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Review

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TREM2 Function in Alzheimer's Disease and Neurodegeneration

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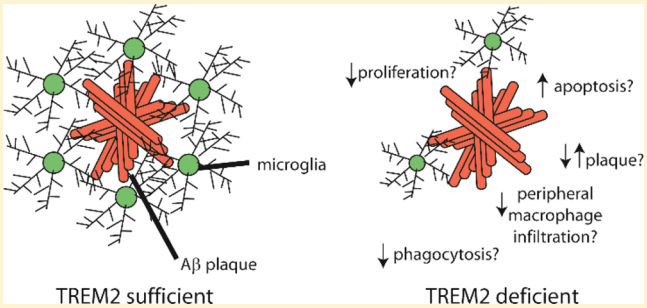
ABSTRACT: Alzheimer's disease (AD), the most common cause of dementia in the elderly, is a complex neurodegenerative disease marked by the appearance of amyloid-β (Aβ) plaques and hyperphosphorylated tau tangles. Alzheimer's disease has a strong genetic component, and recent advances in genome technology have unearthed novel variants in several genes, which could provide insight into the pathogenic mechanisms that contribute to AD. Particularly interesting are variants in the microglial-expressed receptor TREM2 which are associated with a 2−4-fold increased risk of developing AD. Since the discovery of a link between TREM2 and AD, multiple studies have emerged testing whether partial or complete loss of TREM2 function contributed to Aβ deposition or Aβ-associated microgliosis. Although some confounding conflicting data have emerged from these studies regarding the role of TREM2 in regulating Aβ deposition within the hippocampus, the most consistent and striking observation is a strong decrease in microgliosis surrounding Aβ plaques in TREM2 haploinsufficient and TREM2 deficient mice. Interestingly, a similar impairment in microgliosis has been reported in mouse models of prion disease, stroke, and multiple sclerosis, suggesting a critical role for TREM2 in supporting microgliosis in response to pathology in the central nervous system. In this Review, we summarize recent reports on the role of TREM2 in AD pathology and hypothesized mechanisms by which TREM2 function could influence AD-induced microgliosis.



KEYWORDS: *TREM2, microglia, Alzheimer's disease, neurodegeneration, amyloid-β, apolipoprotein E*

Alzheimer's disease (AD), the most common cause of dementia in the elderly, is a complex neurodegenerative disease marked by the presence of extracellular amyloid-β (Aβ) plaques, intracellular hyperphosphorylated tau tangles, and significant synaptic loss, brain atrophy, and neuronal death. Genetic and biomarker evidence suggest that deposition of soluble Aβ into oligomers, fibrils, and other aggregated forms is the initiating step in the pathology of AD and occurs 15−20 years prior to the onset of dementia.[1] Aβ peptides of varying length are produced by the sequential cleavage of the amyloid precursor protein (APP) by β- and γ-secretases. Most mutations in *APP* and mutations in *PSEN1* or *PSEN2*, components of the γ-secretase complex, increase the relative production of an aggregation prone Aβ_{1-42} peptide and lead to an autosomal dominantly inherited, early onset form of AD.[2] The causes of the more common, late-onset AD (LOAD) are more complex, but there is also a strong genetic component to the risk of developing LOAD. The strongest genetic risk factor for developing LOAD is the ε4 allele of the apolipoprotein E (*APOE*) gene, which encodes the major lipoprotein within the CNS.[3] Approximately 25% of the population carry at least one copy of the ε4 allele, a single copy of which confers an ∼4-fold increased risk of developing AD, and two copies confer ∼12-fold increased risk. Since the link between apoE4 and AD was first discovered over 20 years ago, a large body of evidence has emerged indicating that apoE4 influences AD, at least in part, by increasing Aβ aggregation and plaque deposition.[3]

Recent advances in genome-wide associated studies and in whole-exome sequencing have identified rare, AD-associated variants in a number of genes. Using the whole-exome sequencing approach, two independent studies initially identified rare missense variants in triggering receptor expressed on myeloid cells-2 (*TREM2*) that were associated with a relatively strong (∼2−4 fold) increased risk of developing AD.[4,5] Although the genetic link between TREM2 and AD is now well-established, the function of TREM2 within the central nervous system (CNS), and in particular in the setting of AD pathology, is still poorly understood. In this Review, we will summarize the basic biology of TREM2 and recent advances and controversies involving the role of TREM2 in AD and neurodegenerative disease.

