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Neuroinflammation in Alzheimer's Disease

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Abstract

Increasing evidence suggests that Alzheimer's disease pathogenesis is not restricted to the neuronal compartment but strongly interacts with immunological mechanisms in the brain. Misfolded and aggregated proteins bind to pattern recognition receptors on micro- and astroglia and trigger an innate immune response, characterized by the release of inflammatory mediators, which contribute to disease progression and severity. Genome wide analysis suggests that several genes, which

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increase the risk for sporadic Alzheimer's disease en-code for factors that regulate glial clearance of misfolded proteins and the inflammatory reaction. External factors, including systemic inflammation and obesity are likely to interfere with the immunological processes of the brain and further promote disease progression. This re-view provides an overview on the current knowledge and focuses on the most recent and exciting findings. Modulation of risk factors and intervention with the described immune mechanisms are likely to lead to future preventive or therapeutic strategies for Alzheimer's disease.

Introduction

At first glance, realms of immunology and neurobiology could not be further apart. From a cellular perspective, the brain represents stasis whereas the immune system represents motion. These two perspectives come together as the importance of neurodegenerative disease is increasingly appreciated. Indeed, understanding and controlling their interactions may hold the keys to the prevention or delay of a majority of late onset CNS diseases. In Alzheimer's disease (AD) neuroinflammation, instead of being a mere bystander activated by emerging senile plaques and neurofibrillar tangles, contributes as much or more to the pathogenesis as do the plaques and tangles themselves [1]. This is underlined by recent findings that genes for immune receptors, including TREM2 [2] and CD33 [3,4], are associated with AD. Analysis of clinical manifestations that precede AD, such as mild cognitive impairment (MCI), further argue for an early and substantial involvement of inflammation in the pathogenesis of the disease. Therefore, we give a current view on the neuroinflammatory landscape during AD including the cell types and mediators involved, the ways used to visualize neuroinflammation, as well as its clinical presentation and potential treatments.

Cellular Players

Microglia

Microglia, the resident phagocytes of the CNS, are ubiquitously distributed in the brain. They constantly survey their assigned brain regions using their highly motile processes for the presence of pathogens and cellular debris, and simultaneously providing factors that support tissue maintenance (Figure 1) [5]. At the same time, microglia contribute to the protection and remodeling of synapses for proper maintenance and plasticity of neuronal circuits [6]. To some extent, this action is mediated by the release of trophic factors including brain derived neurotrophic factor, which contributes to memory formation [7]. Once activated by pathological triggers, like neuronal death or protein aggregates, microglia extend their processes to the site of injury, later start migrating to the lesion, and initiate an innate immune response (Figure 2 A,B). The perception of pathological triggers is mediated by receptors originally designed to recognize danger or pathogen associated molecular patterns (DAMPs/PAMPs). In AD, microglia are able to bind to soluble amyloid β (Aβ) oligomers and Aβ fibrils via receptors including class A scavenger receptor A1, CD36, CD14, α6β1 integrin, CD47 and toll like receptors (TLR2, TLR4, TLR6 and TLR9) [8–11], which is thought to be part of the inflammatory reaction in AD. The Aβ peptide derives from a larger precursor, the amyloid precursor protein, by subsequent cleavages of two membrane-bound proteases (for review see [12]). The initial cleavage is mediated by a protease termed BACE1

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(β-site APP cleaving enzyme 1) followed by an unconventional cleavage by the γ-secretase complex within the transmembrane region of APP resulting in differentially truncated C-termini, ranging from amino acid 37 to 42 [13] (Figure 3). In particular, the 42 amino acid long form of Aβ has a strong tendency to form the aforementioned soluble oligomers and fibrill. The binding of Aβ with CD36, TLR4 and TLR6 results in activation of microglia which start to produce proinflammatory cytokines and chemokines (Figure 4) [10,14]. In turn, genetic deletion of CD36, TLR4, or TLR6 in vitro reduces Aβ-induced cytokine production [10,14,15] and prevents intracellular amyloid accumulation and inflammasome activation [15].

Microglial Aβ clearance mechanisms—As a response to receptor ligation, microglia start to engulf Aβ fibrills by phagocytosis. As a consequence, these fibrils enter the endosomal/lysosomal pathway. In contrast to fibrillar Aβ, which is largely resistant to enzymatic degradation, soluble Aβ can be degraded by a variety of extracellular proteases [16]. In the microglial context, two proteases, neprilysin and insulin degrading enzyme (IDE) are of major importance.

In sporadic cases of AD, inefficient clearance of Aβ has been identified as a major pathogenic pathway [17]. It has been suggested, that increased cytokine levels are responsible for the insufficient microglial phagocytic capacity by downregulating Aβ phagocytosis receptors [18]. Further support for the hypothesis that compromised microglial function comes from two recent studies identifying rare mutations, which convey a higher risk of AD: a rare mutation in the extracellular domain of TREM2 increases AD risk to a similar extent as apoEε4 [2]. TREM 2 is highly expressed by microglia [19,20] and mediates phagocytic clearance of neuronal debris [21]. Although TREM2 is an orphan receptor so far, TREM2 binding activity (putative TREM2 ligand expression) is detected on reactive astrocytes surrounding amyloid plaques and on damaged neurons and oligodendrocytes [21]. Likewise a SNP in the gene encoding the microglial surface receptor CD33 reduces Aβ phagocytosis by peripheral macrophages isolated from hetero- and homozygous mutation carriers. In addition, increased Aβ deposition as determined by Pittsburgh compound B (PiB)-PET was detected in the brain of these patients.

Microglial diversity—Microglial activation is a complex process that produces multiple phenotypes. Outside of the CNS, activated macrophages have been categorized as classical, proinflammatory (M1) phenotype associated with the expression of cytotoxic genes [22] and a non-inflammatory, alternative activation (M2) phenotype, based upon induction of specific proteins like arginase-1, FIZZ1, YM-1 and IGF-1 [23,24]. Classical M1 activation is characterized by elevated pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6, IL-12 and IL-18, and is accompanied by impaired phagocytic capacity [25]. The M2 state is characterized by secretion of the anti-inflammatory cytokines IL-4, IL-10, IL-13 and transforming growth factor-beta (TGF-β), and elevated phagocytic capacity without production of toxic NO [26–28]. A third phenotype may be a deactivated one associated with corticosteroids or TGF-β [29,30]. The M1/M2 activation states represent the polar extremes of myloid cell activation. There is a large diversity and graduation of phenotypic states in peripheral monocyte-derived macrophages, in particular under conditions of chronic inflammation [31]. It is therefore most likely that this applies to

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microglia as well. Microglia exhibit a diverse range of phenotypes reflective of their response to the local environment, including physical interaction with other cells and their physiological activity in the brain. Central to this matter is our limited ability, at present, to isolate or image subsets of unperturbed microglia in order to characterize their gene expression and mode of action as discriminated by physiological markers.

