhancement of synaptic transmission.

### Microglia
A subset of glial cells of the CNS. They are yolk sac-derived macrophages that reside in the brain and spinal cord parenchyma and are the first and main line of immune defence in these tissues. Microglia are responsible for CNS homeostasis and have a central role in removing unnecessary or damaged neurons and in pruning synapses as well as in recognizing and removing plaques and infectious particles.

### Mini-Mental State Examination
(MMSE). A screening test that can be used to systematically and thoroughly assess cognitive functions.

### Neurovascular coupling
Alterations in local perfusion that occur in response to changes in neuronal activity.

### Neutrophil extracellular traps
Neutrophil extracellular traps are web-like structures that form from DNA and other neutrophil intracellular proteins. They are released by activated neutrophils and bind and kill pathogenic microbes.

### Prodromal AD
The prodromal stage of AD refers to patients with mild cognitive impairment and evidence of AD-associated pathology.

### Quadripartite synapse
A term proposed to describe presynaptic and postsynaptic neuronal terminals and the neighbouring astrocytes and microglia.

### Regulatory T ($T_{reg}$) cells
A specialized subpopulation of T cells that act to suppress effector immune responses, thereby maintaining tissue homeostasis and self-tolerance.

### Tau
Tau protein is encoded by the *MAPT* gene and stands for tubulin-associated unit. In dementias such as AD but also in Parkinson disease and other tauopathies, p-tau can form insoluble aggregates called neurofibrillary tangles.

### Tau PHF6 fragment
A hexapeptide fragment of tau that can self-assemble and initiate full-length tau protein aggregation.

### TDP43 disease
Neurodegenerative diseases associated with a TDP43 dysfunction. Examples include amyotrophic lateral sclerosis, frontotemporal lobar degeneration and limbic predominant age-related TDP43 encephalopathy.

### T effector memory CD45RA$^+$ cells
A terminally differentiated subset of memory T cells that re-expresses CD45RA, a marker normally associated with antigen-inexperienced T cells.

### Translocator protein
(TSPO). The protein translocation systems found in mitochondria, chloroplasts and the general secretory pathways (Sec and Tat) responsible for the efficient delivery and folding of globular and membrane proteins into their correct compartment or into the membrane.

disease" under "controlled clinical trials" retrieved only 26 citations as of 6th November 2023. The more recent citations report approaches such as treatment with Boswellic acids[575], caloric restriction[576] and oral hygiene intervention[577]. Investigators described phase I trials of Lomecel B, a cell therapy comprising allogeneic mesenchymal stem cells, in patients with mild AD[578,579]; of note, some have proposed rebranding mesenchymal stem cells as 'medicinal signalling cells' to diminish the implied stemness of the cell product[580]. Recipients of Lomecel B showed no safety issues but measurements of plasma cytokines, hippocampal volume and MMSE produced variable results with no clear dose–response or biomarker–clinical relationship. One high-profile initiative (NCT05450549) using DNL919, a brain-penetrant TREM2 antibody, was discontinued following the observation of moderate, reversible haematological toxicity in a single ascending dose safety study in healthy volunteers[581].

From the present Review, and from examining the clinical trial literature, it becomes apparent that the community of neuroinflammation and neurodegeneration researchers currently lacks a unifying hypothesis that would enable the generation of panels of core-pathology biomarkers. Our field would be well-advised to consider ways to accelerate clinical development given underlying biological uncertainty. For example, basket trials performed within a platform trial structure allow the establishment of a combined, enlarged placebo group and standardized protocols against which to evaluate multiple agents simultaneously. At the same time, considering how to enhance diversity of trial populations promises to augment the potential for real-world success.

