# Immune attack: the role of inflammation in Alzheimer disease

*Frank L. Heppner[1,2], Richard M. Ransohoff[3] and Burkhard Becher[4]*

Abstract | The past two decades of research into the pathogenesis of Alzheimer disease (AD) have been driven largely by the amyloid hypothesis; the neuroinflammation that is associated with AD has been assumed to be merely a response to pathophysiological events. However, new data from preclinical and clinical studies have established that immune system-mediated actions in fact contribute to and drive AD pathogenesis. These insights have suggested both novel and well-defined potential therapeutic targets for AD, including microglia and several cytokines. In addition, as inflammation in AD primarily concerns the innate immune system — unlike in 'typical' neuroinflammatory diseases such as multiple sclerosis and encephalitides — the concept of neuroinflammation in AD may need refinement.

Myeloid cells
The subset of leukocytes that are not lymphocytes. They include granulocytes, monocytes, macrophages and dendritic cells.

[1]*Department of Neuropathology, Charitéplatz 1, Charité - Universitätsmedizin Berlin, D-10117 Berlin, Germany.*
[2]*Cluster of Excellence, NeuroCure, Charitéplatz 1, D-10117 Berlin, Germany.*
[3]*Biogen, 225 Binney Street, Cambridge, Massachusetts 02142, USA.*
[4]*Institute of Experimental Immunology, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland.*
*Correspondence to F.L.H., R.M.R. or B.B.*
*e-mails: frank.heppner@charite.de; richard.ransohoff@biogenidec.com; becher@immunology.uzh.ch*
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Dementia is an emerging global public health challenge for our generation: over 35 million people are affected by this condition worldwide and the global estimated financial cost of dementia in 2010 was in excess of US$600 billion[1]. The most prevalent cause of dementia is Alzheimer disease (AD), which is a fatal neurodegenerative disorder that is characterized by progressive cognitive and functional impairment and memory loss. Most cases of AD are late-onset and sporadic, with no proven evidence for a Mendelian pattern of inheritance. The prevalence of the disease increases with life expectancy, and it affects more than one-third of people over the age of 90 (REF. 2). There are no treatments to cure or halt the progression of AD; the currently approved pharmacotherapies provide only modest and transient symptomatic benefit. Validated biomarkers for early diagnosis of the disease also do not exist.

The amyloid cascade hypothesis has been the major pathogenic concept in the field of AD research for the past few decades. It states that the pathological sequence of events leading to AD are the accumulation of the amyloid-β peptide (Aβ), followed by the deposition of neurofibrillary tangles (NFTs), which are composed of the microtubule-associated protein tau, and the onset of synaptic and neuronal dysfunction and loss[3]. AD pathology is also characterized by an inflammatory response, which is primarily driven by the brain's intrinsic myeloid cells (known as microglia) and escalates with disease progression. For more than a decade, there have been data indicating that the immune system may have a role in AD; however, the importance of inflammation to AD pathogenesis has only very recently been appreciated, and inflammation is now thought to contribute to and exacerbate AD pathology[4–12]. We propose that a better understanding of the role of inflammation in the pathogenesis of AD will deliver new therapeutic targets and attractive biomarkers for this disease that are relevant for diagnostics.

The overall aim of this article is to review our current knowledge of the contribution of the immune system to AD pathogenesis. We first summarize the current consensus view of AD pathogenesis and then integrate immune actions into the existing knowledge of pathogenic events in AD. Finally, we refine the concept of neuroinflammation in AD by specifying the reactive cells, their products and their signalling pathways that are associated with the disease, without any preconception about whether these immune actions are deleterious or helpful. These novel immune-related insights broaden our overall understanding of AD pathogenesis and may ultimately lead to novel therapeutic targets for controlling the disease process.

## The amyloid cascade hypothesis

The two primary pathological hallmarks of AD are Aβ plaques, which are extracellular deposits of Aβ (which is derived from the β-amyloid precursor protein (APP)), and NFTs, which are primarily composed of hyperphosphorylated tau. Although the pathophysiology of AD is still unknown, much evidence indicates that Aβ and tau species make an important contribution to disease progression. Indeed, according to the amyloid cascade

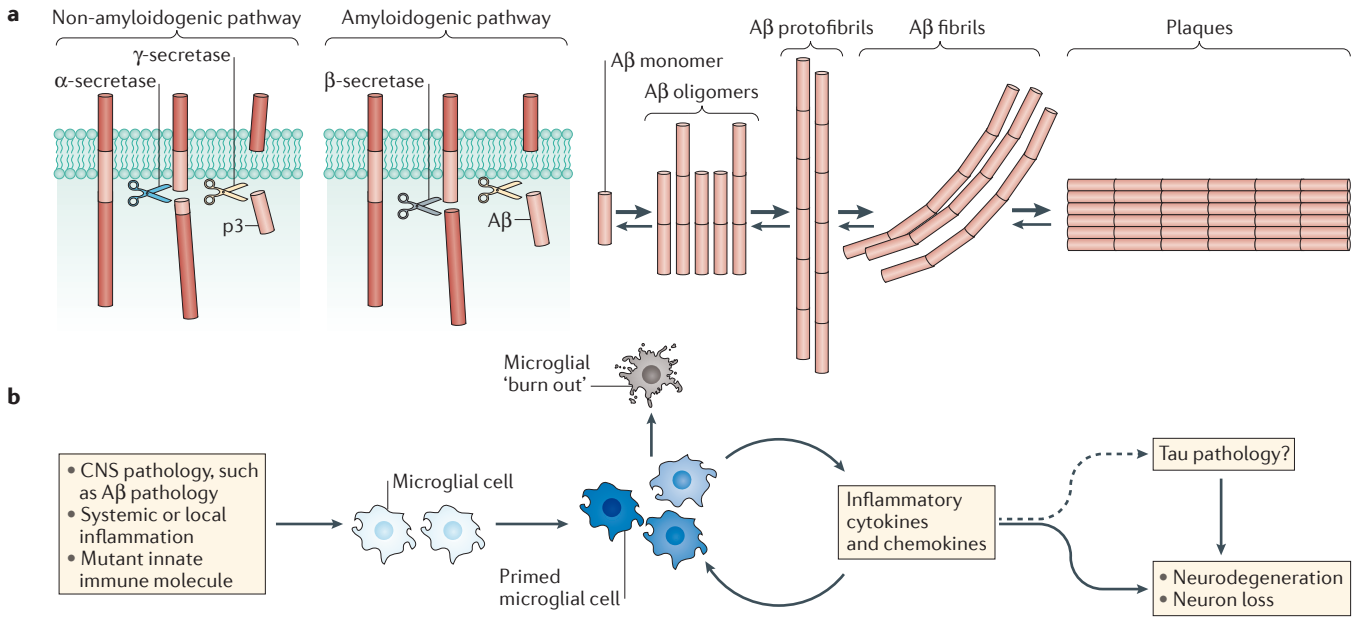



Figure 1 | **Pathological events in Alzheimer disease and microglial priming.** **a** | The increase in production and/or reduced clearance of amyloid-β (Aβ), which is derived from the β-amyloid precursor protein (APP), is throught to be a central event in Alzheimer disease (AD). Cleavage of APP occurs either in a non-amyloidogenic ('physiological') or in an amyloidogenic ('pathological') fashion; only the latter results in the production of amyloid-β (Aβ). In the non-amyloidogenic pathway, APP is cleaved first by α-secretase and then by γ-secretase, whereas in the amyloidogenic pathway, γ-secretase cleavage of APP is preceded by β-secretase cleavage, releasing Aβ into the extracellular compartment[16]. The cleavage site used by γ-secretase in the amyloidogenic pathway determines whether the predominant Aβ40 or the more aggregation-prone and neurotoxic Aβ42 species of the peptide is generated. Aβ monomers may then go on to form oligomers or other arrays, depending on mutations in the Aβ coding region of *APP* and post-translational modifications[16,204]. The arrow thickness indicates the likelihood of conversion of Aβ species or arrays. **b** | The presence of Aβ (as well as other pathological protein deposits, alterations in the CNS, systemic or local inflammation, and mutations in genes encoding innate immune molecules) can 'prime' microglial cells; that is, Aβ makes these cells susceptible to a secondary stimulus and/or promotes their activation. Priming results in various functional microglia phenotypes (indicated by different colours), presumably accompanied with no or only minor morphological alterations and/or no (major) cell-surface marker differences. In AD, Aβ sustains chronic activation of primed microglia (due to the peptide's accumulation), which results in a constant production of inflammatory cytokines and chemokines by these cells; in turn, the cytokines and chemokines maintain activation of the primed cells. This process results in a vicious circle, which ultimately impairs microglia (although this impairment is reversible for some time); moreover, it affects surrounding CNS resident cells (astrocytes, oligodendrocytes and neurons), possibly aggravating tau pathology (denoted by the dashed line and a question mark), and finally causing neurodegeneration and neuron loss. If these processes perpetuate over a prolonged period, it forces microglia into a senescent, 'burn-out'-like (dystrophic) phenotype, which is thought to be irreversible.

hypothesis, Aβ accumulation and deposition in the brain — resulting from the aberrant processing of APP or dysfunctional clearance of the Aβ peptide — are the initiating events in AD[3] (FIG. 1a).