Microglia priming—In the aging CNS of mice, rats and primates, microglia show enhanced sensitivity to inflammatory stimuli (reviewed in Perry and Teeling, 2013), similar to that seen in microglia in brains with ongoing neurodegeneration. This phenomenon has been termed priming. Priming may be caused by microglial senescence and may represent a consequential element of the “time factor” for age-related neurodegenerative disease. On the transcriptomic level, endogenous ligands are downregulated during aging, whereas transcripts involved in host defense and neuroprotection are upregulated [20]. It remains uncertain to what extent age-related microglial priming results from cell-autonomous cellular aging, as opposed to prolonged exposure to the aged neural environment. In physiologically-aged and senescence-accelerated mice, profound microglial priming was characterized by increased production of cytokines and reactive oxygen species as well as enhanced phagocytic capacity. This model provided proof of principle that environmental influences, such as neuronal aging, can drive microglial priming. Weighted gene correlation network analysis revealed a characteristic pattern of gene expression for microglia priming, featuring increased pattern recognition and interferon signaling genes. A similar gene expression network was also found in mouse models for age-related neurodegeneration, including APP/PS1 transgenic mice [33]. As a further component, microglia may be primed by systemic inflammation in response to peripheral immune reaction.

Blood-derived mononuclear cells

The precise contribution of blood-derived mononuclear cells infiltrating the CNS in AD like innate immune responses of the brain remains unclear to date and the current knowledge is restricted to animal studies. Those have shown infiltration of peripheral mononuclear cells associated with amyloid plaques in mouse models [34]. Further, ablation of $CD11b^+$ cells in the APP/PS1 model of AD showed that peripheral mononuclear phagocytes play an important role in restricting Aβ plaques [34]. Restricting the entry of blood-derived mononuclear cells into the brain, by deletion of the chemokine receptor CCR2 in the Tg2576 mouse model, led to increased plaque load [35], although the particular mononuclear cell type was not specified. However, most of these studies used bone marrow irradiation and subsequent transplantation with fluorescent, and therefore traceable, cells. Irradiation of whole animals is likely to cause damage to the blood brain barrier. A further study shielding the brain, thereby restricting irradiation to the rest of the body, did not find any cerebral infiltration by peripheral macrophages, but concluded that perivascular macrophages, protected by the shielding of the brain, were able to modulate Aβ deposition depending on the presence of CCR2 [36]. The involvement of perivascular macrophages has also been shown for the removal of Aβ in a mouse model of cerebral amyloid angiopathy [37]. Nevertheless, recruitment of bone-marrow derived cells is almost absent in parabiosis mouse models, even 12 months after initiation [38]. In this context it is interesting that ablation of microglia in APP/PS1 mice by HSV thymidine kinase/ganciclovir system did not change the amyloid

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pathology, although 95 % of microglia were lost and blood-derived monocytes were spared by the use of bone marrow-chimeric mice [39]. This result argues against the participation of peripheral cells in the phagocytosis of amyloid plaques, albeit the observation time was only 2-4 weeks. Currently, these results speak against a significant contribution of blood-derived monocytes, but support the idea that at least perivascular macrophages have some impact on the removal of CNS Aβ depositions.

Modulating innate immunity

The emerging role of microglial activation for AD pathogenesis makes these cells a legitimate therapeutic target. However, a caveat is that in some circumstances microglial activation appears in both beneficial and detrimental guises. Part of the confusion is, that depending on the particular disease stage and particular model in which a brain region is affected, microglia may have different roles and effects. Upon exposure to a DAMP or PAMP, the acute microglial reaction aims at the removal of the recognized abnormality or pathology. In the case of AD, this type of inflammatory reaction is sterile, as it involves the very same receptors but no living pathogens. Under normal circumstances such a reaction quickly resolves pathology with an immediate benefit to the nearby environment. In AD however, several mechanisms including the ongoing formation of Aβ and positive feedback loops between inflammation and APP processing compromise cessation of inflammation. Instead, the further accumulation of Aβ, neuronal debris, and most likely further activating factors establish a chronic, non-resolving inflammation. The sustained exposure to Aβ itself, chemokines, cytokines, and other inflammatory mediators seems responsible for the persistent functional impairment of microglial cells observed at plaque sites [40,41]. As an intracellular regulator of microglial function, the autophagy protein beclin 1 was found to be reduced in the brains of AD patients [42]. Beclin 1 plays a role in retromer-mediated sorting of cellular components, including Trem2, APP, BACE 1 and CD36, in the endosomal-lsosomal pathway. Reduction of Beclin 1 in vitro and in vivo interferes with efficient phagocytosis resulting in decreased receptor recycling of CD36 and Trem2 [42], but more receptors may be affected.

Plasticity of the microglial phenotype is of fundamental importance, since it has become clear that the resolution of inflammation involves conversion to an “alternative”, i.e. similar to M2, activation state associated with tissue repair, phagocytosis and anti-inflammatory actions. Turning microglia from villains to samaritans may be achieved by the modulation of proinflammatory signaling pathways such as the NLRP3 inflammasome. Modifying these pathways, however, implies that they are exclusively restricted to microglia and do not possess critical functions in other cell types. Pharmacologically, the transition to an “alternative” activation state could be achieved through the heterodimeric type II nuclear receptors, PPARγ:RXR, PPARδ:RXR, and LXR:RXR. Agonists of these receptors are robustly anti-inflammatory and stimulate phagocytosis, through induction of CD36 leading to increased microglial Aβ uptake [43]. Another target is the RXR itself, which might have a positive effect on both LXR and PPARγ controlled genes. Recently, it was shown that agonism of RXR by bexarotene causes rapid reduction of soluble Aβ, plaque load, and behavioral deficits by apoE-dependent clearance of Aβ[44]. Nevertheless, this study could not be reproduced by others in its entirety [45–48]. Although aberrant and ineffective activation of

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microglia has been relatively well documented for pre- and moderate-Alzheimer stage disease, but late stage effects are less understood. There is even some evidence of focal microglial senescence particularly surrounding neurofibrillary tangles [40].

Astroglia

Pathological responses of astrocytes are represented by reactive astrogliosis, a complex, multi-stage and pathology-specific reaction with remodeling of astrocytes generally aimed at neuroprotection and recovery of injured neural tissue [49,50]. Next to activated microglia, hypertrophic reactive astrocytes accumulate around senile plaques and are commonly found in post-mortem human AD tissue [51] as well as in AD animal models [52] Glial cell activation may occur early in AD, even before Aβ deposition [53]. Reactive astrocytes are characterized by increased expression of glial fibrillary acidic protein (GFAP) and signs of functional impairment [54], however astrocytes do not seem to lose their domain organization and there are no indications for scar formation (Figure 2 C,D). In animal models of AD the early response is represented by astroglial atrophy that may have far reaching consequences for synaptic connectivity since astrocytes are central for maintaining synaptic transmission thereby contributing to cognitive deficits [52,54–57]. These signs of atrophy demonstrate clear spatio-temporal progression appearing first in the entorhinal cortex and affecting astrocytes located distantly from senile plaques in the later stages of AD. Similarly to microglia, astrocytes release cytokines, interleukins, nitric oxide, and other potentially cytotoxic molecules upon exposure to Aβ thereby exacerbating neuroinflammatory response. The importance of astroglial inflammation in AD has been recently investigated by AAV-driven suppression of the astrocytic reaction in APP/PS1 mice. Interfering with the calcineurin/nuclear factor of activated T-cells signaling pathway revealed improved cognition, reduced astrogliosis, and lower Aβ levels [58]. Astrocytes also have a potential role in internalizing and degrading Aβ *in vivo* [59]. Astrocyte-mediated clearance of Aβ requires apoE [60], and astrocyte-dependent lipidation of ApoE increases the capability of microglia to clear Aβ [61,62]. Furthermore, adult astrocytes up-regulate expression of extracellular Aβ-degrading proteases [63], such as neprilysin, “insulin degrading enzyme”, endothelin-converting enzyme-2, and angiotensin-converting enzyme-1 upon exposure to native Aβ deposits [64]. These proteases and the impaired function and atrophy of astrocytes may contribute to reduced proteolytic clearance of Aβ. In addition to the above mentioned clearing pathways, astrocytes are involved in the clearance of soluble Aβ from the parenchyma by paravenous drainage [65]. This pathway depends on the astrocytic water channel aquaporin-4, since deletion resulted in a strong decrease of clearance via this pathway.