## Next-generation models and open questions

This Review has highlighted how diverse cell types in the brain parenchyma contribute to neuroinflammation in the setting of AD. It is clear that the culprit in AD is not any one given cell type but rather a community of cells whose mutual interaction accelerates AD pathophysiology[582]. It seems also obvious that any therapy designed to target immune processes runs the risk of interfering with mechanisms of immune defence and organ homeostasis. The complexity of neuroinflammation in AD calls for precise temporal and spatial targeting of cell interactions for therapeutic purposes, meaning that, along the decade-long course of the disease, the best time for interference has to be identified and, ideally, the effects of any therapies confined to the brain. Disruption of these interactions that drive neuroinflammation is an important therapeutic target, and will require more sophisticated studies at the human level, such as using in vitro iPS cell-derived model systems to identify suitable immune targets. Such challenges are being addressed by many groups and, while no one model system is ideal at present, some in vitro systems show promising results in capturing features of AD pathophysiology such as the response to Aβ toxicity[583]. Simpler model systems of cellular monocultures derived from iPS cells have also shown that certain in vitro measures correlate with complex traits captured during life such as cognitive decline[8,584]. An added challenge is that iPS cell-derived cell types, and even cell lines, display heterogeneity in cell states even in monocultures[585]. Therefore, next-generation models will need a higher level of characterization to either account for the diversity of cell states or, preferably, differentiate the component cell types to the target cell states needed for an experiment.

The recent development of chimeric models where human microglia are transplanted into the mouse brain opens new avenues to tackle some of the challenges connected to the complex molecular and cellular interplay occurring in a whole living organism. They provide a complex platform in which human cells are placed into a living brain 'bioreactor', where they can interact with other CNS and systemic components and be exposed to relevant disease challenges[264,586,587]. Initial characterization of this model showed that transplanted human microglia recapitulate several baseline transcriptomic, proteomic and functional aspects of human primary cells[195,225,586]. The analysis of human microglia transplanted into the brain of AD mice revealed that they display a wide heterogeneity of cell states that mimic time-dependent phenotypes and transcriptional features of AD[227,587]. An additional key advantage of chimeric models is the wide range of patient-derived iPS cell lines that could shed light on the impact of single or poly-genetic risk associated to AD[588] as well as relatively straight-forward genetic modifications that can be introduced at stem cell level and can help in translating from cell state to function. Although transplantation studies may provide relevant biological and mechanistic insights into different AD genetics, microglia cell states and functions, they also come with significant limitations as the human cells are placed in an immunodeficient mouse host.

With enhanced multicellular in vitro and in vivo models, we will not reproduce the human brain but we will have a manipulable approximation of cellular communities with which to test mechanistic questions and obtain reproducible results that can inform therapeutic pipelines. Key questions to pursue include defining how different microglial cell states translate into function within the brain. This would enable us to target the nodes in the intercellular communication network of microglia that drive pathology so that the cell community is instead driven towards protective states. One does not necessarily have to perturb all cells in a community equally; perhaps perturbing a key driver cell subtype can then effect the desired changes in the other cell types in the community. In vitro models with a pseudo-vascular component or refined chimeric systems with re-introduction of adaptive immune cells via T cell transfer are particularly interesting, as leveraging the propagation of immune responses from the periphery to the CNS would be ideal for a therapeutic, avoiding the many challenges of BBB penetration.

With the advent of anti-Aβ passive vaccination therapies in AD, even if limited in efficacy, and the beginning of clinical testing of immune-modulatory drugs in AD, future strategies will also have to test possible combinations. The success of these therapies either alone or in combination may depend on the identification of the optimal treatment period and biomarkers to monitor target engagement in the decade-long course of this disease.