Several lines of evidence support the amyloid cascade hypothesis. Individuals with Down syndrome have a third copy (or part of a third copy) of chromosome 21, on which *APP* is located, and such individuals frequently develop the typical histopathological and clinical signs of AD even at young ages, thus linking the manifestation of AD in older individuals to APP processing. Furthermore, mutations in *APP* have been found in families with a history of early-onset AD. Indeed, all known mutations linked to familial AD affect the generation or aggregation propensity of Aβ (note that most cases of familial AD are caused by dominant mutations in the genes that encode the presenilin proteins, which form part of the γ-secretase complex that processes APP (FIG. 1a)). Finally, *APP* variants that protect against AD have been reported[13]. Thus, the genetic evidence strongly supports the hypothesis that abnormal production or accumulation of Aβ is a pathogenic event in both familial AD and sporadic AD[3,14]. The fact that transgenic mice harbouring human *APP* mutations develop Aβ pathology that is similar to the pathology that is observed in patients with AD, and that cell lines carrying *APP* mutations overexpress Aβ (for reviews, see REFS 15,16), further corroborates this idea.

Importantly, various (soluble and insoluble) species and aggregation states of Aβ coexist, including monomers, oligomers, protofibrils, fibrils and Aβ plaques, and recent insights into their biology show that they probably have varying levels of pathogenic impact. This is not only of therapeutic but also of diagnostic significance, as different

Familial AD
An uncommon form of AD that usually occurs before the age of 65 and is inherited in an autosomal dominant fashion.

Aβ species are, at least by today's conventional diagnostic measures, not equally well detectable. Consequently, Aβ plaques — which are typically used as a neuropathological measure in the evaluation of AD brains — are only one of many ways in which Aβ presents, and may not always and necessarily correlate with the clinical signs of AD such as cognitive decline[16,17], whereas other, pathogenically more relevant Aβ species remain undetected.

The overwhelming evidence for the pathogenic relevance of Aβ — or at least of certain species thereof — in AD has motivated the design of interventional strategies to clear excess Aβ, prevent its formation or remove it. This particular focus may explain, at least in part, why AD-associated alterations other than those at the centre of the APP or tau processing machinery have been largely ignored by researchers and have been considered pathogenically irrelevant. This explains also why immune system-related events in AD have only recently become a central topic of pathogenic and, ultimately, possible therapeutic relevance. It has been proposed that the original amyloid cascade hypothesis should be slightly modified to incorporate a more central role for tau in the pathogenesis of AD[18], and further modification is justified to incorporate a role for neuroinflammation.

## Does neuroinflammation occur in AD?

Neuroinflammation was assumed to occur only at late to end stages of AD and possibly to represent merely an epiphenomenon. In particular, glial cell activation was thought to accompany but not significantly contribute to amyloid pathology (for reviews, see REFS 11,19). However, the spectrum of glial cell actions and other immune-related changes in AD had not been fully dissected, and is still far from being well understood.

Recently, preclinical, genetic and bioinformatic data have shown that activation of the immune system accompanies AD pathology and contributes to the pathogenesis of this disease[20]. As has often been the case in AD research, genetics has led the way in forging these links. The identification of associations between AD and mutations in genes encoding triggering receptor expressed on myeloid cells 2 (TREM2)[21,22] and myeloid cell surface antigen CD33 (REF. 23) proved to be conceptually transformational, as it was the first time that the link between immune alterations and AD pathogenesis was supported beyond the purely descriptive level. The discovery of risk variants of genes encoding immune system molecules prompted a reassessment of previously reported findings that levels of inflammatory cytokines, chemokines and other immune mediators are increased in the tissues and body fluids of individuals with AD or prodromal forms of this disease[24,25].

Recent studies have not only identified various novel alterations in immune system molecules, pathways and genes in AD but have shifted our understanding of the timing of immune system changes in the course of this disease. According to the amyloid cascade hypothesis[3], immune-system activation — ultimately mediated mainly by glial cells such as microglia and astrocytes — follows Aβ deposition. However, correlative analyses of the clinical symptoms that precede AD (that is, mild cognitive impairment (MCI)) and the presence of inflammatory changes (for example, in the cerebrospinal fluid (CSF)) have indicated a much earlier involvement of the immune system[24,25]. Moreover, one study[26] showed that systemic immune challenge by the viral mimic polyriboinosinic–polyribocytidilic acid 'sporadically' triggered and drove the development of AD-like neuropathology comprising Aβ plaques and tau aggregation, microglia activation and reactive gliosis in wild-type mice, suggesting that immune actions can precede AD-like pathology and are sufficient to cause it. The modulation of the neurodegenerative disease course by specific immune molecules in preclinical experimental approaches and the upregulation of inflammatory genes in arrays on tissues derived from patients with degenerative CNS diseases also point to a relationship between inflammation and neurodegenerative disorders (including AD), and implicate immune actions early in the pathogenic process[5–7,9–11,27–31]. These observations imply that immune processes may — at least at a given time point — drive AD pathology independently of Aβ deposition and sustain increased Aβ levels, thus exacerbating pathology and culminating in a vicious, pathophysiological cycle (FIG. 1b).

Neuroinflammatory responses can be induced by both CNS-intrinsic factors and systemic influences (factors from outside the CNS). Systemic inflammation[29,32] may result from chronic diseases — such as psoriasis, which recently has been shown to be associated with an increased risk of developing dementia (including AD-linked dementia)[33,34] — or from obesity and (obesity-associated) type 2 diabetes, in which CNS inflammation and microglia activation have been described as important components[35,36]. CNS-intrinsic neuroinflammatory conditions (for example, traumatic brain injury[37] and degeneration of the locus coeruleus[38]) have also been found to facilitate the development of AD pathology.

## Refining neuroinflammation

The immune system activation that is observed in AD is often labelled 'neuroinflammation'. We know that there is virtually no disorder of the CNS in which the immune system — or parts thereof — is not involved. It has become widely accepted that pathological changes within all tissues are sensed by the immune system. In particular, tissue-resident immune cells sense alterations in the tissue through so-called damage-associated molecular patterns (DAMPs)[39], which in AD comprise misfolded proteins and amyloid (such as Aβ plaques)[11]. Traditionally defined neuroinflammatory diseases (such as multiple sclerosis (MS) or encephalitides) used to be distinguished from neurodegenerative diseases (such as AD or Parkinson disease (PD)) by virtue of the kind of inflammation they evoked. For example, tissue invasion of blood-derived leukocytes of the adaptive immune system — namely, T and B lymphocytes — is a prominent feature of MS and encephalitides, but as far as we know it is not a prominent feature of AD or PD[12,40–43]. Indeed, the inflammatory reaction observed in AD is driven primarily (but perhaps not entirely) by CNS-resident immune cells —namely, microglia, perivascular myeloid cells[44] and other reactive elements

Microglia activation
A term used to describe a functional activation of microglial cells, for example, in response to a defined stimulus in pathophysiological settings or during development; however, it is often used to describe a change in the morphological appearance of microglia that does not necessarily correspond to the functional status of these cells. Reactive microglia is a term used when microglia respond to pathological changes and deviate from the normal steady-state.