Mediators and Modulators of Neuroinflammation

Cytokines

Microglia and astrocytes are arguably the major source of cytokines in AD. Cytokines contribute to nearly every aspect of neuroinflammation, including pro- and anti-inflammatory processes, bystander neuronal injury, chemoattraction and response of microglia to Aβ deposits. Microglial activation is both characterized and modulated by cytokines. Increase in Aβ in aging TgAPPsw and PSAPP transgenic mice is associated with increased pro-inflammatory cytokines including TNF-α, IL-6, IL-1α and granulocyte

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macrophage-colony stimulating factor (GM-CSF) [66]. This observation suggests that pathological accumulation of Aβ is a key factor that drives neuroinflammatory responses in AD. In addition, exposure of microglia to pre-aggregated $A\beta_{1-42}$ increases production of pro-inflammatory cytokines (*i.e.,* pro-IL-1 β, IL-6, TNF-α), macrophage inflammatory peptide (MIP-1α) and macrophage colony-stimulating factor (M-CSF) [67]. Furthermore, M-CSF levels in the plasma and CNS of AD patients are significantly elevated when compared to age-matched healthy controls or patients with mild cognitive impairment [68,69]. Caspase-1 activation, which is required to maturate IL-1β from its inactive pro-forms is similarly elevated in the brains of patients suffering from MCI and AD [70]. Consequently, high levels of the cardinal pro-inflammatory cytokine IL-1β are detected in microglial cells surrounding Aβ plaques in AD patient brains (Figure 2E) and cerebrospinal fluid (CSF). *In vitro*, IL-1β is released by activated microglia after stimulation with Aβ [71]. IL-1β can, at least under certain circumstances, favor Aβ deposition by modulating APP expression and proteolysis [72]. In addition to these cytokines, IL-12 and IL-23, well known from leukocytes, have been found to be produced by microglia in AD mouse models [73] and inhibition of IL-12/23 improves AD-like pathology [73,74], even so the regulation of IL-12 in human CSF is controversial [73,75].

There are multiple evidences suggesting that the pro-inflammatory enviroment present in the AD brain and in transgenic mouse models of cerebral amyloidosis assumes damaging proportions. For instance, risk for conversion from MCI to AD is higher in subjects with elevated CSF presence of the pro-inflammatory cytokine TNF-α and decreased antiinflammatory TGF-β levels [76]. IL-1β, TNF-α and other cytokines may impair neuronal function even before leading to structural changes, as evidenced by suppression of long-term potentiation of synaptic transmission (LTP). Multiple interactions as well as elevated expression of additional cytokines/chemokines and innate immune receptors favor an M1-like activation state in AD. For example, in neuron-microglia co-cultures, the synergistic action of Aβ with either interferon-γ (IFN-γ) or CD40 ligand triggers TNF-α secretion and production of neurotoxic reactive oxygen species [77–79]. In addition, the innate immune toll-like receptor 4 is responsible for elevated levels of TNF-α and MIP-1α in AD model mice [80].

Conversely, stimulation of some pro-inflammatory signaling pathways seems to be a beneficial approach in AD mouse models. Transgenic expression of IL-1β in APP/PS1 led to robust neuroinflammation and a reduction of amyloid plaque pathology [81,82]. These findings implicate IL-1β expression in activating a “good” form of neuroinflammation in APP/PS1 mice. In another study, AAV-mediated expression of IFN-γ in the brains of the TgCRND8 mouse model demonstrated the ability of this pro-inflammatory cytokine to enhance clearance of amyloid plaques, alongside with a widespread increase astrogliosis and microgliosis [83]. In addition, these mice exhibited decreased levels of soluble Aβ and Aβ plaque burden, without altered APP processing. Similar results were obtained using AAV-mediated expression of IL-6 and TNF-α [84,85]. Using the opposite approach, expression of the anti-inflammatory cytokine IL-4 resulted in the exacerbation of Aβ deposition [86]. These results suggest that certain “good” forms of pro-inflammatory microglial activation are potentially beneficial for reducing AD-like pathology in transgenic mouse models.

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Chemokines

Chemokines in AD have been suggested to regulate microglial migration to areas of neuroinflammation, thereby enhancing local inflammation [87]. In AD up-regulation of CCL2, CCR3 and CCR5 in reactive microglia has been reported [88,89], whereas CCL4 has been detected in reactive astrocytes near Aβ plaques [88]. In vitro, Aβ causes the generation of CXCL8 (IL-8), CCL2, CCL3 and CCL4 in human macrophages and astrocytes [90], and microglia cultured from autopsies of AD revealed an increased expression of CXCL8, CCL2, and CCL3 after experimental exposure to Aβ [91]. In AD mouse models a modulation of neuronal survival [92], plaque load [93], and cognition [94] by the CX3CR1/CX3CL1 system has been shown. Further, the receptors CCR5 [95] and CCR2 [35,96,97] can modulate the course of the disease by influencing microglial positioning and function.

Caspases

Caspases are a family of intracellular proteases, which are key mediators of apoptosis and inflammation. Of the inflammatory caspases, the catalytic activity of caspase-1 is tightly regulated by signal-dependent auto-activation within multiprotein complexes called “inflammasome”, that mediate caspase-1 autocatalytic activation and the subsequent cleavage of the precursors of IL-1β and IL-18 into bioactive cytokines [98,99]. Aβ fibrils can activate NRLP3 inflammasomes via lysosomal damage in mouse microglia [100]. Elevated levels of active caspase-1 are detected in the brains from AD patients and APP/PS1 mice. In addition, APP/PS1 mice deficient in NLRP3 or caspase-1 are largely protected from spatial memory impairment, loss of hippocampal synaptic plasticity, associated behavioral disturbances and other consequences associated with AD [70]. Deficiency of NLRP3 or caspase 1 in APP/PS1 mice appeared to skew microglial cells from a pro-inflammatory ‘M1-like’ phenotype to a more neuroprotective ‘M2-like’ phenotype [70]. Further, stimulation of microglia with various inflammogens, led to the orderly activation of the apoptotic caspase-8 and caspase-3/7. Activated caspase 3 modulates nuclear factor-κB activation via protein kinase Cδ and increases the production of neurotoxic pro-inflammatory mediators such as IL-1β, tumor necrosis factor-α and nitric oxide. Inhibition of these caspases hindered microglia activation and neurotoxicity [101]. Incidentally these caspases were activated in microglia in AD subjects [102]. Pharmacological interventions have been reported to successfully exert neuroprotective effects in AD mouse models [103,104].

Prostanoids and neuroprotectin D1

Prostanoids are derivatives of the arachidonic acid synthesized by the cyclooxygenase-1 and the inducible cyclooxygenase-2, both produced by microglia. In AD, the suppressive effect of cyclooxygenase-1 inhibition on glial activation, amyloid deposition and the expression of inflammatory marker, switching microglia to an alternative phenotype has recently been demonstrated in an AD mouse model [105]. In addition, the proinflammatory prostaglandin PGE_2, which binds to EP1-4 receptors, has been found to be elevated in patients with probable AD [106]. EP1-3 receptors are expressed by microglia cells [107], but are also found in other cells of the brain, in particular neurons. In vitro, microglial EP2 receptors inhibit Aβ phagocytosis and enhance neurotoxic activities of microglia [108]. This is complemented by

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the findings that deletion of the prostaglandin EP2 or EP3 receptor in AD mouse models decreased oxidative stress, neuroinflammation, Aβ-burden, and BACE expression [109–111].