TREM2

The *TREM2* gene is located within the *TREM* gene cluster located at chromosome 6p21.1 in humans and chromosome 17 in mice. In humans, the *TREM* gene cluster encodes four TREMs (*TREM1*, *TREM2*, *TREM4*, and *TREM5*) as well as two TREM-like genes (*TREML1* and *TREML2*). The mouse

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trem gene cluster contains an additional *trem3* gene. Prior to the discovery of a link between TREM2 variants and AD, homozygous loss of function variants in *TREM2* or TYRO protein tyrosine kinase binding protein (*TYROBP*), which encodes DNAX-activating protein 12 (DAP12), were known to cause Nasu-Hakola disease (NHD), also known as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL).[6] PLOSL patients typically die in their forties and the disease is characterized by the appearance of bone cysts and fractures in the third decade of life and the development of personality changes consistent with frontal lobe dysfunction and dementia in the fourth decade of life.[7] Multiple studies have found that heterozygous carriers of rare variants within the *TREM2* gene increase the risk of developing LOAD.[4,5,8−10] The most common of these variants in Caucasian populations, rs75932628, encodes an R47H missense mutation, which is hypothesized to be deleterious to TREM2 function. However, subsequent studies have identified several additional variants associated with AD risk, including an R62H mutation, which confers an ∼2-fold increased risk of developing AD.[10] Other variants within the *TREM* gene cluster may also influence AD risk. The rs6910730G variant in *TREM1* and the rs7759295C variant upstream of *TREM2* were found to be associated with increased AD pathology and an increased rate of cognitive decline.[11] Conversely, a missense variant in TREML2 (S144G) was associated with a modest decrease in AD risk.[12]

TREM2 is a member of the Ig superfamily of receptors that is expressed in a number of cell types including dendritic cells, osteoclasts, tissue macrophages, and in the brain within microglia. TREM2 consists of an ectodomain containing a type V Ig-super family domain and three putative N-glycosylation residues, a transmembrane sequence containing a positively charged lysine residue, and a short intracellular tail.[13] TREM2 associates with the signaling adaptor protein DAP12 via an electrostatic interaction within the lipid membrane between a lysine residue in TREM2 and an aspartate residue in DAP12.[14] DAP12 forms a homodimer via disulfide bridges between cysteine residues located within a short extracellular region and contains an ITAM-motif in the intracellular region. Upon stimulation of TREM2, tyrosine residues within the ITAM motifs in DAP12 become phosphorylated by Src family kinases, permitting the binding of Syk and ZAP70 kinases via their SH2 domains. Subsequently, these kinases activate a number of downstream signaling cascades including PI3K, PKC, ERK, and increased intracellular Ca^{2+} (Figure 1).

TREM2 is implicated in a number of cellular processes including phagocytosis, proliferation, survival, and regulation of inflammatory cytokine production. Studies from cultured microglia or bone marrow-derived macrophages implicated TREM2 as important for the phagocytosis of apoptotic cells and bacteria.[15,16] Moreover, exogenous expression of TREM2 in CHO or HEK293 cells increased phagocytic activity.[15,17] TREM2-DAP12 signaling synergizes with activation of the CSF1R to promote the survival and proliferation of macrophages.[18−20] TREM2 activity is also important for repressing inflammation following activation of Toll-like receptors (TLRs).[21]