Published online: 9 December 2024

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## Acknowledgements

A.F. received funds from Germany's Excellence Strategy (EXC 2067/1 390729940). A.J.T. is supported by the National Institutes of Health (NIH) grant (U54 AG054349). D.L.F. is supported by grant IK6BX004852-01 from the Department of Veterans Affairs. D.B. acknowledges support from the Medical Research Council UK, Alzheimer's Research UK and the European Union. She thanks the UK Brain Banks and BRAIN UK for providing tissue for her studies. D.J.B. is supported by the NIH (R01AG053229, R01AG068076, U54AG079779), the Minnesota Partnership for Biotechnology and Medical Genomics (MNP #18.04), and the Glenn Foundation for Medical Research. C.Cunningham is funded by the Irish Research Council, National Institutes of Health, the Dutch Research Council (ZonMW) and Alzheimer's Research UK. D.G.-N. was supported by grants from the Medical Research Council (MR/P024572/1, MR/Y004116/1). C.V. was supported by the RYC2022-036191-I, funded by MCIN/AEI/10.13039/501100011033 and European Social Fund Plus. C.T. is supported by the European Commission Marie Curie International Training Network, grant agreement No. 860197 (MIRIADE) and TAME, Innovative Medicines Initiatives 3TR (Horizon 2020, grant No. 831434), EPND (IMI 2 Joint Undertaking (JU), grant No. 101034344) and JPND (bPRIDE, CCAD), European Partnership on Metrology, co-financed from the European Union's Horizon Europe Research and Innovation Programme and by the Participating States (22HLT07 NEuroBioStand), CANTATE project funded by the Alzheimer Drug Discovery Foundation, Alzheimer Association, Michael J Fox Foundation, Health Holland, ZonMW, Alzheimer Drug Discovery Foundation, The Selfridges Group Foundation, and Alzheimer Netherlands. C.T. is a recipient of ABOARD, which is a public–private partnership receiving funding from ZonMW (#73305095007) and Health Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). C.T. is a recipient of TAP-dementia, a ZonMw-funded project (#10510032120003) in the context of the Dutch National Dementia Strategy. D.M. is supported

