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Focus Issue: Feature Review

TREM2, Microglia, and Neurodegenerative Diseases

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Alzheimer's disease (AD) is the most common form of dementia and the 6th leading cause of death in the US. The neuropathological hallmarks of the disease are extracellular amyloid-β (Aβ) plaques and intraneuronal hyperphosphorylated tau aggregates. Genetic variants of TREM2 (triggering receptor expressed on myeloid cells 2), a cell-surface receptor expressed selectively in myeloid cells, greatly increase the risk of AD, implicating microglia and the innate immune system as pivotal factors in AD pathogenesis. Recent studies have advanced our understanding of TREM2 biology and microglial activities in aging and neurodegenerative brains, providing new insights into TREM2 functions in amyloid plaque maintenance, microglial envelopment of plaque, microglia viability, and the identification of novel TREM2 ligands. Our increased understanding of TREM2 and microglia has opened new avenues for therapeutic intervention to delay or prevent the progression of AD.

TREM2: Presenting Microglia Front and Center in AD

AD is a chronic neurodegenerative disease and the most common cause of dementia in humans worldwide [1–3]. AD symptoms include memory loss, impaired executive function, personality changes, and a progressive inability to perform the activities of daily living. AD is characterized histologically by an abundance of extracellular **amyloid-β (Aβ) plaques** (see Glossary) in the brain as well as the widespread presence of hyperphosphorylated tau (microtubule-associated protein tau, MAPT) aggregates within neurons (**neurofibrillary tangles**) [1–3]. Accumulation of amyloid plaque in the brain takes place over many years and typically precedes tau tangles and cognitive decline by a decade or more [4–7].

Another histological feature of AD is the presence and accumulation of reactive astrocytes and microglia (Box 1) around plaques [8,9], loosely called 'neuroinflammation' but more aptly classified as astrogliosis and microgliosis [10–12]. Microglia are a self-renewing population of myeloid cells that establish permanent brain residence during embryonic development and function as the innate immune cells of the brain throughout life [13]. In addition to their known macrophage-like role as primary responders when the brain is injured or infected, in recent years microglia have become recognized for their active participation in shaping synaptic connections in the developing and adult mammalian central nervous system (CNS) [14].

In the healthy brain microglia exhibit a dynamic behavior, using their highly motile processes to survey the surrounding environment [15]. Moreover, microglia are involved in **synaptic pruning** and may release neurotrophic factors, including insulin-like growth factor 1 and brain-derived neurotrophic factor, demonstrating that these cells are architects in the developing brain [16–20]. Based on studies in mice, synaptic pruning might be achieved via a **complement-**dependent mechanism because disruption of complement receptor 3 on microglia led to deficits in synaptic engulfment [21,22]. These microglial functions have been shown to be

Trends

A recent discovery has shown that the R47H variant of *TREM2* enhances the risk of AD by about threefold – similar to the risk conferred by *APOE4*. This finding has focused the attention of the field on microglia, the resident macrophages of the brain.

In mouse AD models, TREM2 deficiency reduces the microglial response to Aβ plaque pathology: there is reduced number of microglial cells surrounding plaques and impaired activation of microglial gene expression.

Evidence suggests that microglia participate in amyloid plaque compaction via a TREM2-dependent mechanism, forming a protective barrier that attenuates toxicity towards nearby neurons.

Phospholipids and lipoproteins (including APOE and CLU) have been identified as ligands for TREM2. The R47H variant of TREM2 impairs TREM2 ligand binding, phagocytosis by microglia, and downstream transcriptional responses.

The genetic associations of TREM2 loss-of-function variants with AD and other forms of dementia highlight the essential role of microglia in maintaining a healthy brain and suggest that enhancing microglial function may have therapeutic benefit.

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Box 1. Plaque-Associated Myeloid Cells: Identity and Impact

A controversy exists over whether the myeloid cells surrounding plaque in brains with AD pathology arise from proliferation of resident microglia or from infiltration of peripheral macrophages [151]. Origins of brain myeloid cells have often been inferred using isolated markers such as elevated CD45 or CD11c to identify peripheral myeloid cells, but resident microglia can upregulate those markers in disease [51,152]. Brain myeloid cells lacking microglial markers such as CX3CR1 or P2RY12 have also been inferred to be of peripheral origin, but resident microglia commonly downregulate such markers upon challenge [153–155]. In addition, blood-derived macrophages upon entering tissue may acquire several properties of tissue-resident macrophages [156]. Because infiltrating macrophages have been reported to possess heightened capacities for Aβ clearance or inflammatory signaling [157–160], the origin for myeloid cells in AD brains is an important question.

To determine whether peripheral macrophages contribute to the brain myeloid population in β-amyloidosis models, one study [140] used **parabiosis** to combine the circulatory systems of mice from either the 5×FAD model or from the APPPS1-21 model (each expressing the CD45.2 allele) to age-matched mice expressing CD45.1. After 4 weeks (5×FAD) or 9 weeks (APPPS1-21) of conjoined circulation, myeloid cells in the spleens and lungs showed substantial contributions from both parabionts [140]. In the brains, however, essentially all myeloid cells displayed only the CD45 reactivity of the host animal, providing strong evidence that the proportion of plaque-associated myeloid cells derived from infiltrating macrophages was negligible.