Several ligands have been proposed to activate TREM2 signaling, including lipids and nucleotides. Although the precise endogenous ligand(s) that activates TREM2 has yet to be fully characterized, accumulating evidence suggests that lipids may play an important role in regulating TREM2 function. TREM

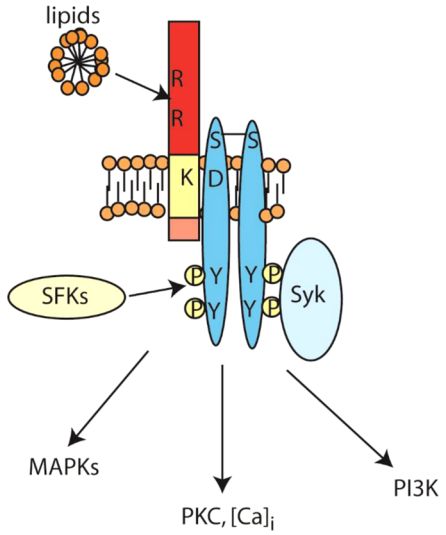

Figure 1. Schematic of TREM2-DAP12 signaling. Activation of TREM2, potentially by lipid species, results in phosphorylation of tyrosine residues within the ITAM motifs of DAP12 by Src-family kinases (SFKs) and subsequent activation of Syk. Syk, in turn, can activate a number of signaling cascades resulting in increased PI3K and MAPK activation or increases in intracellular Ca^{2+} ($[Ca^{2+}]i$) and PKC.

receptors physically associate with specific lipid species and zwitterionic and anionic lipids activate TREM2 signaling in vitro.[18,22,23] Interestingly, lipid-dependent TREM2 activation was blunted in the AD-associated TREM2 R47H mutation.[18] This lack of activation may suggest that the positively charged arginine residue is important for interaction with anionic ligands. Indeed, several AD-associated variants in TREM2 result in arginine missense mutations, suggesting that these charged residues may be critical for some aspect of TREM2 function.[10] An intriguing recent set of results found that recombinant or cell- secreted apoE bound to TREM2 with high affinity, as did other lipoproteins, such as apoA-I and apoB.[24,25] TREM2 fusion proteins were also able to precipitate apoE, and other lipoproteins from CSF and serum.[25] In agreement with previous results using isolated lipids, apoE affinity for TREM2-R47H was reduced compared to WT TREM2, however there were no differences among apoE isoforms in their affinity for TREM2.[24,25] Nonetheless, given that apoE is the predominant lipoprotein in the CNS, these findings raise a tantalizing question of whether apoE and TREM2, functionally interact in the context of AD.

THE BIOLOGY OF TREM2 IN AD

The association between TREM2 variants and AD is now widely accepted; however, investigations into the pathological basis for how TREM2 variants influence AD onset and progression are in their infancy. Indeed, it is still uncertain whether the AD-associated TREM2 variants confer a loss or gain of TREM2 function. The initial evidence indicates that AD-associated TREM2 variants impair TREM2 function. Among the missense mutations initially identified in AD, but not control cases were Q33X, Y38C, and T66M, which are known to result in loss of TREM2 function.[4,10] While the rarity of these mutations precludes definitively linking them to altering the risk of developing AD, this may suggest that more common AD-associated TREM2 variants also impair TREM2 function. In support of this hypothesis, TREM2-R47H