Recently, the use of EP4 receptor agonist on microglia revealed suppression of inflammation and increased update of synthetic Aβ, whereas the deletion of the EP4 receptor in the APP/PS1 mouse model of AD increased the plaque burden and the production of proinflammatory cytokines like Il1-β and CCL3 [112]. Interestingly, the expression of the EP4 receptor was found to be decreased in the cortex of both MCI and AD patients [112], suggesting that this may contribute the inflammatory reaction in AD. However, the role of PGE_2 in neurodegeneration is probably more complex due effects of PGE_2 on other cell types like neurons.

The neuroprotective docosahexaenoic acid derivative 10R, 17S-DHA (neuroprotectin D1) is a major components of cell membranes [113], which has been found to be decreased in early stages of AD [114]. Neuroprotectin D1 is an autocrine/paracrine mediator involved in the resolution response during early stages of neuroinflammation, that downregulates amyloidogenic processing of APP, switches off pro-inflammatory gene expression, and promotes neural cell survival. Moreover, anti-amyloidogenic processing by neuroprotectin D1 targets α- and β-secretases and PPARγ receptor activation. sAPPα, a peptide with neurotrophin-like activity, is an agonist for NPD1 synthesis and part also of a cycle to sustain generation of the lipid mediator [115].

Complement system

The complement system is a major constituent of the innate immune system mostly involved in the defense against pathogens. Activation of the proteolytic complement cascade results in the opsonization and ultimately in the lysis of microorganisms. In the brain the major cells that contribute in the production of proteins of the complement system are microglia and to a minor extend astrocytes (reviewed in [116]). In AD, activated complement factors products have been found to be associated with Aβ deposits [117]. In addition, Aβ is able to activate the complement system in vitro via the so-called alternative pathway. The finding that variants of clusterin, or apolipoprotein J, as soluble inhibitor of the complement system and the complement receptor 1 (CR1), involved in processing and clearance of opsonized immune complexes and a regulator of C3 convertase activity, are associated with AD has further substantiated the importance of the complement system in AD [118,119].

Nitric oxide and reactive oxygen species

Next to their direct actions via surface receptors, cytokines stimulate inducible nitric oxide synthase (iNOS) in micro-and astroglia, producing high levels of NO that can be toxic to neurons. iNOS is upregulated in AD brains [120], and genetic knockout of iNOS is protective in mouse models of AD [121]. Likewise, NADPH oxidase (PHOX) is highly expressed by microglia, upregulated in AD, and rapidly activated by inflammatory stimuli such as Aβ, resulting in hydrogen peroxide that further promotes microglial activation [122,123]. Superoxide from PHOX reacts with iNOS-derived NO forming peroxynitrite [124]. Increased expression of iNOS in AD has also been shown to introduce NO-caused posttranslational modifications [125], which include nitration, S-nitrosylation and dityrosine formation [125].

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Nitration of the Aβ peptide at tyrosine 10 has been recently shown to increase the propensity of Aβ to aggregate and has been identified in the core of the amyloid plaques [126]. More compelling, this modified peptide was able to initiate plaque formation in APP/PS1 mice, suggesting a central role during the early phase of AD. Nitrated Aβ suppressed hippocampal LTP more effectively when compared to non-nitrated Aβ, indicating that this post-translational modification exerts functional as well as structural damage to the AD brain. There is evidence that oxidative stress supports the formation of this Aβ species [127]. Other NO-mediated modifications that may relevant for AD have already been reported [128] and it is to be expected that there are more to follow.

Inflammatory changes of the neurovascular unit in AD

Numerous epidemiological, clinical and neuropathological studies have shown that vascular pathology represents the an important risk factor for the development of AD. Moreover, it has been shown that AD is associated with distinct inflammatory, functional and morphological alterations of cerebral blood vessels and perivascular glia and neurons. These early-onset and progressive changes, which are induced by combined effects of soluble Aβ oligomers and vascular Aβ deposits [129,130], ultimately lead to decreased cerebral blood flow and an impairment of functional hyperemia, i.e. the ability of local blood flow to increase in response to neuronal activation [131]. Chronic cerebral hypoxia is further amplified by blood-bourne factors such as platelets, which are chronically activated in AD models and patients [132], ultimately resulting in micro-infarcts and neuronal injury. Moreover, the combination of mild hypoxia, inflammation of the neurovascular unit, and progressive Aβ accumulation in brain parenchyma, induces upregulation of the receptor for advanced glycation end products (RAGE), which mediates Aβ transport into the brain across the blood-brain barrier [133]. Hypoxia also directly induces amyloidogenic APP processing through multiple pathways involving β-secretase, γ-secretase, neprilysin, and others [134]. Taken together, chronic hypoxia in AD directly induces neuronal injury, but also amplifies neurodegeneration by inducing amyloidogenic pathways and decreasing brain clearance of Aβ.

Factors facilitating neuroinflammation

Aβ deposition alone may be sufficient to induce an inflammatory reaction which subsequently contributes to cognitive decline and development of AD. Given the possibility that Aβ deposition precedes “cognitive deficits” OR “clinical manifestation” by decades, one may speculate that exogenous or endogenous factors can modify the innate immune response mounted by Aβ exposed microglia. Thus environmentally modifiable AD risk factors including systemic inflammation, obesity and traumatic brain injury may impact risk through sustained neuroinflammatory drive.

Systemic inflammation

The development of sickness behavior [135] following a peripheral inflammatory challenge, such as an infection or an aseptic injury [136], demonstrates the communication of systemic inflammation to the brain. Sickness behavior in response to an acute event is usually self limited due to the presence of multiple regulatory mechanisms that dampen down the central inflammatory response to the peripheral challenge [137]. However, it may be prolonged in

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response to chronic, low grade inflammation [138], possibly due to the lack of a anti-inflammatory response [139]. Neuroinflammation in AD represents such a chronic reaction, since microglia may already be "primed", and are therefore highly responsive to further insults causing a rapid switch to a damaging M1 phenotype [23,140]. This microglial priming is likely to result from various activators including the chronic exposure to Aβ, neuronal debris and chronic vascular changes including cerebrovascular dysregulation and cerebral microinfarcts. This hypothesis is supported by animal studies showing an exaggerated inflammatory and oxidative stress response to peripheral stimuli in aged mice [141], increases in CNS IL-1β and neuronal apoptosis in the ME7 prion mouse following a peripheral LPS or poly-IC challenge [142–144]. Another example are the consequences of osteoarthritis in the APP/PS1 / Col1-IL1βXAT mouse model resulting in accelerated neuroinflammation and Aβ pathology [145]. In addition, clinical studies of AD showing increased cognitive decline and exacerbation of sickness behavior following acute and chronic systemic inflammation [146,147].