However, can peripheral macrophages, if delivered into the brain or induced to enter the brain, clear toxic amyloid species more effectively than microglia? Two research groups rigorously addressed this question using CD11b–HSVTK mice which express ganciclovir-sensitive thymidine kinase in all myeloid cells [161,162]. In these mice, intracerebroventricular delivery of ganciclovir for 2 weeks conditionally ablated microglia without depleting peripheral myeloid populations. After drug washout, within 2 weeks the microglia-depleted regions were fully repopulated by peripheral myeloid cells. In the APPPS1-21 and APP23 β-amyloidosis models, brains repopulated with blood-derived macrophages showed no difference in amyloid load, irrespective of whether repopulation occurred early or late in disease pathogenesis or whether assay was after weeks or months of repopulation. Surprisingly, the peripheral cells did not even home to plaque upon entering the tissue, remaining conspicuously aloof during initial weeks, but eventually developing some proclivity toward plaque association months after repopulation [161,162]. These studies argued against a role for peripheral macrophages that is substantially distinct from the function of microglial cells, meaning that attempts to use non-resident myeloid cells as tools for amyloid clearance in brain will probably require some extra engineering to augment their capabilities.

impaired in neurodegenerative conditions where microglia can be dysfunctional and/or excessive synaptic pruning might take place [23–27]. To visualize microglial activation *in vivo*, **positron emission tomography** (PET) imaging has been employed in human AD studies [28–31]. By using tracers that specifically bind to the translocator protein TSPO – expressed by microglia – it was suggested that microglial activation in AD brain could track temporally and spatially with the spread of amyloid as well as tau pathology [32,33]. Interestingly, higher binding of TSPO ligand has been documented in AD patients with a slower rate of disease progression, raising the possibility that microglial activation can exert a protective effect [34]. Microglia play a myriad of functions in the healthy and diseased brain; however, emerging data from the field suggests that microglia become impaired during neurodegenerative disorders.

In this review we examine the recent explosion of genetic data which implicate microglia as a crucial cell type in AD. Focusing on TREM2, given its strong effect on AD risk, we explore key aspects of microglia function that are dysfunctional in neurodegeneration. The recent identification of certain ligands for TREM2 has helped to illuminate the genetic association of TREM2 with AD risk, providing additional rationale for understanding how microglia may play a protective role in the development of AD pathology. New studies utilizing AD mouse models as well as human tissue have found that loss of TREM2 prevents microglia from accumulating around amyloid plaques, causing deficits in the barrier that limits neuronal injury. By highlighting recent work as well as gaps in our understanding, we hope to spur further elucidation of the molecular mechanisms of TREM2 and microglia in AD that may enable the development of novel therapeutic approaches to treat this devastating disorder.

Glossary

5×FAD: AD mouse model combining the Swedish KM670/671NL, Florida I716V, and London V717I mutations in the human *APP* transgene, and the M146L and L286V mutations in the human *PSEN1* transgene, with both genes under the control of the *Thy1* promoter.
α-Synuclein: aggregated α-synuclein is a major constituent of Lewy bodies, the hallmark pathology found in Parkinson's disease, dementia with Lewy bodies, and multiple systems atrophy. In the healthy brain its function is thought to involve clustering synaptic vesicles at the presynaptic terminal.
Amyloid-β (Aβ) plaques: a defining pathological feature of AD, plaques are extracellular accumulations of aggregated fibrillar Aβ peptide. Aβ can also exist in a soluble form. The peptide is generated from amyloid precursor protein through sequential cleavage by β and γ secretases.
Amyotrophic lateral sclerosis (ALS): progressive disease where degeneration of upper and lower motor neurons leads to weakness and paralysis of voluntary muscles, resulting in respiratory failure and death, usually within 5 years after onset of symptoms. Also known as Lou Gehrig's disease or motor neuron disease.
Apolipoprotein E (APOE): exists in three polymorphic forms differing at two amino acids APOE-ε2 (cys112, cys158), APOE-ε3 (cys112, arg158), and APOE-ε4 (arg112, arg158). The *ε4* allele increases AD risk ~threefold while *ε2* reduces risk ~0.6 fold. The major apolipoprotein in brain, APOE is produced mainly by astrocytes and is found in high-density lipoprotein (HDL)-like particles.
APP23: AD mouse model containing the Swedish APP KM670/671NL human transgene under the control of the thymus cell antigen-1 (*Thy1*) promoter.
APPPS1-21: an AD mouse model (also known as APPPS1) containing the Swedish *APP* KM670/671NL and *PSEN1* L166P human transgenes under the control of the *Thy1* promoter.
APPswe/PS1dE9: an AD mouse model (also known as APP/PS1) containing the Swedish *APP* KM670/671NL and *PSEN1* deltaE9 human