by ZEN24-1070221 from the Alzheimer's Association and R01 AG055072, R01 AG077651, and P30 AG072931 from NIH. D.R.T. received support from Research Foundation – Flanders (FWO; G065721N), Stichting Alzheimer Onderzoek (SAO/FRA 2023/0009) and Alzheimer's Association (22-AAIIA-963171). D.S. was supported by NINDS-R01NS117533, NIA-RF1AG068281 and NIH-R24OD036199. G.C. is supported by the NextGenerationEU and National Recovery and Resilience Plan, National Biodiversity Future Center and PE grant MNESYS (PE0000006). G.C.P. received funding from the German Science Foundation (PE1193/6-2), ERA-NET (MICRO-BLEEDs and TACKLE-CSVD), and the Fondation Leducq (Transatlantic Network of Excellence 23CVD03); he is a member of the Deutsche Forschungsgemeinschaft (DFG; German Research Foundation) excellence cluster ImmunoSensation2. G.D. thanks the Agence Nationale de la Recherche (grants #ANR-21-CE17-0054-01; #ANR-24-CE18-2770-02), Fondation Alzheimer, Fondation pour la Recherche Médicale, Fondation Pierre Deniker, Association France Alzheimer and Fondation Vaincre Alzheimer for funding his research. H.Z. is a Wallenberg Scholar and a Distinguished Professor at the Swedish Research Council supported by grants from the Swedish Research Council (#2023-00356; #2022-01018 and #2019-02397), the European Union's Horizon Europe Research and Innovation Programme under grant agreement No. 101053962, and Swedish State Support for Clinical Research (#ALFGBG-71320). J.B. was supported by a research grant from the Canada Institute for Health Research. J.G. was funded by the JPB Foundation, the Cure Alzheimers Fund and The Alzheimer's Association. J.C.M.S. is supported by a clinical fellowship from the Alzheimer's Association (AACSF). J.V.S.-M. is supported by grants from the Pasqual Maragall Foundation (PMRP/2022/1184) and Spanish (PID2022-143263OB-I00) and Valencian (PROMETEO/2021/045) governments. K.-A.N. has been supported by grants from the DFG (TRR274), European Research Council (ERC; AdG MyeliNANO) and the Adelson Medical Research Foundation (AMRF). K.B. was funded by the NIH grant RF1NS083704. L.A. is supppoted by the Austrian Science Fund FWF Project #P35417-B. K.A. is the Edward F. and Irene Thiele Pimley Professor of Neurology and Neurological Sciences and is supported by NIH grants RF1 AG070839, RF1 AG079131, and RF1 AG080742, the Wu Tsai Neurosciences Institute Knight Initiative for Brain Resilience at Stanford University, and she is a Chan Zuckerberg Biohub-San Francisco Investigator. M.K.O. is supported by grant 80NSSC21K0542 from NASA. O.B. is funded by grants from NIH-STTR (R41AG073059), Cure Alzheimer Fund, BrightFocus Foundation (2020A016806), NIH/NIA (R01 AG051812), NIH (R01 AG054672), NIH (R01 AG075509), NIH (R01 NS088137-10), NIH (R21AG076982), and NIH/NINDS (R01 NS088137). R.Mancuso has funding from the ERC under the European Union's Horizon 2020 Research and Innovation Programme (project no. 101041867 - XenoMicrogliaAD), Fonds voor Wetenschappelijk Onderzoek (grants No. G0C9219N, G056022N and G0K9422N), the Alzheimer's Association USA (2018-AARF-591110, 2018-AARF-591110-RAPID, E2A-23-1148152, ABA-22-968700). He also receives funding from BrightFocus Foundation (A2021034S), SAO-FRA (grants No. 2021/0021 and SAO-FRA 20230019) and the University of Antwerp (BOF-TOP 2022-2025). R.McManus is supported by grants from the European Union Joint Programme Neurodegenerative Disease (JPND) (01ED2409B), the Alzheimer's Association (24AARF-1243474) and from the DFG, under Germany's Excellence Strategy – EXC2151 – 390873048, along with Project-ID 432325352 – SFB 1454. S.C.G. is supported by the Alzheimer Forschung Initiative e.V (Grant 21060), the Hertie Network of Excellence in Clinical Neuroscience (Grant 2021-1A-12), the Bonn Neuroscience Clinician Scientist Program (Neuro-aCSis), and the DFG (EXC2151–390873048). S.H. is supported by the UK Dementia Research Institute (UKDRI-1011) and the Chan Zuckerberg Initiative Neurodegeneration Network. J.J.N. is currently supported through Germany's Excellence Strategy (EXC 2145 SyNergy– ID 390857198), the Else Kröner-Fresenius Stiftung (2018-A158), the Charitable Hertie Foundation (P1200024), the BrightFocus Foundation (A2021035S) and Alzheimer's Association (ADSF-24-1345513-C). W.M.vdF. performs research at the Alzheimer Center Amsterdam as part of the neurodegeneration research programme of Amsterdam Neuroscience. Alzheimer Center Amsterdam is supported by Stichting Alzheimer Nederland and Stichting Steun Alzheimercentrum Amsterdam. The chair held by W.M.vdF. is supported by the Pasman Stichting. W.M.vdF. is a recipient of ABOARD, which is a public–private partnership receiving funding from ZonMW (#73305095007) and Health Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). W.M.vdF. is a recipient of TAP-dementia (www.tap-dementia.nl), receiving funding from ZonMw (#10510032120003).

## Author contributions

The authors contributed equally to all aspects of the article.