Obesity

Obesity is defined as a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health. Obesity increases the propensity to acquire more bacterial or viral infections and thus directly increases the likelihood for systemic inflammation [148,149]. Moreover, the white fat tissue itself contains a high percentage of activated macrophages, which constantly secrete pro-inflammatory cytokines [150]. Interestingly, midlife obesity has been identified as a risk factor for AD [151], which is partly caused by other AD risk factors, such as high cholesterol diet, reduced physical activity and a sedentary life style [152] . As a possible consequence of obesity, diabetes type II has been demonstrated to accelerate memory dysfunction and neuroinflammation in an AD mouse model [153]. Obesity associated reduced gut microbial diversity was associated with increased levels of proinflammatory markers in the peripheral blood and thus could be viewed as factor contributing to AD risk [154]. Together it seems possible that obesity increases the risk for AD by the systemic, chronic presence of proinflammatory cytokines.

Traumatic brain injury

Several studies have established traumatic brain injury (TBI) as a risk factor for the development of AD [155]. Experimentally TBI aggravates learning and memory deficits and the deposition of Aβ in murine AD models [156,157]. Experimental and human studies have shown that microglial activation can persist for months and years after TBI [158,159]. This inflammatory reaction may initially be important for the phagocytic clearance of debris. However, a sustained cerebral inflammation may either directly or indirectly promote pathological development in AD. Certain cytokines implicated in TBI can potentially increase BACE-1 levels [160], thereby shifting the APP processing to the amyloidogenic generation of Aβ [161]. The chronic release of cytokines may also decrease the capability of microglia to phagocyte and degrade Aβ or directly affect neuronal functions.

Locus coeruleus degeneration

Norepinephrine (NE), in addition to its role as a neurotransmitter, possesses potent anti-inflammatory, anti-oxidative, neurotrophic, and neuroprotective actions [162]. The primary

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source of NE in the brain is the locus coeruleus (LC), located at the dorsal part of the brain stem. The LC neurons project throughout the brain, albeit the majority of terminals target the hippocampus and neocortex. NE released from LC projections acts on adrenergic receptors expressed on neurons, microglia and astrocytes [162]. The number of cells in the LC as well as NE levels in the brain decrease during normal aging [163] although a much more pronounced cell loss occurs in AD [164]. Experimental lesions of the LC in AD mouse models led to increased inflammation and neuronal damage, as well as increases in Aβ plaque burden [165,166]. Thus, an early degeneration of the LC and the subsequent loss of NE-mediated innervation may substantially facilitate the inflammatory response to any stimulus including Aβ. Experimental loss of NE compromised microglial migration and Aβ phagocytosis *in vivo*, suggesting that the failure in the NE tone not only increases inflammation but also Aβ deposition. Increasing endogenous NE levels by use of selective NE re-uptake inhibitors [167] or α-2-adrenoceptor antagonists [165] or the NE precursor L-threo-DOPS reduces neuroinflammation and partly rescues microglial functions.

Analysis of immune activation

In vivo-laser scanning microscopy

Over the past decades, analyzing innate immunity of the brain was restricted to cell culture experiments and immunohistochemical detection of microglia. Little was known about the functional state of these cells *in vivo*. Recent methodological advances such as the generation of transgenic mice with eGFP-labeled microglia, cranial window implantation, and Aβ plaque-labeling with the fluorescent dye methoxy-XO4 have enabled longitudinal and live monitoring of the functional state of microglia in murine models of disease. This technique now permits the analysis of microglial phenotypes over time and in relation to the deposition of Aβ. These data revealed that both in control and plaque-bearing mice microglia migrate within the brain parenchyma with an average speed of 5-9 mm/month [168]. Upon the formation of Aβ plaques the microglia rearranged their processes becoming polarized and moved their somata towards the plaque temporarily leaving the formerly surveyed area [168]. Individual microglia migrated towards new or preexisting plaques within one-two days [168,169], similar to observations made upon acute laser-induced brain injury [170]. In addition to Aβ deposits, microglia are also attracted to neurons that underwent Alzheimer's disease-associated elimination [92]. Of note, microglial cells were recruited to neurons up to 7 days before their elimination and neuronal loss could be completely rescued by knockout of the receptor for chemokine fractalkine (CX3CR1) [92].

Imaging inflammation in animal models

There are various molecular imaging techniques used in experimental and clinical settings to study the temporal and spatial relationship of inflammatory changes associated with neurodegeneration. Since microglial respond very fast to lesions, these cells are good candidates for diagnostic markers of disease progression [171]. Therefore, several microglial cell surface and mitochondrial receptors were used for the development of in vivo imaging ligands. One of these targets is the translocator protein 18 kD (TSPO) [172], a protein of the outer mitochondrial membrane that has been found to be increasingly expressed under conditions of neuronflammation. Binding of the radiolabeled ligands ^{11}C-(R)-PK11195 and

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^{18}F-DPA-714 to TSPO can be visualized using PET and SPECT [173]. In AD mouse models progressive binding of PK11195 with age has been described [174,175]. This binding could only reliably detected in APP/PS1 mice at a late age, when microglial and astroglial activation are already massive by immunohistological means [176]. Binding of both ^{3}H-(R)-PK11195 and ^{3}H-DPA-713 could be decreased by the PPARγ-agonists pioglitazone and ciglitazone in the TASTPM mouse model of AD [175] have been shown to have anti-inflammatory and Aβ lowering effects in AD mouse models [177]. The development of new TSPO ligands and other probes with improved bio-availability, decreased non-specific uptake, and higher specific binding [178,179], may permit the detection of activated microglia at an even earlier disease stage.

Imaging inflammation in humans

Similarly to the studies on animals, increased microglial activation has been detected in AD patients using the TSPO ligand ^{11}C-PK11195. Binding potentials have been reported to be increased up to 50% in association cortex [180]. Uptake of another TSPO ligand ^{11}C-DAA1106 was reported to be elevated by up to 33% in AD [181]. The cortical distribution of ^{11}C-PK11195 binding parallels that of amyloid deposition, as detected by the thioflavin analogue ^{11}C-PIB [182]. Levels of cortical ^{11}C-PK11195 signals in AD also correlate with cognitive impairment rated with the mini-mental state examination (MMSE) [183,184], suggesting that cortical microglial activation is detrimental to cognitive function in AD. In addition, a correlation of neuroinflammation and the severity of AD has been reported for the TSPO marker ^{11}C-PBR28 [185]. In MCI patients, ^{11}C-PK11195 PET detected inflammation in 40% of amnestic cases [186], although another study using the same tracer failed to detect microglial activation. A group of seven MCI cases showed a significant 27% mean increase in ^{11}C-DAA1106 uptake across brain regions [181]. Five of these seven MCI subjects, with ^{11}C-DAA1106 uptake more than 0.5 standard deviations above the mean in controls, progressed to frank dementia over a two year follow up period.

Characterization and monitoring neuroinflammation in AD

While emerging evidence suggests that inflammation plays a causal role in AD pathogenesis, the detection of inflammatory markers has not yet been established as valuable tool for the diagnosis or monitoring of AD. Nevertheless, novel data from a recent study of postmortem late-onset AD brains by gene-expression analysis highlighted an immune and microglia network, which is dominated by genes implicated in phagocytosis [187]. These data along with the new analysis of inflammation related biomarkers in the CSF, peripheral blood or directly in the brain by imaging, will be the focus of future studies. An important aspect of this search will be the discovery of inflammatory biomarkers that identify prodromal AD stages.