Encephalitides
Acute inflammatory diseases of the brain, typically consisting of tissue-invading leukocytes (mainly T cells).

such as astrocytes — and reflects by and large the tissue reaction to pathological events that occur in the disease course. Irrespective of the ongoing discussion about whether neuroinflammation has not only a pathogenically relevant role but also a disease-initiating role in neurodegenerative disorders, the contribution of microglia and astroglia in degenerative diseases of the CNS such as AD is held to be a naturally occuring and concomitant part of AD pathology, be it benign, reparative or detrimental. By contrast, immune activation in traditional neuroinflammatory diseases (such as MS and encephalitides) is widely accepted to be disease-promoting.

We propose that the feature that distinguishes traditionally defined neuroinflammatory diseases from neurodegenerative disorders is the nature of inflammation; more precisely, whether the pathological process is driven by cardinal adaptive immune cells (as seen in encephalitides), or CNS-resident and/or potentially blood-derived innate immune cells. Thus, it might be more useful to discriminate diseases of the CNS as being characterized by an innate immune element or by an adaptive immune component (FIG. 2). The translational implication of this distinction will be that therapeutic development can focus on the respective type of immune system contribution that is active in the disease, and it will be irrelevant or even insufficient for patients or translationally minded scientists to separate CNS disorders with immune involvement per se from those that lack neuroinflammation. With respect to the translation of treatments, it will also not matter whether the immune contribution is primary and disease-causing (such as in encephalitides), or secondary and involved in maintaining or exacerbating disease (such as in AD).

The following points could be used to contrast AD with MS at the pathogenic level. First, the genetics of MS suggest that T cells have a role in this disease[45], whereas recent genome-wide association studies (GWASs) of sporadic AD cases have found associations between AD and other genes that are involved in innate immunity, as indicated by AD-linked mutations in the microglial or myeloid genes encoding TREM2 (REFS 21,22), CD33 (REFS 23,46), complement receptor 1 (CR1)[47,48], myeloid cell-expressed membrane-spanning 4-domains subfamily A member 6A (MS4A6A) and putative membrane-spanning 4-domains subfamily A member 4E (MS4A4E)[49,50]. Second, the disease process in MS

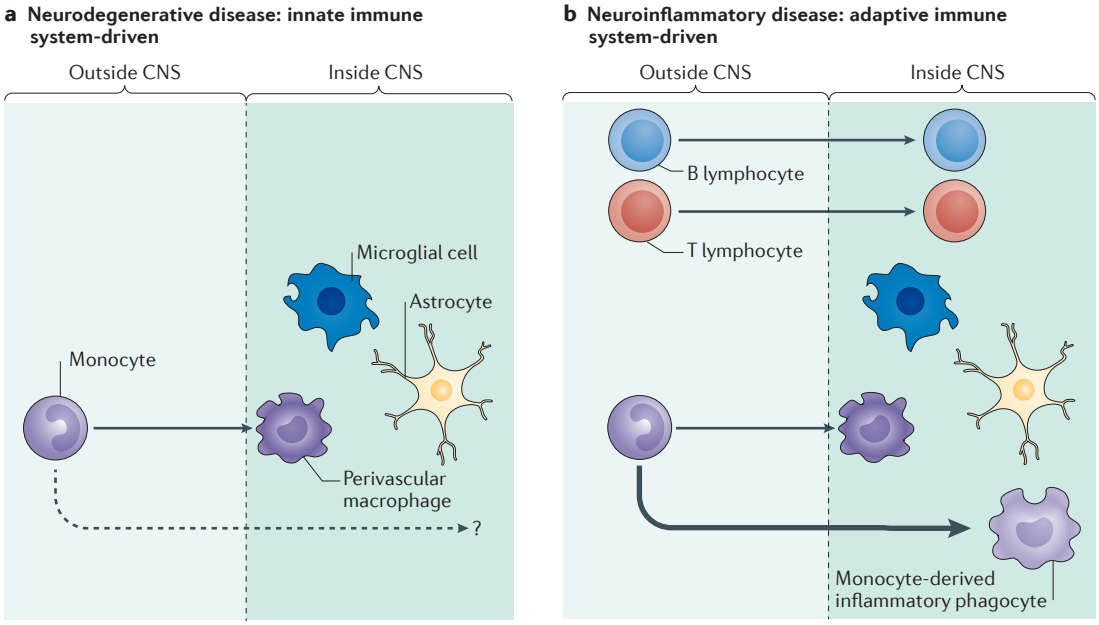



Figure 2 | **Distinguishing neuroinflammation: innate immune-driven versus adaptive immune-driven neuroinflammation.** Neuroinflammation in various CNS disorders can be differentiated by the nature of inflammation; that is, diseases may be classified according to if CNS-resident and/or potentially blood-derived innate immune cells are the major pathogenic component (as in neurodegenerative diseases such as Alzheimer disease) (**a**), or if predominantly adaptive immune cells (B and T lymphocytes) drive the pathological process (as seen in encephalitides or multiple sclerosis (MS)) (**b**). The main contribution — apart from astrocytes — of the innate immune system in neurodegenerative diseases occurs within the CNS through resident microglia and perivascular macrophages, whereas the involvement of other blood-derived myeloid cells such as dendritic cells and monocytes appear to have no major impact on the course of neurodegeneration. Whether — and if so, to what extent — monocytes are recruited from the periphery to the CNS in the course of the disease is not entirely clear (denoted by the dashed arrow and a question mark) (**a**). Traditionally defined neuroinflammatory diseases such as MS are primarily driven by cells of the adaptive immune system such as T and B lymphocytes; various subtypes of myeloid cells have, however, also important pathogenic implications; blood-derived monocytes represent in fact the most numerous infiltrate into the CNS where they transform into monocyte-derived inflammatory phagocytes (macrophages or dendritic cells) and are thought to mediate much of the tissue damage observed (denoted by the thick arrow). As in neurodegenerative diseases, astrocytes and microglia also react to pathology, although it is not clear whether the type of response is similar to what happens in neurodegeneration (**b**).

begins with T cell autoimmunity, as indicated by findings in informative animal models[51], whereas the disease process in AD may begin with abnormal protein processing and, in its early stages, involve aberrant innate immunity[11]. Third, the expression of quantitative trait loci that are implicated in AD are expressed in monocytes, whereas those that are involved in MS are mainly found in T lymphocytes[52].

Activation of the immune system in AD can act at least as pacemaker, perpetuating and accelerating the course of the disease; although at present it is not generally thought to be the trigger of the disease process, it cannot be excluded that immune actions, at least in part, may also have a detrimental role in initiating the disease process[4,7,10–12,26,28,29,31,53].

## Neuroinflammatory mechanisms in AD

***Microglia promote neuroinflammation in AD.*** Microglia are CNS-resident myeloid cells of embryonic haematopoietic origin. Like most tissue macrophages, microglia survey the brain for pathogens and support CNS homeostasis and plasticity; for example, by guarding and remodelling synapses (for a review, see REF. 54). Microglia are equipped to sense so-called danger signals, such as protein aggregates in AD, and to respond to changes in neuronal health by adopting a set of morphological and functional attributes; such cells are termed 'reactive' or 'primed' (for a review, see REF. 4).

Among all non-neuronal CNS cells, microglia are the most intimately associated with the tissue changes that are observed in AD: in brain tissue taken at autopsy from individuals with AD, macrophages derived from microglia and, possibly, from infiltrating monocytes surround Aβ plaques, and the morphology of parenchymal microglia indicates that these cells are responding to challenge.

Soluble Aβ oligomers and Aβ fibrils can bind to various receptors that are expressed by microglia, including CD14, CD36, CD47, α6β1 integrin, class A scavenger receptor, receptor for advanced glycosylation end products (RAGE) and toll-like receptors (TLRs)[55–62]. Binding of Aβ to, for example, CD36 or TLR4 results in the production of inflammatory cytokines and chemokines *in vitro*[59,63]. *In vivo*, interleukin-1 (IL-1) (REF. 64), IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF)[65], IL-12 and IL-23 (REF. 66), and tumour necrosis factor (TNF)[67] — all markers of inflammation — are detectable or upregulated in animal models of AD or in the brains or CSF from humans with AD (for details, see REF. 4). In studies in transgenic mouse models of AD, TNF release by microglia in response to Aβ was triggered by an interaction of CD40 with CD40L or by TLR4 engagement[68–70].