## Competing interests

A.J.T. serves/served on scientific advisory boards and/or as a consultant with Alnylam, Apellis, and Montis and has a research contract from Visterra. C.Cruchaga has received research support from GSK and EISAI. C.Cruchaga is a member of the scientific advisory board of Circular Genomics and owns stocks. C.Cruchaga is a member of the scientific advisory board of Admit. D.J.B. has a financial interest related to this research. He is a co-inventor on patents held by Mayo Clinic, patent applications licensed to or filed by Unity Biotechnology, and a Unity Biotechnology shareholder. Research in the Baker Laboratory has been reviewed by the Mayo Clinic Conflict of Interest Review Board and is being conducted in compliance with Mayo Clinic Conflict of Interest policies. D.M. serves on the advisory board of Mindimmune, InMed and SynapsDx. He collaborates with Hesperos Inc. C.Cunningham has acted on the advisory board for Exalys Therapeutics and has received a small research grant from IONIS Therapeutics. C.T. has research contracts with Acumen, ADx Neurosciences, AC-Immune, Alamar, Aribio, Axon Neurosciences, Beckman-Coulter, BioConnect, Bioorchestra, Brainstorm Therapeutics, Celgene, Cognition Therapeutics, EIP Pharma, Eisai, Eli Lilly, Fujirebio, Instant Nano Biosensors, Novo Nordisk, Olink, PeopleBio, Quanterix, Roche, Toyama and Vivoryon. She is editor in chief of *Alzheimer Research and Therapy*, and serves on editorial boards of *Molecular Neurodegeneration*, *Neurology: Neuroimmunology & Neuroinflammation*, *Medidact Neurologie* Springer, and serves on committee to define guidelines for cognitive disturbances and one for acute neurology in the Netherlands. She had consultancy/speaker contracts for Aribio, Biogen, Beckman-Coulter, Cognition Therapeutics, Eli Lilly, Merck, Novo Nordisk, Olink, Roche and Veravas. D.B. has served as a consultant for Biogen. D.R.T. collaborated with Novartis Pharma AG (Switzerland) and GE-Healthcare (UK). G.D. holds two patents on immunomodulatory treatments in Alzheimer disease and tauopathies, has served on the scientific advisory board of Coya Therapeutics, and received lecturer fees from Eisai and research support from Institut Roche. H.Z. has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, LabCorp, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, Roche, and WebMD, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). K.A. is co-founder and member of the SAB for Willow Neuroscience, Inc. L.A. has been consultant for Intelgenx. M.C. is a member of the scientific advisory board of Vigil, NGMBio, Cell Signalling Technology, Cartesian, and Halyard; receives research support from Ono Pharmaceutical; and has patents pending on LILRB4 and TREM2. O.B. co-founded and is on the scientific advisory board of Glial Therapeutics and GliaX. O.B. collaborates with GSK and Regulus Therapeutics and received research funding from Sanofi, GSK, honoraria for lectures, and consultancy for UCB, Camp4, Ono Pharma USA, and General Biophysics. R.Mancuso has or had scientific collaborations with Alector, Nodthera, Alchemab and Roche, and has been consultant for Sanofi. R.R. is a full time employee at Third Rock Ventures, a firm that creates new biotech companies, including those addressing neurodegeneration. He is also Co-Founder and holds equity at Abata Therapeutics. S.A.L. maintains a financial interest in AstronauTx Ltd. and Synapticure, and sits on the SAB of the Global BioAccess Fund. S.H. has received speaking fees from Eisai Ltd, Novo Nordisk, and Alnylam, receives research funding from Eisai Ltd., and has a collaborative project with Ionis Ltd. W.M.vdF. receives or has received funding by ZonMW, NWO, EU-JPND, EU-IHI, Alzheimer Nederland, Hersenstichting CardioVascular Onderzoek Nederland, Health Holland, Topsector Life Sciences & Health, stichting Diorapthe, Gieskes-Strijbis fonds, stichting Equilibrio, Edwin Bouw fonds, Pasman stichting, stichting Alzheimer & Neuropsychiatrie Foundation, Philips, Biogen MA Inc., Novartis-NL, Life-MI, AVID, Roche BV, Eli Lilly-NL, Fujifilm, Eisai, Combinostics. W.M.vdF. has been an invited speaker at Biogen MA Inc., Danone, Eisai, WebMD Neurology (Medscape), NovoNordisk, Springer Healthcare, and European Brain Council; consultant to Oxford Health Policy Forum CIC, Roche, Biogen MA Inc., and Eisai; all funding paid to her institution. W.M.vdF. participated in advisory boards of Biogen MA Inc., Roche, and Eli Lilly. W.M.vdF. is a member of the steering committee of EVOKE/EVOKE+ (NovoNordisk); all funding paid to her institution. W.M.vdF. is a member of the steering committee of PAVE and Think Brain Health. W.M.vdF. was an Associate Editor of *Alzheimer's Research & Therapy* in 2020/2021 and is an Associate Editor at *Brain*. P.E. was funded by the Medical Research Council and now by Higher Education Funding Council for England (HEFCE). He has also received grants from Alzheimer's Research, UK, Alzheimer's Drug Discovery Foundation, Alzheimer's Society, UK, Medical Research Council, Alzheimer's Association US, Van-Geest foundation, and European Union grants. P.E. is a consultant to Roche, Pfizer, and Novo Nordisk. He has received educational and research grants from GE Healthcare, Novo Nordisk, Piramal Life Science/Life Molecular Imaging, Avid Radiopharmaceuticals and Eli Lilly. He was a member of the Scientific Advisory Board at Novo Nordisk. All other authors have no conflicts of interest to declare.