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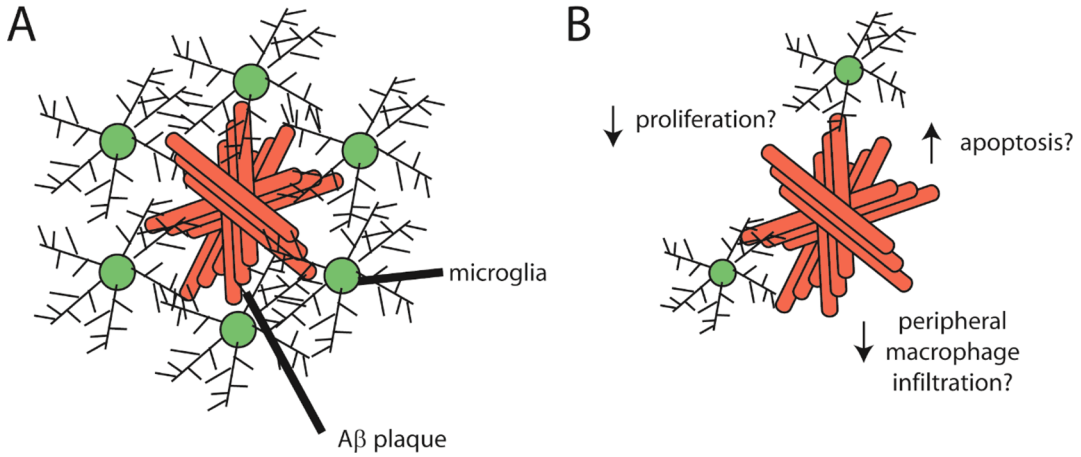

Figure 2. TREM2 is critical for Aβ-associated microgliosis. (A) Microglia normally cluster around Aβ plaque deposits in humans and mouse models of Aβ deposition. (B) TREM2 deficiency markedly impairs microgliosis around Aβ plaques. The mechanistic basis for reduced microgliosis is as yet unclear, but increased apoptosis, reduced proliferation, or reduced infiltration of peripheral macrophages may result from TREM2 deficiency.

exhibited decreased activation by lipids compared to WT TREM2.[18] Furthermore, maturation of TREM2-R47H expressed in HEK293 cells was reduced compared to WT TREM2, which could indicate that the R47H mutation impairs TREM2 processing.[17] In contrast, TREM2 knockout reduces hippocampal Aβ deposition in APPPS1-21 mice (see below).[26] If in fact TREM2 affects AD onset and progression by regulating Aβ deposition, this could suggest that TREM2 variants may not impair, but otherwise alter TREM2 function. Additional studies into the cell biology and structural biology of TREM2 are needed to better understand precisely how AD-associated variants affect TREM2.

TREM2 is upregulated within the vicinity of Aβ plaques in mouse models of Aβ deposition and TREM2 expression is positively correlated with amyloid deposition in individuals with AD.[4,27−29] TREM2 expression was also increased following tau deposition in the P301L mouse model.[30] To what degree the pathology-dependent increase in TREM2 expression on the tissue level is due to microglial upregulation of TREM2 versus expansion of the microglial population remains to be resolved. However, in mouse models of Aβ deposition, the increase in TREM2 expression exceeds the expansion of the microglial population, suggesting that microglia upregulate TREM2 expression in response to Aβ pathology.[27,30] Interestingly, analysis of TREM2 expression on monocytes found that other AD-risk associated alleles such as *CD33 rs3865444*^{C} and *TREM1 rs6910730*^{G} may affect TREM2 biology.[28] The AD-associated *TREM1 rs6910730*^{G} decreased the TREM1:TREM2 ratio on peripheral monocytes, and the AD-associated CD33 rs3865444C allele was associated with increased TREM2 expression, also on peripheral monocytes.[28] The implications of these potential trans relationships on the expression of AD-risk genes are still unclear, but could provide further insight into the role of the innate immune system in AD.