Besides the production of inflammatory mediators upon binding of Aβ to various microglia receptors, Aβ has been shown to be cleared by microglia *in vitro* through receptor-mediated phagocytosis and degradation. However, the relevance of these reports is uncertain, as it remains unclear whether microglia themselves phagocytose Aβ fibrils in a pathophysiological AD setting *in vivo* (for a review, see REF. 4). Nevertheless, microglia possess the machinery to degrade the more 'digestible' (and pathogenically more relevant[71]) soluble Aβ species via extracellular proteases such as neprilysin and insulin-degrading enzyme (IDE) (for a review, see REF. 72).

Aside from a few visionary investigators[43,73,74], most researchers consider it axiomatic that the amoeboid morphology of microglia in AD equates to a toxic microglial phenotype that is accompanied by the production of soluble inflammatory factors, and this morphology is often habitually — but erroneously — interpreted as a sign of microglial 'activation'. Remarkably, however, there is now strong evidence for a progressive, Aβ-dependent impairment of microglial function, as shown by a decrease in the phagocytosis of beads and in a reduced capacity to extend processes towards a tissue lesion in a mouse model of AD[75]. These findings are in line with another study showing that microglia from transgenic AD mice had reductions in the levels of Aβ-binding scavenger receptor and Aβ-degrading enzyme[76]. Importantly, efficient phagocytosis has recently been shown to involve a component of the autophagy pathway, namely beclin 1, the levels of which were found to be markedly reduced in microglia derived from people with AD[77]. The idea that microglial impairment might represent the functional correlate of their amoeboid phenotype in AD carries considerable relevance for understanding AD pathogenesis, especially in light of the finding that inefficient clearance of Aβ — including that mediated through microglial proteases — is a major pathogenic factor in sporadic AD[78]. It is therefore noteworthy but not surprising that transient depletion (using suicide-gene technology) of microglia that have acquired a dysfunctional phenotype has no impact on Aβ burden in an animal model of AD[79].

Microglial impairment might paradoxically be sustained by inflammatory cytokines such as TNF, IL-1, IL-12 and IL-23 (REFS 64,66,67). This idea suggests that AD pathology could be accelerated through this negative feedback loop. Ultimately, prolonged microglia impairment will also be accompanied by a loss of trophic functions and the elimination of protective properties. As the microglia-specific deficiency of brain-derived neurotrophic factor (BDNF) has recently identified microglia-produced BDNF to be key for achieving a motor-learning task by promoting learning-related synapse formation[80], a lack of functional microglia providing trophic factors such as BDNF may further impact neuronal integrity in the course of AD.

Aβ oligomers impair neuronal function in part because they can interact with neuronal membranes in a receptor-independent fashion[81,82]. Thus, it is tempting to speculate that microglial dysfunction in the early stages of AD may also be due to an interaction with such Aβ species, as these hydrophobic amyloid moieties can bind any cell membrane[83] (FIG. 3).

In summary, it is necessary to view the transformed microglial cell as being indicative of a loss of tissue homeostasis. Because microglia carry out critical physiological tasks in the healthy brain[84,85], a phenotypically transformed microglial cell should raise suspicions that their intrinsic tasks are not being performed efficiently and that the loss of microglial integrity may contribute

Quantitative trait loci
Stretches of DNA that contain or are linked to the genes that underlie a quantitative trait. Quantitative traits refer to certain phenotypes.

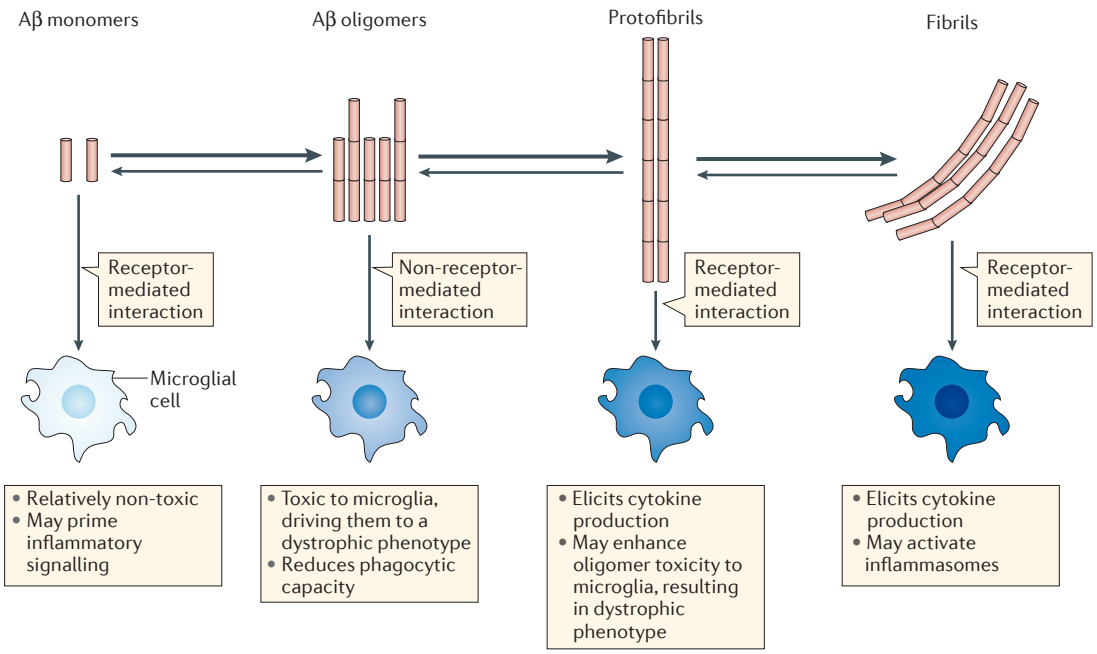



Figure 3 | **Dynamic, multifaceted interactions with amyloid-β mediate microglial phenotypes in Alzheimer disease.** In both *in vitro* and *in vivo* experiments, microglia exhibit receptor-dependent interactions[58,61,205,206] with various forms of amyloid-β (Aβ; from monomers to oligomers, protofibrils, fibrils and plaques) as well as non-receptor mediated interactions (particularly with oligomers)[81]. Aβ species can stimulate changes in microglial function or production of inflammatory mediators through signalling receptors[207], by inducing production of such mediators by other cells such as astrocytes[208] and through post-phagocytic processes within microglia, including lysosomal injury, which acidifies the cytosol and contributes to activating the NLRP3 (NACHT, LRR and PYD domains-containing protein 3) inflammasome[149]. Receptor-mediated interactions between microglia and Aβ monomers do not show evidence for altered microglial function aside from induction of a 'primed' state, typified by heightened responses to subsequent DAMP (damage-associated molecular pattern) or cytokine stimuli. Microglia function, as monitored by motility in response to laser lesion and phagocytic activity of latex beads, is severely impaired in APPPS1 Alzheimer disease (AD) mice[75], known to also exhibit oligomeric Aβ[209]. This functionally compromised state affects the microglial response to downstream Aβ species such as fibrils and plaques, culminating in a morphology and irreversible phenotype that is termed 'dystrophic' — corresponding to a 'burn out' of microglia (see also FIG. 1b). The arrow thickness indicates the likelihood of conversion of Aβ species or arrays.

to tissue pathology as readily as do other impaired elements of the CNS. The idea of neuroinflammation in AD therefore goes beyond the degree of mere alterations in microglial morphology and instead implies changes in this cell's phenotype and function, and the relevant consequences.