## Additional information

**Peer review information** *Nature Reviews Immunology* thanks V. Miron, L. Ryan and Y. Huang for their contribution to the peer review of this work.



**Michael T. Heneka[1] ✉, Wiesje M. van der Flier[2], Frank Jessen[3], Jeroen Hoozemanns[4], Dietmar Rudolf Thal[5,6,7], Delphine Boche[8], Frederic Brosseron[9], Charlotte Teunissen[10], Henrik Zetterberg[11], Andreas H. Jacobs[12], Paul Edison[13], Alfredo Ramirez[14,15], Carlos Cruchaga[16], Jean-Charles Lambert[17], Agustin Ruiz Laza[18],**

**Jose Vicente Sanchez-Mut[19], Andre Fischer[20,21], Sergio Castro-Gomez[22,23,24], Thor D. Stein[25], Luca Kleineidam[9,26], Michael Wagner[26], Jonas J. Neher[27,28], Colm Cunningham[29,30], Sim K. Singhrao[31], Marco Prinz[32,33], Christopher K. Glass[34,35], Johannes C. M. Schlachetzki[34,36], Oleg Butovsky[37], Kilian Kleemann[37], Philip L. De Jaeger[38,39], Hannah Scheiblich[22], Guy C. Brown[40], Gary Landreth[41], Miguel Moutinho[41], Jaime Grutzendler[42,43], Diego Gomez-Nicola[44], Róisín M. McManus[9], Katrin Andreasson[45], Christina Ising[15,46], Deniz Karabag[15], Darren J. Baker[47,48], Shane A. Liddelow[49,50,51], Alexei Verkhratsky[52], Malu Tansey[53], Alon Monsonego[54], Ludwig Aigner[55], Guillaume Dorothée[56], Klaus-Armin Nave[57], Mikael Simons[58], Gabriela Constantin[59], Neta Rosenzweig[37], Alberto Pascual[60], Gabor C. Petzold[9,61], Jonathan Kipnis[62,63], Carmen Venegas[1,64,65], Marco Colonna[62], Jochen Walter[66], Andrea J. Tenner[67,68,69], M. Kerry O'Banion[70,71], Joern R. Steinert[72], Douglas L. Feinstein[73], Magdalena Sastre[74], Kiran Bhaskar[75], Soyon Hong[76], Dorothy P. Schafer[77], Todd Golde[78,79], Richard M. Ransohoff[80], David Morgan[81], John Breitner[82], Renzo Mancuso[83,84] & Sean-Patrick Riechers[1]**