Given the positive correlation between TREM2 expression and Aβ pathology, it is perhaps unsurprising that TREM2 haploinsufficient or deficient mice exhibit a striking phenotype related to Aβ-associated microgliosis (Figure 2). Microglia migrate to sites of Aβ plaques and cluster around the plaque assuming a hypertrophied morphology commonly associated with an activated state. In the initial study of the effect of TREM2 on Aβ pathology TREM2$^{+/-}$;APPPS1-21 exhibited a significant reduction in the size and number of plaque-associated microglia compared to TREM2$^{+/+}$;APPPS1−21 mice.[31] Subsequent studies observed similar reductions in Aβ plaque-associated Iba1^{+} cells in TREM2 deficient APPPS1-21 and 5xFAD mice.[18,26] In contrast to the reduction in plaque-associated microglia, there was no apparent reduction in nonplaque associated microglia in TREM2 deficient 5xFAD or APPPPS1-21 mice, suggesting that TREM2 deficiency specifically affected microglia responding to Aβ pathology.[18,26] The decrease in plaque-associated microgliosis in TREM2$^{-/-}$;APPPS1-21 and TREM2$^{-/-}$;5xFAD mice was accompanied by decreased expression of inflammatory cytokines such as interleukin 1β (IL1β) and tumor necrosis factor (TNF).[18,26] Interestingly, overall Iba1 staining was reduced in a small cohort of TREM2 R47H carriers, although whether this reduction was a result of impaired Aβ-plaque associated microgliosis was not reported.[32]

The mechanism underlying the reduction in plaque-associated microglia remains unclear. One study found that TREM2 expression levels in APPPS1-21 mice were higher in CD11b^{+}/CD45^{Hi} than in CD11b^{+}/CD45^{Lo} cell populations, which are thought to represent peripheral myeloid cells and resident microglia, respectively.[26] Furthermore, there was no apparent decrease in the microglial-specific marker P2RY12 in TREM2$^{-/-}$;APPPS1-21, but pronounced decreases in the CD11b^{+}/CD45^{Hi} cell population within the brain, suggesting that TREM2 expression on peripheral myeloid cells was important for peripheral cell infiltration and localization around plaques in mouse models of Aβ deposition.[26] However, in a model of myeloid cell infiltration following ablation of microglia in APPPS1-21 mice, peripheral myeloid cells exhibited very little or greatly delayed localization to amyloid plaques.[29,33] Furthermore, similar TREM2 expression as detected by qPCR was observed in brains populated by either peripheral myeloid cells or resident microglia.[33] Additionally, TREM2 expression was observed only on plaque-associated myeloid cells within the brain, suggesting that high TREM2 expression was a result of a response to amyloid pathology rather than a distinguishing feature of peripheral myeloid cells.[29] Similarly, microglia can upregulate CD45 expression in response to inflammatory stimuli, which may complicate the clean distinction of peripheral myeloid versus resident microglia.[34] Whether the reduction in CD11b^{+}/CD45^{Hi} cells in TREM2$^{-/-}$;APPPS1-21 mice was due to reduced peripheral cell infiltration or impaired

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upregulation of CD45 by plaque-associated microgliosis is still unclear.

Another possible explanation for the decrease in plaque-associated microgliosis in TREM2 deficient mice is increased microglial apoptosis around Aβ plaques. Microglial viability and proliferation are dependent upon signaling through the colony stimulating factor-1 receptor (CSF1R) by either CSF1 or IL-34, and TREM2 is important for CSF1-depedent signaling.[19,35,36] TREM2-deficient microglia exhibited increased cell death under low CSF1 conditions in vitro and increased microglial apoptosis was observed around Aβ plaques in TREM2-deficient 5xFAD mice.[18] In addition, a 3-month, low-dose treatment of the CSF1R antagonist PLX5622 preferentially reduced plaque-associated microglia in the 3xTg model of Aβ deposition and tauopathy, suggesting plaque-associated microglia may be particularly sensitive to perturbations in CSF1R activity.[37] However, it is currently unknown whether there is a localized paucity of CSF1R ligand around Aβ plaques in vivo that would sensitize plaque-associated microglia to apoptosis. The potential contribution of other potential mechanisms which could lead to decreased plaque-associated microgliosis, such as decreased microglial translocation to Aβ plaques or decreased microglial proliferation is currently unknown and will require future study.