Rare structural variants of genes encoding the immune receptors TREM2 (REFS 21,22,86,87), CD33 (REFS 23,46) and CR1 (REF. 47), all of which are expressed on microglia and other myeloid cells, have been found to be associated with a higher risk of AD. These findings support the concept of altered microglial function in AD. As TREM2 has previously been shown to be involved in regulating microglial phagocytosis[88,89], it was surprising to learn that the chief impact of TREM2 *in vivo* in various AD mouse models is to promote the survival of activated microglia and their peripherally derived myeloid counterparts[90,91], and to engage these cells with Aβ plaques[90–92] through sensing lipids associated with Aβ accumulation and neuronal loss[90]. Interestingly, a TREM2 deficiency in APPPS1 mice, which express mutant forms of human APP and presenilin 1 (PS1) (and hence model AD), was shown to ameliorate hippocampal Aβ accumulation[91], whereas 5XFAD mice (an AD-like mouse model expressing human mutant variants of APP and PS1), in which Aβ deposition develops less rapidly than in APPPS1 mice, showed an increase in hippocampal Aβ in the absence of TREM2 (REF. 90). Future studies will need not only to address the reasons for the differences in Aβ pathology in the various AD-like mouse models lacking TREM2, but also to distinguish between potential differences in phenotypes resulting from TREM2 deficiency versus *TREM2* mutations. Accordingly, genetic variation in the gene encoding TYRO protein tyrosine kinase-binding protein (TYROBP; also known as DAP12) — the TREM2 adaptor protein — has been shown to be associated with late-onset AD[20]. Together, these findings suggest that impaired TREM2 function and, consequently, altered myeloid cell (monocyte or microglia) function, have a role in AD pathogenesis.

*CD33* encodes a cell-surface protein of the sialic acid-binding Ig-like lectin (SIGLEC) family[93] and provides another example of a myeloid-cell- or microglial-cell-expressed gene in which variants have been associated

with an increased risk of developing AD[23,46]. One study showed that CD33 expression was upregulated on microglia from post-mortem samples of human AD brains, and that a *CD33* variant, namely the protective *CD33* single-nucleotide polymorphism (SNP) rs3865444, was associated with reductions in both CD33 expression and insoluble Aβ levels in the AD brain[94]. By contrast, another study found that monocytes derived from carriers of this risk genotype showed a decrease *in vitro* in phagocytosis of Aβ fibrils[23].

GWAS-based discoveries of alterations in genes that regulate innate immune system functions in people with AD, along with insights into the contribution of the immune system to AD from a variety of experimental approaches, provide good evidence for a pathogenic role of CNS-resident myeloid cells such as microglia in the course of the disease. It is thus conceivable that mutations in innate immune molecules compromise microglia function, similar to the way in which Aβ impairs microglial performance over time[75]; microglia dysfunction, irrespective of whether it is caused by genetic alterations or by prolonged exposure to the Aβ-rich AD environment, will ultimately — if not interrupted — culminate in a state of these cells that has been termed 'dystrophic'[73,95]. In this state, microglia lack their beneficial functions and have acquired a detrimental, senescent-like phenotype, which could justifiably be termed a cellular 'burn out' of microglia that resembles an irreversible end stage (FIG. 1b).

***Myeloid cells other than resident microglia.*** The CNS has a rich complement of non-microglial myeloid cells including meningeal and choroid plexus macrophages, as well as perivascular macrophages. Of these, perivascular macrophages seem to have a particularly crucial role in the physiological removal of Aβ and protection from amyloid pathology[96,97]. Perivascular macrophages are, in contrast to microglia, continuously replaced from progeny of the circulating monocyte pool during adulthood[98]. Preclinical studies using animal models of AD based on amyloid deposition[96,97,99,100] have shown that all CNS myeloid cells are, in principle, capable of promoting Aβ clearance and, thereby, of limiting the deposition of vascular amyloid, thus influencing disease outcome. It remains uncertain whether infiltrating myeloid cells — monocyte-derived macrophages that typically do not contribute substantially in numerical terms to parenchymal macrophages in the course of AD[100] or in other proteinopathies such as prion disease[101] — can, in principle, modulate AD pathology when experimentally instructed to enter the AD brain, as reports are not conclusive[44].

***Astrocytes promote neuroinflammation in AD.*** Astrocytes are CNS-resident cells of neuroectodermal origin that can — like microglia — respond to pathological stimuli through reactive gliosis[102,103]. Also similarly to myeloid cells, astrocytes surround Aβ plaques[104], and studies using transgenic mice exhibiting cerebral amyloidosis[105] have shown that their activation occurs early in the course of pathogenesis. Although reactive astrocytes typically upregulate their expression of glial fibrillary acidic protein (GFAP), they do not form 'glial scars' in the brain of individuals with AD as they do in CNS diseases such as MS or in stroke[102]. In transgenic mouse models of AD, astrocytes underwent atrophy that preceded the Aβ plaque-related astrogliosis (except those astrocytes surrounding plaques, which show hypertrophy), and this eventually resulted in deficient glutamatergic transmission, possibly contributing to the cognitive impairment[106,107]. Furthermore, reducing astrocyte activation through a viral vector driving the expression of VIVIT, a peptide that interferes with the immune or inflammatory calcineurin–nuclear factor of activated T cells (NFAT) signalling pathway, in an Aβ-overexpressing mouse model of AD ameliorated AD-like pathology[108]. Several studies have shown that reactive astrocytes that are localized near plaques take up and degrade Aβ[109–111]. Furthermore, astrocyte activation followed by the release of apolipoprotein E (APOE) from astrocytes has been shown to be crucial for the ability of microglia to remove fibrillar Aβ in an animal model of AD[112]. Moreover, astrocytes, like microglia, increase their expression of Aβ-degrading enzymes when exposed to native Aβ extracts *ex vivo*[113–115]. However, the atrophy of astrocytes (as shown in a mouse model of AD[106,107]) may also result in a reduced proteolytic clearance of Aβ. Hence, AD pathogenesis may entail altered astrocyte function, which may be considered an integral part of the neuroinflammatory response.

***Neuroinflammatory actions of other CNS cells in AD.*** Besides microglia and astrocytes, other CNS-resident cells such as endothelial cells, oligodendrocytes and neurons can contribute to neuroinflammation. Oligodendrocytes and myelin are known targets of immune reactions in neurological disorders such as MS. Despite the fact that AD research lacks more detailed studies in this context, there is evidence for changes in oligodendrocytes and myelin abnormalities in AD white matter (reviewed in REFS 115–117). As oligodendrocytes have been shown to express the complement components C1q, C1s, C2, C3, C4, C5, C6, C7, C8 and C9 (REF. 118), and complement-activated oligodendrocytes are found in various neurodegenerative conditions with a neuroinflammatory component including AD[119], these cells may contribute to neuroinflammation by providing increased levels of complement in the AD brain (for details on the complement system in AD see REF. 115).

Neurons are equipped with a variety of molecules that protect against inflammation, of which fractalkine[120,121], the complement defense protein CD59 (REFS 122,123) and CD200 (REF. 124) have been shown to be decreased in pathology-affected regions of the AD brain. Thus, neurons can potentially contribute to the neuroinflammatory aspect of AD perhaps mainly by reducing their expression of inhibitors of inflammation in part due to cell death or dysfunction.

Endothelial cells, besides being a key element of the neurovascular unit that contributes to the transport of Aβ species between the brain and the periphery (for a review, see REF. 125), have also been described

Cerebral amyloidosis
This term describes all forms of CNS diseases that feature the deposition of proteins (so-called proteinopathies).

Hypertrophy
The increase in the volume of an organ, tissue or cell.

Apolipoprotein E
(APOE). A class of apolipoprotein that is required for the catabolism of triglyceride-rich lipoprotein constituents. In the CNS, APOE is generated primarily by astrocytes, and transports cholesterol to neurons via APOE receptors, whereas in the periphery, APOE is mainly produced by the liver and macrophages, and mediates cholesterol metabolism.

Neurovascular unit
(NVU). This consists of vascular cells such as brain endothelial cells, pericytes and vascular smooth muscle cells, glial cells such as astrocytes, microglia and oligodendroglia, and neurons. It links neural activity to blood flow and controls the exchange of biologically relevant protein interactions between brain and the periphery.

to influence inflammation in AD. Brain endothelial cells produce immune molecules such as IL-6, IL-1β and CCL2 *in vitro* upon exposure to Aβ peptides and in human AD brains[126]. Moreover, the vasoconstrictor endothelin 1 is upregulated upon Aβ binding to RAGE — the latter confers pleiotropic effects in the AD setting — which ultimately also regulates vascular inflammation in patients with AD[127]. For a more detailed review on endothelial actions in AD, including mechanisms influencing the efflux of amyloid and/or neurotoxic species as well as other proteins such as growth factors, and the expression of adhesion molecules enabling influx of immune cells to the brain, see REFS 125,128,129.