Detection of neuroinflammatory markers in the CSF

Over the last 25 years numerous studies have investigated levels of pro- and anti-inflammatory cytokines in the CSF of MCI and AD patients. The results of these studies are often controversial [188]. Yet, there are indications that the time point of sampling – in other words, the stage of the disease – is a critical factor for investigation. Some studies highlight

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elevated CSF cytokines as risk factors for MCI to AD conversion or as correlates of the speed of cognitive decline and disease progression [76,189]. As with imaging consortia, to overcome inter-individual variances and to obtain a more definite description of cytokine regulation and function in AD, a high degree of method harmonization and patients characterization, together with longitudinal sampling over years seems essential to leave the stage of cross-sectional descriptions.

Systemic biomarkers

A growing number of studies point to a sophisticated interaction between the systemic environment and the brain. Thus, systemic immune cells and secreted signaling proteins communicate with the brain and have been associated, not only with neuroinflammation, but neurodegenerative processes in general [190]. While some of these interactions may involve cells entering the nervous tissue, it is likely that many more are mediated by soluble signaling molecules, like blood-borne factors, present in the systemic environment. These factors can inhibit or promote adult neurogenesis in an age-dependent fashion or restore regeneration of the aging brain in mice [191,192]. In order to identify such factors, scientists have tried to discover molecular or cellular changes in blood associated with neurodegenerative diseases (reviewed in [193]. Various proteomic methods have been used to identify blood-based biomarkers. Typical biomarkers have been cytokines and trophic factors such as brain-derived neurotrophic factor (BDNF) [194–197]. Using multiplex ELISA in plasma from AD patients protein signatures were described which may be specific to prodromal stages of the disease [198], or which characterize patients who progress from a prodromal stage to AD [199]. Other signatures appear to correlate with APOE [200] or with pathological changes such as Aβ and tau protein levels in CSF of AD patients [201]. Close to 200 “communicome” proteins were measured in plasma samples from patients participating in the AD neuroimaging initiative yielding protein signatures that correlated with patients who converted from mild cognitive impairment to AD 202.

Clinical trials and epidemiological findings

Anti-inflammatory drugs

Although NSAID epidemiology and clinical trial results have produced some healthy skepticism about apparent stage-dependent outcomes, the normal physiological cytokine regulation of glial activation and microglial phenotypes is highly context and stage-dependent [5]. Contextual factors modulating glial “activated” phenotypes include immune-modulatory apoE genotype and newer AD genes. Normal aging is also associated with chronic glial activation [203] and more focal stage-dependent injury-induced factors. Context-dependent responses should be expected for NSAIDs that act as cyclooxygenase (COX) inhibitors to reduce levels of prostaglandin products, notably PGE2, that act through EP receptors 1-4 to produce very different outcomes. For example, EP2 activation engages predominantly pro-inflammatory neurotoxic pathways and downregulates Aβ phagocytosis while EP4 ligands can produce anti-inflammatory and neuroprotective effects [204,205]. Most significantly these receptors play a significant role in promoting the resolution of chronic neuroinflammation [206]. Thus, it is understandable if conventional cyclooxygenase-inhibiting NSAIDs can block incipient inflammation-driven AD pathogenesis at early stages. They can

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also have adverse effects with advanced disease by potentially limiting resolution and interfering with phagocytic clearance of Aβ and extracellular tau aggregates.

Stage-dependent efficacy has also been hypothesized for anti-Aβ immunotherapy that stimulates microglial phagocytosis of Aβ and potential benefits may only be observed with early intervention. It is plausible to argue that aging, Aβ- or injury-induced inflammation may initiate tauopathy to drive neurodegeneration and downstream clinical decline. Thus, possible explanations for the lack of success with immunotherapy or anti-inflammatory therapy with more established dementia include a likely failure to halt the spread of fully established and seeded tauopathy and failure to rescue deficits driven by neuron loss. Whatever the explanations for past NSAID trial failures are, based on compelling new genetic evidence for a causal role for innate immunity in AD risk, new trials with both longer and earlier interventions and alternative approaches to favorably modulate neuroinflammation are warranted.

Interventional anti-inflammatory trials

Randomized placebo controlled trials (RPCT's) with NSAID's in AD evidence of success. Early trials with indomethacin hinting at reduced cognitive decline [207] were not replicated [208] and large scale trials with other NSAID's appeared unsuccessful [209,210]. RPCT's with other anti-inflammatory agents including prednisone [211], hydroxychloroquine [212]; simvastatin [213]; atorvastatin [214,215]; aspirin [216] and rosiglitazone [217] also failed to show significant changes in primary cognitive outcomes in subjects with AD dementia or prodromal symptoms. Although a large RPCT prevent study of the NSAIDs naproxen and celecoxib initially reported a detrimental effect for both [218], a longer term follow up of these subjects suggested that timing and choice of specific NSAID might be key [219]. Thus, the early detrimental effects were largely attributable to a small group of subjects with early cognitive impairment and, in keeping with epidemiological studies, naproxen appeared thereafter to be protective in subjects who had been asymptomatic at baseline [219].

Immunization in AD mouse models and humans

In some instances (but not all) the characterization into M1 versus M2 phenotypes has been observed in response to specific conditions and cytokine exposures. With aging, Aβ-depositing mice increase in the expression of alternative activation state genes and deactivation state genes at the expense of classical activation state genes [220], however see also [221]. When these mouse models are treated with antibodies, there is a shift in the activation state over the time with treatment. Initial studies [222] noted reciprocal changes in markers such as kinases, with MAP kinase p38 declining and MAP kinase 44/42 increasing over the duration of antibody treatment. Subsequent work using mRNA markers to distinguish the M1 versus M2 phenotype identified a transition from an initially elevated M2 phenotype before treatment to an M1 phenotype after antibody treatment [220]. Similar shifts in microglial activation states appear associated with vaccination studies in humans with Alzheimer's disease. In comparison to other AD tissues, tissue from vaccinated patients have reduced staining for a number of microglial markers including the scavenger receptor A and Fcγ receptors, as was the amount of deposited Aβ [223]. In cases coming to autopsy within 2 years of the vaccination, these cases also showed increased levels of microhemorrhage and

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vascular amyloid deposits, plus the appearance of phagocytic microglia [224]. Similar outcomes were previously observed in aged mice treated with antibodies [225]. In the phase 2 and phase 3 trials with the antibody bapineuzimab, events referred to as Aβ related imaging abnormalities (ARIA) were found on MRI scans [226]. To some extent, these abnormalities in mouse models could be diminished by reducing antibody affinity for Fcγ receptors via deglycosylation [227], implying that the microglial activation caused by the antibody-antigen interaction may play a role in these vascular responses to immunotherapy.

Summary and outlook

The brain is no longer perceived as an immune privileged organ: we are in need of integrating advances in immunology into pathogenesis of diverse neurodegenerative conditions. The ligand-receptor interactions in the CNS micro-environment that keep microglia under tight control in the healthy brain are perturbed in chronic neurodegenerative disease but “the when” and “how” remain to be worked out. The notion of “activated microglia” is clearly useful shorthand but has hindered advances in the recognition of the diversity of the microglia phenotype and the extraordinary plasticity of these cells. The impact of systemic comorbidities and the associated systemic inflammation as well as ageing as a major risk factor, must be considered. The innate immune cells of the brain rapidly respond to systemic events and these responses are exaggerated in the ageing and diseased brain. The limited tools that allow us to assay the different states of microglia activation *in vivo* compound the difficulty of understanding the role of neuroinflammation in the human CNS. This is clearly an area with important unmet needs; better ligands for PET or other imaging modalities are vital. Clearly, the recognition that modifying the immune system contributes to the pathogenesis of chronic neurodegenerative diseases offers many potential routes to delaying the onset or progression.