The data described above support the hypothesis that TREM2 is important for regulating the microglial response to pathology; however, it is not clear how a reduction in microgliosis would affect AD onset or progression. One possibility is that TREM2-mediated microgliosis is important for phagocytic clearance of Aβ plaques, thus limiting Aβ accumulation. Expression of TREM2 variants in HEK293 or BV2 cells impaired cellular phagocytic capacity compared to WT-TREM2-expressing cells.[17] Furthermore, primary microglia cultured from P5−P6 TREM2$^{-/-}$ mice exhibited reduced phagocytosis of $A\beta_{1-42}$ aggregates compared to TREM2$^{+/+}$ microglia.[17] However, *ex vivo* experiments using primary microglia from adult mice found that TREM2 deficiency had no impact on the uptake of aggregated $A\beta_{1-42}$.[18] These disparate observations may stem from the different culturing conditions and cellular sources used, which can dramatically impact the phenotype of cultured microglia.[38] Whether microglia are ultimately capable of phagocytosing fibrillar Aβ in vivo is unclear. Ultramicroscopy and in vivo confocal analysis of microglia and Aβ plaques in APP23 or TgCRND8 mice failed to find evidence of amyloid fibrils located within the cytoplasm of plaque-associated microglia.[39,40] Nonetheless, microglial Aβ uptake and lysosomal localization of Aβ within microglia have been observed, suggesting microglia uptake may regulate the level of monomeric or protofibrillar Aβ species around a plaque.[39,41,42] However, whether microglial phagocytosis of Aβ species around a plaque can limit the extent of plaque deposition is unclear as ablation of microglia using ganciclovir treatment in CD11b-HSVTK;APPPS1-21 or CD11b-HSVTK;APP23 mice failed to alter Aβ burden or plaque size.[43]

Somewhat conflicting data have also emerged from studies that examined the role of TREM2 on Aβ deposition in vivo. The 5xFAD and APPPS1-21 models that have been used thus far to study the role of TREM2 in Aβ pathology exhibit aggressive Aβ deposition that begins as early as 2 months of age, with pathology first appearing in the subiculum and deep cortical layers or in the neocortex in 5xFAD and APPPS1-21, respectively.[44,45] An initial report found that TREM2 haploinsufficiency had no effect on cortical Aβ deposition in 3 or 7 month old APPPS1-21 mice.[31] A subsequent study in 4-month old APPPS1-21 mice using an independently generated TREM2$^{-/-}$ mouse similarly found no TREM2-dependent change in cortical Aβ burden, although TREM2$^{-/-}$;APPPS1−21 mice did exhibit a decrease in hippocampal Aβ burden compared to TREM2$^{+/+}$;APPPS1−21 mice.[26] In contrast, 8 month old TREM2$^{-/-}$;5xFAD mice exhibited an increase in hippocampal Aβ burden, although no TREM2-dependent effect on cortical Aβ burden was reported, in agreement with the phenotype observed in APPPS1-21 mice.[18] The mechanism underlying the paradoxical effects of TREM2 knockout on hippocampal Aβ deposition in these studies is unclear.[46] If there is an effect of TREM2 on Aβ burden present in these models, it appears to be relatively small. It is possible that mouse strain dependent-effects on hippocampal Aβ pathology could be differentially modulated by TREM2 in these models.

A final consideration in regard to how TREM2 function may influence AD is what effect TREM2 has on the level of inflammatory signaling in the brain in the context of AD pathology. Microglial production of inflammatory cytokines in the presence of Aβ or tau pathology (i.e., TNFα, IL12, IL1, etc.) is thought to promote neurotoxicity and hasten the progression of the disease.[47] Since TREM2 represses the production of inflammatory cytokines instigated by TLR activation, decreased TREM2 function could increase microglial-mediated, neurotoxic inflammatory signaling.[48] However, TREM2-deficient 5xFAD and APPPS1−21 mice exhibited decreased expression of inflammatory cytokines, likely as a result of the decrease in overall microglial activation.[18,26] Furthermore, WT and TREM2$^{-/-}$ ex vivo microglia produced equivalent amounts of TNFα in response to $A\beta_{1-42}$, which may suggest that TREM2 is not a direct regulator of the production of inflammatory cytokines in response to Aβ pathology.[18]