## Therapeutic neuroinflammatory AD targets

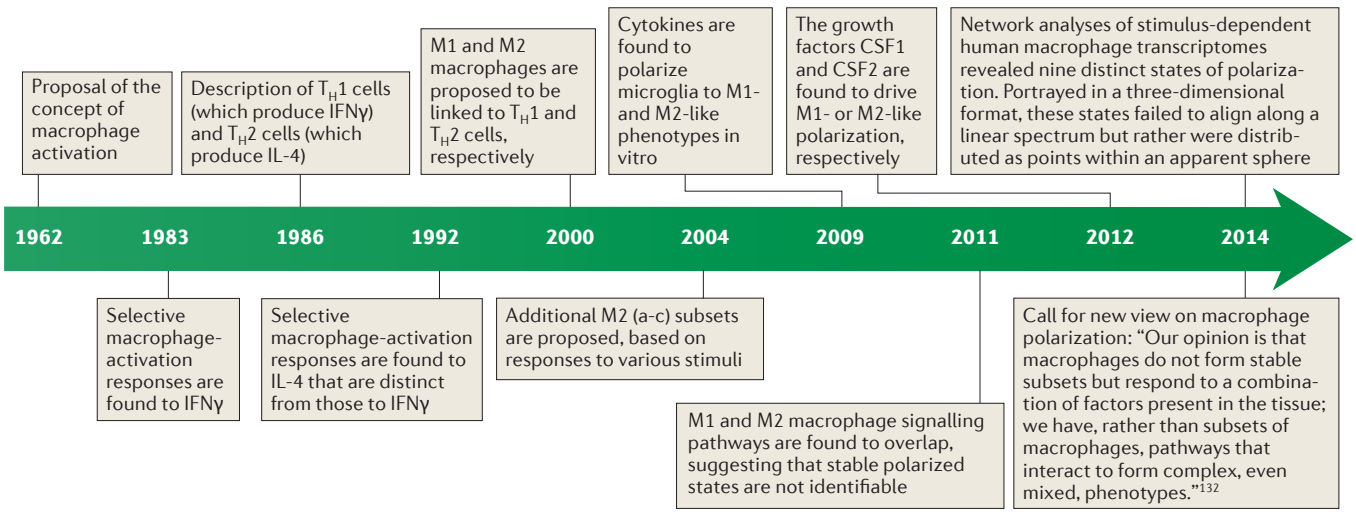
***Which cells should be modulated?*** To date, most therapeutic efforts have been directed towards developing purely symptomatic treatments or agents that target Aβ or tau; however, the strategy of reducing inflammation in AD has recently attracted more interest (for reviews, see REFS 11,130). Based on our current knowledge, innate immune cells such as microglia and macrophages are the prime targets for modulating neuroinflammation.

Resident microglia in AD and other pathological conditions have been shown to produce either inducible nitric oxide synthase (NOS2) or arginase[131]. As NOS2 expression was suggestive of M1 and arginase production of M2 phenotypes proposed for some tissue macrophages (BOX 1), microglia were categorized similarly[18,131]. However, research into macrophage biology over the past 15 years has led to an abandonment of the M1 versus M2 concept for macrophages[132]. Indeed, it has been suggested that macrophages should not be classified according to arginine metabolism[133], at least in part because macrophages and microglia commonly express both arginase and NOS2. Hence, we propose to follow suit and relinquish this framework for microglia. Regardless of how microglial phenotypes may ultimately be classified, these cells produce a large diversity

Box 1 | **M1 and M2 macrophages: the rise and fall of an idea**

In recent years, the concept of macrophage polarization has been widely applied, both to tissue macrophages and monocyte-derived macrophages, largely extrapolating results obtained *in vitro* to the situation *in vivo*. The concept incorporates two precepts: first, that there is a two-dimensional spectrum comprising all macrophage activation states; and, second, that the termini of this spectrum can usefully be modelled by inflammatory macrophages (termed M1 or classically activated) at one end, and reparative (termed M2 or alternatively activated) macrophages at the other. This concept has recently been reviewed and reappraised[132]. This paradigm began with classical findings that resistance to infection was associated with macrophage activation[192]. Seminal reports[193,194] showed that interferon-γ (IFNγ) and IL-4 elicited different reactions from macrophages *in vitro*. At the same time, two different subsets of T helper ($T_H$) cell, producing IFNγ and IL-4, respectively, were shown to orchestrate responses to differing categories of infectious pathogens[195].

It was thus attractive to propose that M1 macrophages versus M2 macrophages responded to the products of different T cell subsets (IFNγ produced by $T_H1$ cells versus IL-4 produced by $T_H2$ cells, respectively), and that $T_H1$ cells and M1 macrophages operated through coordinated teamwork, as did $T_H2$ cells and M2 macrophages[196]. By analogy, microglia were suggested to adopt M1 or M2 states[131] and this idea rapidly gained ascendency. Through application of genome-wide transcriptional profiling and epigenetics, the molecular mechanisms that govern T cell polarization have been identified[197–199]. However, these same approaches were not able to delineate the molecular pathways underlying the expected two types of macrophage responses to stimuli[200,201]. Indeed, the more stimuli were studied, the more 'polarized states' for macrophages were described[202]. The different expression profiles associated with each polarization state stubbornly resisted being aligned along a spectrum whose extremes were defined by the M1 and M2 transcriptomes[203]. Ultimately, this leads to the realization that stable subset commitment is an authentic attribute of $T_H$ cells and is useful for understanding their biology. By contrast, mononuclear phagocytes seem to have a near-infinite plasticity that lends itself ideally to dealing with an endless variety of environmental challenges[132]. Importantly, if macrophages cannot be categorized according to the M1 versus M2 paradigm, then it is also time to abandon this constricting strait-jacket in research into the functions of microglia. A recent perspective article authored jointly by 25 senior investigators[133] reviewed the history of the concept of macrophage activation, proposed a new nomenclature and indicated that a simple bipolar scheme is not sufficient. CSF1, macrophage colony-stimulating factor 1.



of mediators, some of which may be attractive targets for modulating neuroinflammation in AD and thus, potentially, for ameliorating the disease course.

Although astrocytes may also seem to be suitable and attractive targets in this regard, the current limitations in our understanding of astrocyte biology and methodological options to modulate these cells restrict the potential for astrocyte manipulation in the near future. By contrast, cells of the adaptive immune system, such as B and T cells, appear not to be significant components of the neuroinflammatory reaction in AD according to our current knowledge[12,40–43], and thus are not major therapeutic targets. Reports of an involvement of other immune cells such as mast cells are so far mostly descriptive (reviewed in REF. 134) and await experimental confirmation. Nevertheless, a tyrosine kinase inhibitor that inhibits mast cell differentiation and degranulation showed some benefit as an adjunct therapy to the current standard of care in a small Phase II trial in people with AD[135].

***When should modulation occur?*** As the phenotypes and functional properties of microglia obviously change during the course of AD, interventional approaches aimed at modulating neuroinflammation crucially depend on when and where to interfere. This may explain why despite the epidemiological link between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and reduced risk of developing AD[136,137], prospective clinical trials have failed to demonstrate a positive effect of traditional non-selective NSAIDs or of selective cyclooxygenase 2 (COX2) inhibitors in the treatment or prevention of AD[130,138–141]. However, in one large prevention trial, participants showed cognitive improvement for a prolonged period of time after termination of NSAID treatment[142]; thus, the effectiveness of NSAID as well as of COX2 inhibitor treatment in presymptomatic individuals is currently inconclusive[130]. This demonstrates the importance of stringent assessment of both the time point (before or after the onset of symptoms or biomarker changes) of initiation and the duration of anti-inflammatory treatment in AD. Moreover, more-specific immune actions may need to be targeted that are not affected by NSAIDs or COX2 inhibitors.

The lack of success in ameliorating AD by the use of broad anti-inflammatory drugs should thus not diminish the enthusiasm and efforts for research in this direction, as recent insights into pathogenically relevant immune actions will enable a more precise targeting of well-defined immune pathways and molecules, even when considering the existing limitations of AD clinical trials that suffer from the lack of well-defined outcome measures and precise diagnostic assays, and long durations.