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Box 1

Search strategy and selection criteria

We searched PubMed for journal articles that were published between January, 2009 to October, 2014 restricted by the terms “neuroinflammation” or “inflammation” and “Alzheimer” and included those judged most relevant to the field. We also selected papers with groundbreaking findings that led to recent research.

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Possible future directions to advance the field

1. Development of new animal models that reflect multiple facets of AD and are not restricted to the transgenic expression of human mutations of familial Alzheimer's disease.
   - New models should exceed beta amyloid or tau pathology and include aspects of multi-neurotransmitter loss, disease spreading and late onset of disease. Ideally these models would also show Alzheimer-like vascular pathology, synaptic destruction and neuronal loss. Future models and experiments should take disease modifiers such as systemic inflammation, insulin resistance, brain trauma, nutritional states, physical inactivity and obesity into account.
2. Biomarker identification of the inflammatory component of Alzheimer's disease.
   - New biomarkers may be developed for disease diagnosis, but also for the monitoring of preventive and therapeutic strategies. Such biomarkers could be blood, CSF or imaging based and allow to distinguish acute from chronic neuroinflammation.
3. Definition of pathologies and periods of neuroinflammation during the course of Alzheimer's disease.
   - Understanding of the individual contributions of microglia, macrophages, astrocytes, neurons and endothelial cells to neuroinflammation. This will provide information which inflammatory processes are good, which bad and which are irrelevant for disease pathogenesis at different stages of Alzheimer's disease.
4. Exploit the influence of mutations associated with immune function, epigenetics and the microbiome on neuroinflammation in Alzheimer's disease.
   - Recent discoveries which suggest a direct immune-related modification of the onset, progress and phenotype of Alzheimer's disease including SNPs in immune associated genes, epigenetic immune regulation and the influence of the microbiome on innate immunity should be taken into account.
5. Observational and preventive clinical trials, which inhibit detrimental but foster benefical immunity during Alzheimer's disease.
   - Observational trials should closely monitor the clinical course of patients carrying SNPs in immune-related genes, which have been associated with the risk to develop Alzheimer's disease. Clinical trials could include preventive trials, which inhibit detrimental

aspects of neuroinflammation prior to any cognitive decline, relevant to NSAID epidemiology.

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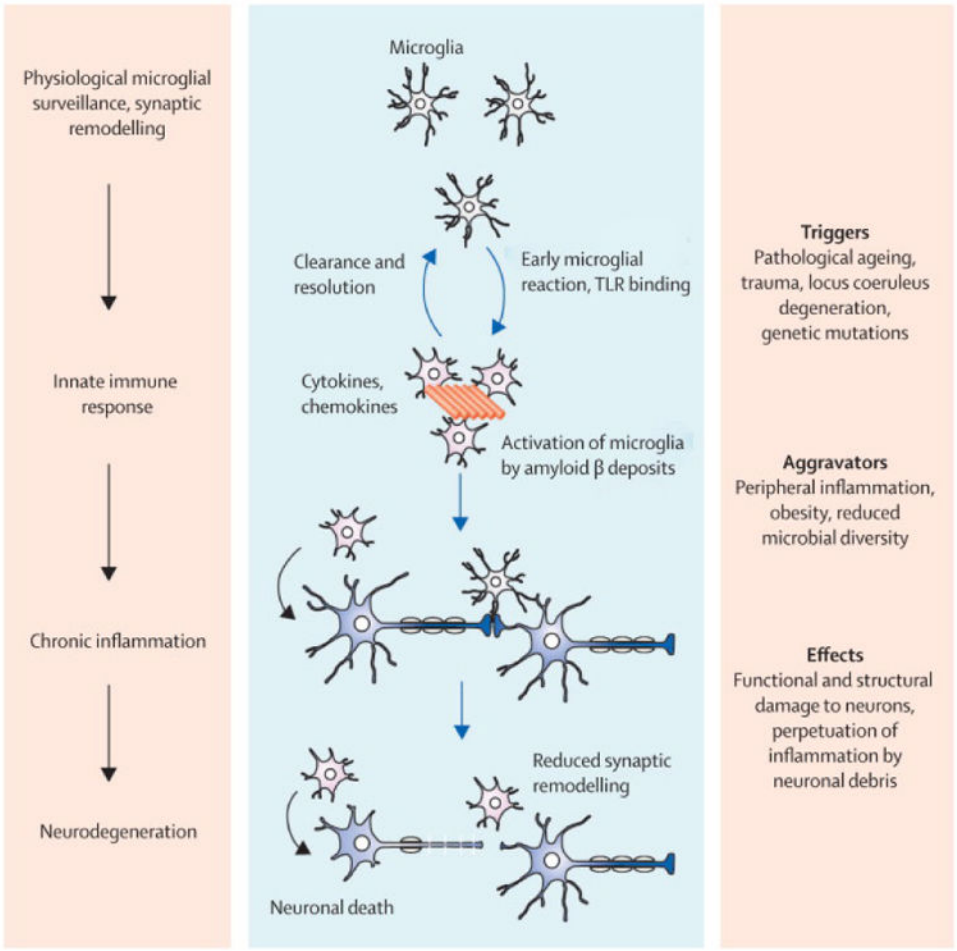

Figure 1. Pathomechanistic sequale of immune activation

Physiological functions of microglia including tissue surveillance and synaptic remodelling are compromized when microglia sense pathological Aβ accumulations. Initially the acute inflammatory response is thought to aid the clearance and to restore tissue homeostasis. Triggering factors and aggravators promote the sustained exposure and immune activation which ultimately leads to chronic neuroinflammation. The perpetuation of microglial activation, persistent exposure to proinflammatory cytokines and process retraction, causes functional and structural changes which finally end in neuronal degeneration.

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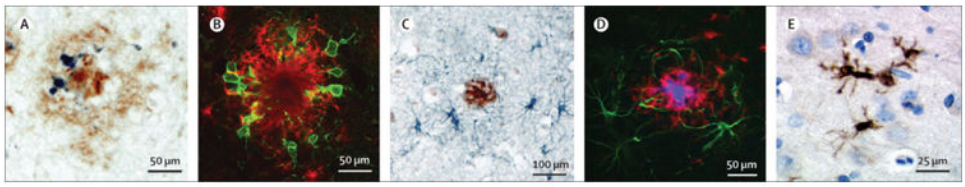

Figure 2. Micro- and astroglial changes in Alzheimer´s disease brain and APP/PS1 mice

(A) CD11b positive microglia (blue) within a Aβ deposit (brown) in the parietal cortex of a human AD brain section (bar = 50 µm). (B) Activated, Iba1-positive microglia (green) at a Aβ plaque site (red) in a section of a APP/PS1 transgenic mouse (bar = 50 µm). (C) GFAP positive astrocytes (blue) surround the site of Aβ deposition (brown) in the parietal cortex of a human AD brain section (bar = 100 µm). (D) GFAP-positive astrocytes (green) at a Aβ plaque site (red) in a section of a APP/PS1 transgenic mouse (bar = 50 µm). (E) Interleukin-1β positive microglia (brown) in the frontal cortex of a human AD brain section (bar = 25 µm). Courtesy of Drs. Markus Kummer and Michael Heneka.