[1]Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Esch-sur-Alzette/Belvaux, Luxembourg. [2]Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Amsterdam, The Netherlands. [3]Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany. [4]Department of Pathology, Amsterdam Neuroscience, Amsterdam University Medical Centre, Amsterdam, The Netherlands. [5]Department of Pathology, University Hospitals Leuven, Leuven, Belgium. [6]Laboratory for Neuropathology, Department of Imaging and Pathology, KU Leuven, Leuven, Belgium. [7]Laboratory for Neuropathology, Department of Imaging and Pathology, Leuven Brain Institute (LBI), Leuven, Belgium. [8]Clinical Neurosciences, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK. [9]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany. [10]Department of Laboratory Medicine, VUMC Amsterdam, Amsterdam, The Netherlands. [11]Department of Psychiatry and Neurochemistry, University of Gothenburg, Gothenburg, Sweden. [12]European Institute for Molecular Imaging, University of Münster, Münster, Germany. [13]Division of Neurology, Department of Brain Sciences, Imperial College London, London, UK. [14]Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany. [15]Cluster of Excellence Cellular Stress Response in Aging-associated Diseases (CECAD), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [16]Department of Psychiatry, Washington School of Medicine in St. Louis, St. Louis, MO, USA. [17]Université de Lille, Inserm, CHU Lille, Institut Pasteur de Lille, Lille, France. [18]ACE Alzheimer Center Barcelona, Universitat Internacional de Catalunya (UIC), Barcelona, Spain. [19]Instituto de Neurociencias, Universidad Miguel Hernández-Consejo Superior de Investigaciones Científicas (UMH-CSIC), Alicante, Spain. [20]Clinic for Psychiatry and Psychotherapy, University Medical Center, Georg-August-University Göttingen, Göttingen, Germany. [21]Epigenetics and Systems Medicine in Neurodegenerative Diseases, German Centre for Neurodegenerative Disease (DZNE), Göttingen, Germany. [22]Center for Neurology, Clinic of Parkinson, Sleep and Movement Disorders, University Hospital Bonn, University of Bonn, Bonn, Germany. [23]Institute of Physiology II, University Hospital Bonn, University of Bonn, Bonn, Germany. [24]Institute of Clinical Chemistry and Clinical Pharmacology, University Hospital Bonn, University of Bonn, Bonn, Germany. [25]Boston University Alzheimer's Disease Research Center and CTE Center, Department of Pathology & Laboratory Medicine, Boston University Chobanian & Avedisian School of Medicine, Boston, MA, USA. [26]Department of Neurodegenerative Disease and Geriatric Psychiatry, University Hospital Bonn, University of Bonn, Bonn, Germany. [27]Biomedical Center Munich, Biochemistry, Medical Faculty, LMU Munich, Munich, Germany. [28]Neuroimmunology and Neurodegenerative Diseases, German Center for Neurodegenerative Diseases (DZNE), Munich, Germany. [29]School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute (TBSI), Trinity College Dublin, Dublin, Ireland. [30]Trinity College Institute of Neuroscience (TCIN), Trinity College Dublin, Dublin, Ireland. [31]Brain and Behaviour Centre, Faculty of Clinical and Biomedical Sciences, School of Dentistry, University of Central Lancashire, Preston, UK. [32]Institute of Neuropathology, Medical Faculty, University of Freiburg, Freiburg, Germany. [33]Signalling Research Centers BIOSS and CIBSS, University of Freiburg, Freiburg, Germany. [34]Department of Cellular and Molecular Medicine, University of California San Diego, La Jolla, CA, USA. [35]Department of Medicine, University of California San Diego, La Jolla, CA, USA. [36]Department of Neurosciences, University of California San Diego, La Jolla, CA, USA. [37]Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. [38]Center for Translational and Computational Neuroimmunology, Department of Neurology, Columbia University Irving Medical Center, New York, NY, USA. [39]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Irving Medical Center, New York, NY, USA. [40]Deparment of Biochemistry, University of Cambridge, Cambridge, UK. [41]School of Medicine, Indiana University, Indianapolis, IN, USA. [42]Department of Neurology, Yale School of Medicine, New Haven, CT, USA. [43]Department of Neuroscience, Yale School of Medicine, New Haven, CT, USA. [44]School of Biological Sciences, University of Southampton, Southampton General Hospital, Southampton, UK. [45]Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA, USA. [46]Center for Molecular Medicine Cologne (CMMC), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [47]Department of Paediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN, USA. [48]Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN, USA. [49]Neuroscience Institute, NYU Grossman School of Medicine, New York City, NY, USA. [50]Department of Neuroscience and Physiology, NYU Grossman School of Medicine, New York City, NY, USA. [51]Department of Ophthalmology, NYU Grossman School of Medicine, New York City, NY, USA. [52]Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK. [53]College of Medicine, University of Florida, Gainsville, FL, USA. [54]Department of Microbiology, Immunology and Genetics, Ben-Gurion University of the Negev, Beer-Sheva, Israel. [55]Institute of Molecular Regenerative Medicine, Paracelsus Medical University, Salzburg, Austria. [56]Sorbonne Université, Inserm, Centre de Recherche Saint-Antoine (CRSA), Hôpital Saint-Antoine, Paris, France. [57]Department of Neurogenetics, Max Planck Institute for Multidisciplinary Sciences, Göttingen, Germany. [58]Institute of Neuronal Cell Biology, Technical University Munich, Munich, Germany. [59]Section of General Pathology, Department of Medicine, University of Verona, Verona, Italy. [60]Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain. [61]Department of Vascular Neurology, University of Bonn, Bonn, Germany. [62]Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO, USA.