TREM2 IN OTHER MODELS OF NEUROLOGICAL DISEASE

Given the link between TREM2 and AD and NHD, multiple studies have emerged testing whether TREM2 is involved in the pathogenesis of other neurodegenerative diseases. Given that one of the features of NHD is extensive demyelination of axons, several studies have examined the role of TREM2 in mouse models of multiple sclerosis (MS). TREM2 expression is strongly upregulated on microglia, dendritic cells, and macrophages within the brain and spinal cord upon the onset of clinical symptoms in the experimental autoimmune encephalomyelitis (EAE) model of MS, and is upregulated on microglia in the cuprizone model of demyelination.[23,49] In both the EAE and cuprizone model, TREM2 appears to mediate a protective function. Administration of a TREM2 antagonist antibody in the EAE model increased the amount of demyelination and the severity of the clinical phase of the disease.[49] Similarly, TREM2$^{-/-}$ mice exhibited increased axonal pathology and poorer performance in motor behavioral tests in the cuprizone model of demyelination.[50] Cuprizone-induced demyelination of the corpus collosum is accompanied by pronounced microgliosis.[51] However, in cuprizone-treated TREM2$^{-/-}$ mice there was reduced microgliosis within the corpus collosum during the acute phase of demyelination, perhaps due in part to decreased microglial proliferation.[23,50] Accompanying the decrease in microgliosis, cuprizone-treated TREM2$^{-/-}$ mice displayed poorer phagocytic removal of damaged myelin debris and impaired remyelination.[23,50] Given that myelin lipids can

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activate TREM2 signaling, these results would suggest that TREM2-dependent microgliosis is required for efficient clearance of myelin debris upon toxic demyelination.[23,50] This conclusion is supported by the observation that TREM2-overexpression facilitates the clearance of myelin debris and limits neuronal damage in the EAE model of MS.[52] No evidence has yet been reported that TREM2 variants alter the risk of developing MS. However, one study reported higher levels of sTREM2 in the cerebral spinal fluid (CSF) of MS patients and TREM2 expression was increased in foamy macrophages within demyelinating MS lesions.[53]

Impaired microgliosis in TREM2-deficient mice is also observed in models of prion disease and stroke. TREM2 expression is also upregulated in a scrapie prion model and prion-induced microgliosis was attenuated in TREM2$^{-/-}$ mice. However, TREM2 deficiency did not affect the pathological progression of prion disease.[54] TREM2 expression is upregulated within the infarct region in the middle cerebral artery occlusion (MCAO) stroke model and TREM2$^{-/-}$ mice exhibit decreased microgliosis within the infarct region.[55,56] In accordance with decreased microgliosis, the production of inflammatory cytokines may also be reduced following MCAO in TREM2$^{-/-}$ mice.[55] TREM2$^{-/-}$ mice also displayed poorer resorption of infarcted brain regions and performed poorer on neurological functional tests following recovery.[56] In addition, reduction of TREM2 expression in cultured microglia or BV2 cells reduced phagocytosis of apoptotic neurons, although this phenotype may be dependent upon the specific culture conditions used.[16,18,56] Overall, these data would suggest that, similar to observations in MS models, TREM2 is important for damage-induced microgliosis which serves a beneficial role in functional neurological recovery.