***Which immune molecules should be targeted?*** Based on preclinical data or findings in AD patients, various immune molecules or signalling pathways have been found to be promising therapeutic targets both from a scientific and a venture capital viewpoint[143]. Below we discuss the most promising or better validated targets (aside from those mentioned in previous sections). TABLE 1 provides a more-complete summary of potential immune targets for AD.

IL-12 and IL-23 are both therapeutically attractive immune targets for AD, as they have been shown to be increased in the CSF of AD and/or MCI patients[66,144]. Moreover, levels of the common subunit of IL-12 and IL-23, namely p40, were higher in the plasma of MCI and AD patients in an unbiased approach performed by the Alzheimer's Disease Neuroimaging Initiative consortium[145], *IL-12* gene expression was augmented in post-mortem brain tissue of individuals with AD compared with control individuals[8], and polymorphisms of the gene encoding the IL-23 receptor were associated with AD in a northern Han Chinese population[146]. In addition, IL-12 and IL-23 were found to be released by a subpopulation of activated CD11c-positive microglia in a preclinical model of AD[66]. Ablation of IL-12, IL-23, p40 or the IL-12 receptor β1 (through which both IL-12 and IL-23 signal) in an Aβ-overexpressing transgenic mouse model of AD resulted in a substantial reduction in cerebral Aβ burden. Administration of neutralizing p40 antibodies before or after the onset of amyloid accumulation in this mouse model likewise markedly reduced the AD-like pathology, including cognitive and behavioural changes[66]. Neutralizing p40 — through antibody administration or through the use of small interfering RNA — in another mouse model of AD had similar effects[147]. Together, these findings point to IL-12 and IL-23 signalling as a tangible target for interventional approaches in AD[130,143,148].

Biologicals that inhibit IL-12 and/or IL-23 have undergone clinical validation in trials for other diseases and, in some cases, have already been approved by the US Food and Drug Administration (FDA) (for example, neutralizing p40 antibodies for the treatment of psoriasis); this means that a drug with a known risk profile specifically targeting IL-12 and IL-23 is, in principle, available for a first clinical trial in patients with AD. Although the non-CNS (that is, peripheral) actions of IL-12 and IL-23 are typically mediated via T and natural killer (NK) cells, in the AD CNS setting, IL-12 and IL-23 seem to act through a novel mechanism that is independent from T and NK cells[66]. In this latter scenario, it seems that IL-12 and IL-23 act directly on astrocytes, which express the respective receptors[66] (FIG. 4). Thus, existing biologicals that inhibit IL-12 and/or IL-23 would be assumed to be equally effective in AD as in IL-12 and IL-23 T cell-mediated peripheral diseases such as psoriasis, in which blockade of the IL-12–IL-23 signalling pathway, irrespective of the cellular source of origin, is regarded as the crucial therapeutic event.

Another attractive approach to modulate immune responses in AD centres on the NLRP3 inflammasome (NACHT, LRR and PYD domains-containing protein 3 inflammasome). *In vitro*, this inflammasome can receive an activation signal when Aβ fibrils damage lysosomal membranes of microglia, leading to cytosol acidification[149]. NLRP3 is involved in regulating the catalytic activity of caspase 1, the enzyme that mediates the cleavage of the precursors of IL-1β and IL-18 into bioactive cytokines. Elevated levels of active caspase 1 have been detected in brain tissue from patients with AD and AD mice, whereas mutations in the genes encoding NLRP3 or caspase 1 reduced AD-like

Adaptive immune system
The immune system that forms the basis for acquired immunity and immunological memory and involves T and B lymphocytes.

Mast cells
These are resident granulocytes of several types of tissues containing many granules rich in histamine and heparin.

Biologicals
Medicinal products that are manufactured in or extracted from biological sources (they may also be termed biopharmaceutical or biologic medical products); they are distinct from chemically synthesized pharmaceutical products.

NLRP3 inflammasome
Inflammasomes comprise a sensor molecule from the NOD-like receptor (NLR) family or the pyrin and HIN domain-containing protein (PYHIN) family, the adaptor protein ASC and caspase 1. The NALP3 inflammasome is expressed in myeloid cells, senses a wide range of aggregated molecules, and promotes the maturation of the inflammatory cytokines interleukin-1 (IL-1) and IL-18.

Table 1 | **Attractive immune targets for manipulating AD pathology at various levels of validation**

| Immune target or signalling pathway | Function | Therapeutic manipulation | Refs |
|---|---|---|---|
| TREM2 or TYROBP | Promotes Aβ uptake and/or sustains microglia or myeloid cell response to Aβ through sensing lipids that are associated with Aβ | Unclear whether targets should be upregulated or inhibited (to date, the collected *in vivo* data have been inconsistent) | 20–22,89–92 |
| CD33 | Inhibits Aβ phagocytosis | Inhibition or downregulation | 23,46 |
| CR1 | Modulates the effect of APOE *ε4* on brain fibrillar amyloid burden | Upregulation or activation | 47,48 |
| PPARγ or RXR | Induces Aβ clearance | Upregulation or activation | 152,153 |
| NLRP3 (or inflammasome-associated molecules IL-1β and caspase 1) | Regulates caspase 1 and IL-1β activation, and Aβ clearance | Inhibition or downregulation | 150 |
| CD36 | Upstream regulator of NLRP3 activation, and binds Aβ | Presumably inhibition or downregulation (absence of *in vivo* data) | 60,63 |
| CD14 | Co-receptor (along with TLR4 and protein MD2) for DAMPs, including Aβ | Inhibition or downregulation | 62,207 |
| IL-12 and/or IL-23 | Part of the Aβ-driven inflammatory response | Inhibition or downregulation | 8,66,145–147 |
| IL-6 | Part of the Aβ-driven inflammatory response | Presumably upregulation or activation | 210,211 |
| TNF–TNFR | Part of the Aβ-driven inflammatory response | Presumably inhibition (inconsistent data) | 212–215 |
| CX3CR1 | Enables homeostatic neuronal–microglia crosstalk | Upregulation or activation | 121,158,159 |
| P2X7R | Microglial-expressed member of purinergic ionotropic receptors | Inhibition or downregulation | 216,217 |
| SCARA1 | Myeloid cell-expressed scavenger receptor for soluble Aβ | Upregulation or activation | 160 |
| TGFβ1 | Member of the transforming growth factor-β family of cytokines | Unclear (overproduction reduces Aβ burden; inhibition in myeloid cells reduces Aβ burden) | 167–170 |

Aβ, amyloid-β; AD, Alzheimer disease; APOE, apolipoprotein E; CR1, complement receptor 1; CX3CR1, CX3C chemokine receptor 1; DAMPs, damage-associated molecular patterns; IL, interleukin; MD2, NLRP3, NACHT, LRR and PYD domains-containing protein 3; PPARγ, peroxisome proliferator-activated receptor-γ; RXR, retinoic acid receptor RXR; SCARA1, macrophage scavenger receptor types I and II; TGFβ1, transforming growth factor β1; TLR4, Toll-like receptor 4; TNF, tumour necrosis factor; TNFR, TNF receptor; TREM2, triggering receptor expressed on myeloid cells 2; TYROBP, TYRO protein tyrosine kinase-binding protein.

pathology in a mouse model of AD, and this was accompanied by a change in microglial phenotype[150]. There are currently no FDA-approved drugs that exclusively and specifically target NLRP3, but the recent identification of a small molecule inhibitor of NLRP3 (REF. 151) and of CD36 as a key upstream regulator of NLRP3 activation[60] may circumvent this problem. However, *in vivo* data on the role of CD36 in animal models of AD are still lacking. CD36 mediates microglia and macrophage responses to Aβ *in vitro* and *in vivo*, thus playing a key part in the inflammatory events associated with AD[63], without compromising the NLRP3 inflammasome activity that is required for host defence against pathogens. Importantly, however, peroxisome proliferator-activated receptor-γ (PPARγ) agonists, such as pioglitazone, induce Aβ clearance in a mouse model of AD by stimulating microglial uptake of Aβ in a CD36-mediated manner[152]. This observation suggests that downregulating CD36 may reduce inflammation but may also diminish the clearance of Aβ — another reason why *in vivo* experiments on CD36 function in animal models of AD are required.