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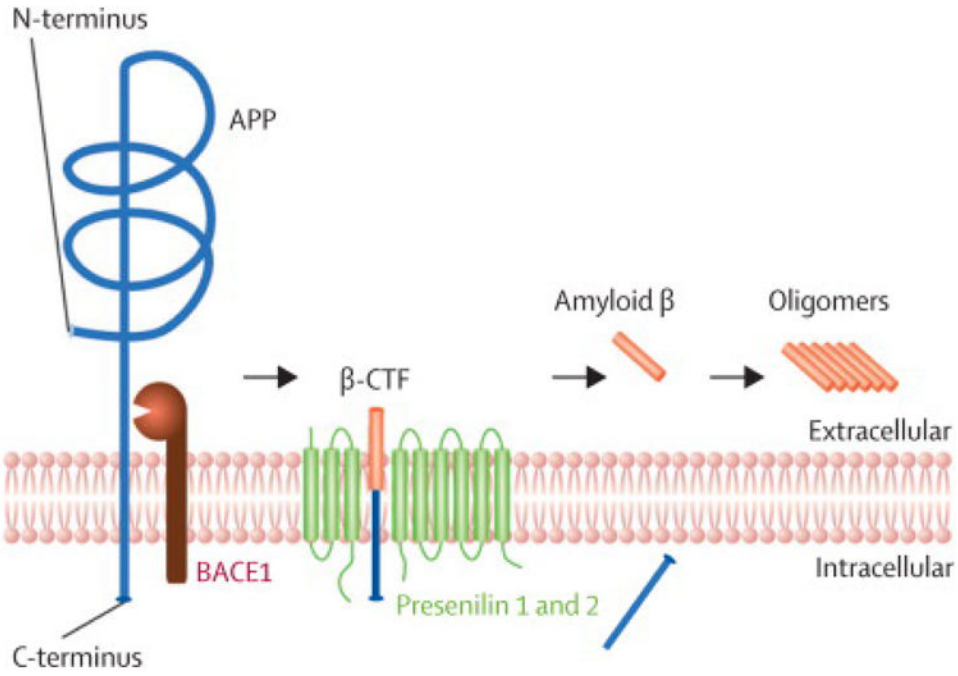

Figure 3. Amyloidogenic processing of the amyloid precursor protein (APP)

APP is processed by subsequent cleavages of two aspartate-proteases: the β-side cleaving enzyme 1 (BACE1) and the presenilin 1 and 2, which are part of the γ-secretase complex. BACE1 cleavage generates a C-terminal fragment (β-CTF) that is finally processed by presenilin 1 or 2 to liberate the amyloid β peptide, that is prone to aggregate into oligomers.

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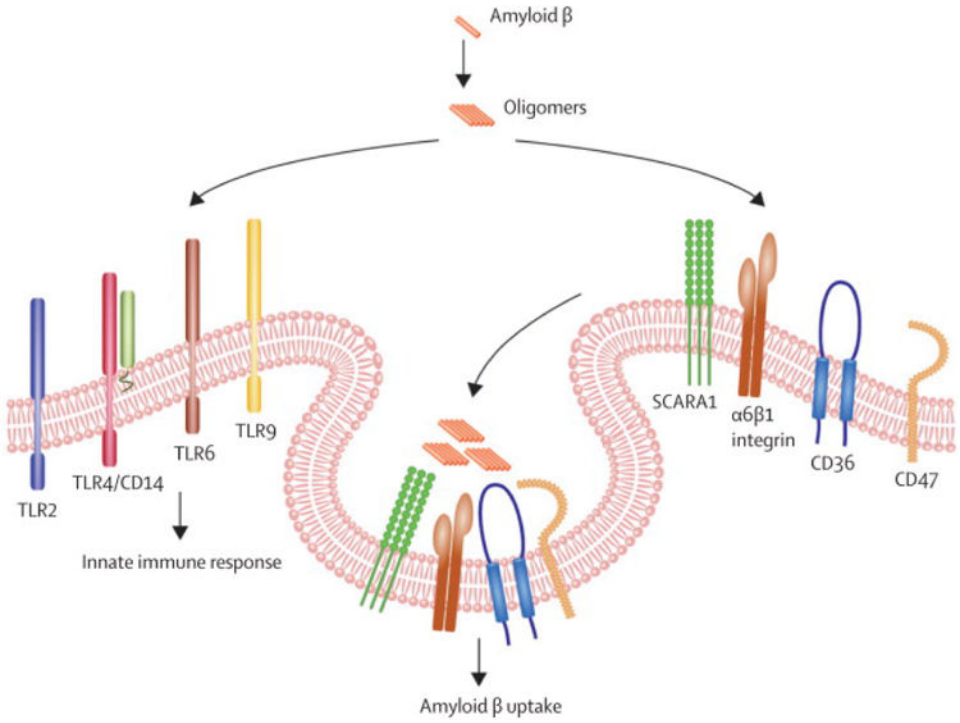

Figure 4. Impact of amyloid β on microglia

Aβ aggregates (oligomers) act on several TLR receptors on the microglial surface provoking reactions of the innate immune system. On the other side Aβ oligomers are internalized by microglia by the help of the the scavanger receptor A1 (SR-A1), α6β1-integrins, CD36 and CD47.

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Table 1

Selected clinicals trials to date

	Drug	Treatment	Outcome	Patients
Rogers et al, 1993[207]	Indomethacin	6 months	Positive effects after marked attrition	41 AD
De Jong et al, 2008[208]	Indomethacin	1 year	Neutral to positive effects after marked attrition	51 mild to moderate AD
Aisen et al, 2000[211]	Prednisone	1 year	Neutral to negative effects	138 AD
Aisen et al, 2003[209]	Naproxen, rofecoxib	1 year	Neutral to negative effects	351 mild-to-moderate AD
Aisen et al, 2002[228]	Nimesulide	3 months	Neutral effects	40 AD
Reines et al, 2004[210]	Rofecoxib	1 year	Neutral to negative effects	692 mild-to-moderate AD
Thal et al, 2005[229]	Rofecoxib	3.5 years, preventive	Neutral to negative effects on conversion to AD	1457 mild cognitive impairment
Van Gool et al, 2001[212]	Hydroxychloro quine	18 months	Neutral effects	168 mild AD
ADAPT Research	Celecoxib	2 years, preventive	Neutral to negative effects	2528 normal with family
Research Group, 2007, 2008[218,230]			effects	with family history of AD
ADAPT Research Group, 2007, 2008[218,230]	Naproxen	2 years, preventive	Neutral to negative effects	2528 normal wit family history of AD
Simons et al, 2002[213]	Simvastatin	26 weeks	No effects on CSF Aβ	44 AD
Sparks et al, 2005[214]	Atorvastin	72 weeks	Neutral effects	640 mild to moderate AD
Feldman et al, 2010[215]	Atorvastatin	1 year	Neutral to positive effects	67 mild AD
Gold et al, 2007[217]	Rosiglitazone	24 weeks	Neutral effects	693 mild to moderate AD
Breitner et al, 2011[219]	Naproxen	4 years, preventive	Neutral to positive effects	2528 normal with family history of AD
Breitner et al, 2011[219]	Celecoxib	4 years, preventive	neutral to negative effects	2528 normal with family history of AD

We searched PubMed for randomised controlled trials published in English. The table provides a list of trial results that have had a notable influence on the field, in our view, and is not an exhaustive list of studies. Priority was given to trials with sufficient numbers of participants, definition of clinical outcomes, and specification of design methodology to allow firm conclusions to be drawn (including inference of uncertainty). Two older trials were included because of their influence on later work, despite the fact that they failed to meet the foregoing criteria.