FUTURE PERSPECTIVES

The initial investigations into the role of TREM2 in the pathology of AD have yielded a mix of apparently conflicting results in regard to hippocampal Aβ deposition and a profound impairment in Aβ-associated microgliosis, both of which provide a solid foundation for additional experimental inquiry. Although no effect of TREM2 deficiency on cortical plaque deposition has been reported, the discrepancy in hippocampal Aβ deposition observed in the APPPS1-21 and 5xFAD models makes it difficult to unequivocally conclude that TREM2 does not regulate Aβ burden. If there is an effect of TREM2 on Aβ burden, it is possible that the fast kinetics of deposition exhibited in these models could obscure a potential TREM2 component. In that regard it would be important to test the role of TREM2 on plaque deposition in a less aggressive model. Furthermore, aging can influence the phenotypic state of microglia, which could further alter how TREM2 deficiency affects Aβ deposition and microglial response to pathology. For example, compared to TREM2$^{+/+}$ mice, TREM2$^{-/-}$ mice fail to demonstrate an age-dependent increase in microglia at 2 years of age, and the microglia in aged TREM2$^{-/-}$ mice appear more dystrophic.[23] Therefore, studying the impact of aging combined with TREM2 deficiency may yield novel insights into the role of TREM2 in Aβ pathology.

However, it is important to note that impairment of Aβ-associated microgliosis in TREM2-deficient mice is observed in multiple mouse models and is detectable even in TREM2-haploinsufficient mice, which in theory would most closely match the human genetic data indicating that a single copy of a variant TREM2 allele is sufficient to strongly increase the risk of AD. It is particularly interesting that deficits in damage-associated microgliosis in TREM2-deficient mice are not limited to Aβ-deposition models, but are also observed in MS and stroke models, where TREM2-deficient mice also exhibit poorer behavioral performance and increased neuronal toxicity. Whether and how reduced microgliosis could influence the progression of AD pathology is unclear. Although microglial mediated inflammation is hypothesized to contribute to synaptic and neuronal toxicity in AD, other studies indicate that plaque-associated microglia can serve a beneficial role. For example, the binding of soluble Aβ_{42} to existing fibrillar Aβ plaques and the incidence of dystrophic neurites preferentially occurred in those regions of the plaque that exhibited low microglial coverage.[57] Furthermore, some studies suggest that nuclear hormone receptor agonists increase the number of TREM2^{+} plaque-associated microglia or peripheral myeloid cells and facilitate the clearance of Aβ deposits.[58,59] Uncovering the mechanism by which TREM2 facilitates neuronal and synaptic damage induced by microgliosis could yield novel insight into how microglia respond to insults in the CNS and how best to modulate microglial activity to mitigate neuronal damage.

To date, studies of TREM2 on AD pathology have focused on Aβ deposition models. However, microgliosis also is associated with tauopathy, the other pathological hallmark of AD. Microgliosis can precede the detection of hyperphosphorylated tau in mouse models of tauopathy and may contribute in some way to the progression of tau pathology throughout the brain.[60−62] Moreover, the activation state of microglia may influence the development of tau pathology and influence the neurotoxicity of tauopathy.[63,64] Given the strong effect of TREM2-deficiency on microgliosis in diverse models of neurodegenerative disease, it will be particularly important to test whether TREM2 influences microgliosis, neurodegeneration, and tau pathology.

ApoE4 and TREM2 are the strongest known genetic risk factors associated with LOAD. However, whereas it is well-established that a major effect of apoE4 is to influence Aβ deposition in humans and mouse models, a major phenotype of TREM2-deficiency appears to be an impairment in the microglial response to Aβ pathology. Although biomarker studies indicate that Aβ deposition begins 15−20 years prior to the onset of clinical symptoms, we know little about how Aβ plaques ultimately promote the development of the neocortical tauopathy, synaptic loss, and neuronal death that correlate with dementia. In this regard, understanding the role of TREM2 and microgliosis in AD may help bridge the knowledge gap between the onset of Aβ pathology and clinical phase of the disease, which could ultimately lead to novel drug targets to delay or prevent the progression to clinical dementia.

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Notes

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