In this context, the retinoid bexarotene, which selectively activates retinoid X receptors (RXRs), also needs to be mentioned. Bexarotene increased the microglia-mediated uptake of soluble Aβ in an APOE-dependent manner in an AD mouse model, resulting in reduced pathology[153]. Several studies confirmed the effects of bexarotene on clearance of soluble Aβ, but some of the initially reported effects of bexarotene on AD-like pathology could not be fully reproduced at a quantitative level[154–157].

A deficiency in CC chemokine receptor type 2 (CCR2), which is expressed by monocytes, amplified and accelerated mortality in a transgenic mouse model of AD[96] by impairing the population maintenance of perivascular macrophages[100], leading to Aβ deposition in cerebral vasculature. Whether overexpression of CCR2 has a positive effect on AD pathology, and thus qualifies

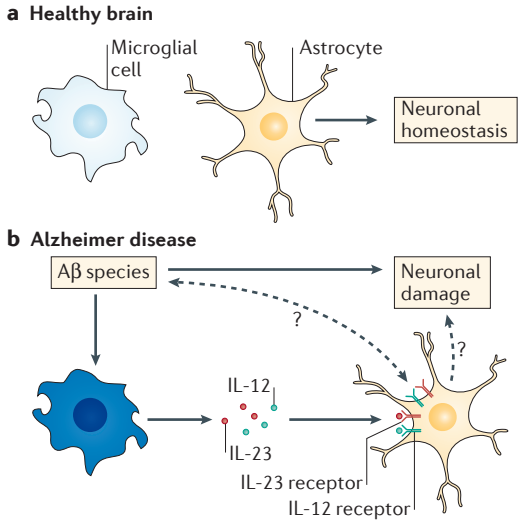



Figure 4 | **Proposed Aβ-dependent CNS specific non-adaptive IL-12 and IL-23 actions in AD.** **a** | In healthy brains, microglia do not express detectable levels of interleukin-12 (IL-12) or IL-23, and astrocytes are largely unresponsive to these cytokines. **b** | In Alzheimer disease (AD), exposure to Aβ leads to expression of both of these cytokines in microglia and reactive astrogliosis is accompanied by the expression of the respective receptors by astrocytes[66]. It is not clear whether the astroglial expression of IL-12 and IL-23 receptors is mediated by other cytokines or whether Aβ per se can also induce IL-12 and IL-23 receptor expression on astrocytes (denoted by the dashed arrows). This rise in IL-12 and IL-23, and their receptors, leads to exacerbation of AD pathology, including increased deposition of Aβ and ultimately to cognitive impairment, presumably through neuronal damage, whereas inhibition of the IL-12–IL-23 signalling pathway ameliorates pathology. However, what remains to be resolved is whether the IL-12- and IL-23-mediated effects in the CNS are conferred by astrocytes and/or by microglia, and whether IL-12 or rather IL-23 acts as the major player in this context.

CCR2 to be of potential therapeutic benefit, remains to be established. Similarly, modulation of the expression of microglial CX3C chemokine receptor 1 (CX3CR1; also known as the fractalkine receptor) had positive effects in mouse models of amyloid deposition while dramatically worsening tau pathology[121,158,159]. Likewise, macrophage scavenger receptor types I and II (SCARA1) has recently been shown to be involved in clearing soluble amyloid-β by myeloid cells *in vivo* and *in vitro*[160], thus offering yet another druggable immune target.

Also of interest are studies linking complement, microglia and AD pathology[161–163]. Microglia have a role in complement-mediated synaptic pruning[164,165] during postnatal development, and a reactivation of this mechanism could drive the progression of neurodegenerative diseases associated with synapse loss[166]. In this context, CR1 needs to be mentioned, which has been shown to modulate the impact of the APOE *ε4* allele on brain fibrillar amyloid burden and is associated with a higher risk of developing AD[47], thus qualifying for being a potential immune target in AD[143].

Finally, transforming growth factor β1 (TGFβ1) is an important regulatory cytokine that inhibits microglia activation and whose levels in plasma, CSF and brain are elevated in AD[145,167–170]. Transgenic overexpression of TGFβ1 decreased Aβ burden in an AD mouse model by promoting microglial Aβ clearance[168]. However, blocking TGFβ1 and downstream SMAD2–SMAD3 signalling specifically in CD11c-positive myeloid cells also reduced Aβ-like pathology in a genetic mouse model of AD[169], but this effect seemed to be due to an increased influx of activated peripheral myeloid cells rather than a modulation of resident microglia activation. This finding emphasizes the need to distinguish the role of CNS-resident microglia from that of blood-derived mononuclear cells that may enter the CNS over the disease course or that are being introduced experimentally to the brains of AD mouse models. Despite some progress in dissecting the various roles of resident versus peripherally derived myeloid cells in AD[44,100,171], it is still unknown whether — and if so, by what means — peripheral myeloid cells may be superior in fighting AD pathology at least when experimentally forced to enter the AD brain. Similarly, in the context of Aβ vaccination, the role of resident microglia, despite some insights, has not been fully elucidated *in vivo*[172–179] — a topic that is discussed in more detail elsewhere[180].

The concept of instructing innate immune cells to facilitate the resolution of inflammatory responses through anti-inflammatory mediators is supported by various recent *in vivo* data: aspirin-triggered lipoxin A4 (LXA4) was shown to reduce nuclear factor-κB (NF-κB) activation, pro-inflammatory cytokines and chemokines in mice exhibiting AD-like pathology, while it increased the levels of IL-10 — yet another prominent anti-inflammatory player — and TGFβ1 (REF. 181). Similarly, IL-10, expressed via adeno-associated virus (AAV) delivery, reduced microgliosis and astrogliosis, and improved cognitive performance in AD-like mice carrying mutated forms of human *APP* and *PS1* (REF. 182). Results using a different AAV delivery system for IL-10 produced an opposite result[183], leaving the part of this complex cytokine in AD pathogenesis uncertain. Treatment of Tg2576 AD-like mice expressing mutated human *APP* with the anti-inflammatory small molecule HPB242 resulted also in amelioration of AD pathology[184], supporting the idea that lowering inflammation confers beneficial effect in AD. However, anti-inflammation is not always favourable: hippocampal expression of the anti-inflammatory IL-4 or, as mentioned above, IL-10 (REF. 183) in AD mice worsened amyloid pathology[185], indicating that a deeper understanding of how and when to manipulate the immune response will be crucial for obtaining favourable outcomes.

## Conclusion and outlook

Recent data clearly show that immune activation in AD has the capacity to facilitate and trigger the pathophysiology of AD. The immune system may thus provide exciting novel and realistic routes for the diagnosis and treatment of AD. However, interfering with neuroinflammatory pathways and molecules requires precise

knowledge about the underlying immune events — which may change during the disease course. Taking into account the heterogeneity of AD, implying that not necessarily all individuals with AD exhibit neuroinflammation, or at all time points in the course of the disease, patients need to be stratified to identify those who may benefit most from anti-inflammatory interventions.

Ultimately, combination therapy consisting of both a drug targeting Aβ and/or tau, and a medication modulating inflammation may be a way to substantially delay progression of the disease. In this respect, repurposing strategies may be useful, for several, obvious reasons. Examples of potentially repurposed drugs are neutralizing antibodies against p40, which are FDA-approved for the treatment of psoriasis[66], and the NSAID derivative CHF5074, which was initially developed as a γ-secretase modulator and has now been reclassified as a novel, first-in-class microglial modulator for the treatment of AD, based on the finding that it reduces both amyloid burden and microglial activation[186,187]. Interim results from an ongoing Phase II trial in MCI patients suggest that CHF5074 confers positive effects by reducing biomarkers of neuroinflammation[130,188,189].

A detailed knowledge of neuroimmune pathways and their molecular underpinnings in AD may also lead to a better understanding and treatment of degenerative and/or proteinopathic CNS diseases other than AD. In addition, it will be equally interesting to learn how systemic immune components from young, healthy individuals that have been shown to positively modulate cognitive performance[190] may also have beneficial effects (for example, upon blood transfer[191]) in pathophysiological conditions, including neurodegenerative disorders such as AD. This would broaden the spectrum of opportunities to modulate CNS diseases by immune factors.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**Competing interests statement**

The authors declare competing interests: see Web version for details.