[63]Center for Brain Immunology and Glia (BIG), Washington University School of Medicine, St. Louis, MO, USA. [64]Departamento de Fisiología, Facultad de Medicina, Universidad de Granada, Granada, Spain. [65]Instituto Biosanitario de Granada (ibs.Granada), Granada, Spain. [66]Center of Neurology, University Hospital Bonn, University of Bonn, Bonn, Germany. [67]Department of Molecular Biology & Biochemistry, University of California Irvine, Irvine, CA, USA. [68]Department of Neurobiology and Behaviour, University of California Irvine, Irvine, CA, USA. [69]Department of Pathology and Laboratory Medicine, School of Medicine, University of California Irvine, Irvine, CA, USA. [70]Department of Neuroscience, University of Rochester Medical Center, Rochester, NY, USA. [71]Department of Neurology, University of Rochester Medical Center, Rochester, NY, USA. [72]Faculty of Medicine and Health Sciences, Queen's Medical Centre, University of Nottingham, Nottingham, UK. [73]Department of NeuroAnesthesia, University of Illinois at Chicago, Chicago, IL, USA. [74]Department of Brain Sciences, Imperial College London, Hammersmith Hospital, London, UK. [75]Department of Molecular Genetics & Microbiology and Neurology, University of New Mexico, Albuquerque, NM, USA. [76]UK Dementia Research Institute, Institute of Neurology, University College London, London, UK. [77]Department of Neurobiology, Brudnick Neuropsychiatric Research Institute, University of Massachusetts Chan Medical School, Worcester, MA, USA. [78]Department of Pharmacology and Chemical Biology, Emory Center for Neurodegenerative Disease, Emory University, Atlanta, GA, USA. [79]Department of Neurology, Emory Center for Neurodegenerative Disease, Emory University, Atlanta, GA, USA. [80]Third Rock Ventures, Boston, MA, USA. [81]Department of Translational Neuroscience, College of Human Medicine, Michigan State University, Grand Rapids, MI, USA. [82]Department of Psychiatry, McGill University Faculty of Medicine, Montreal, Québec, Canada. [83]Microglia and Inflammation in Neurological Disorders (MIND) Lab, VIB Center for Molecular Neurology, University of Antwerp, Antwerp, Belgium. [84]Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium.