TREM2 Variants: New Keys to Decipher Alzheimer's Disease Pathogenesis

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Introduction

Triggering receptor expressed on myeloid cells 2 (TREM2) is a cell surface receptor of the Ig superfamily that is expressed on microglia in the CNS. Recent genetic studies (Benitez et al., 2013; Bertram et al., 2013; Guerreiro et al., 2013a; Jonsson et al., 2013; Reitz et al. 2013; Ruiz et al., 2014; Slattery et al., 2014) have identified a rare variant of TREM2 that is a risk factor for nonfamilial Alzheimer's disease (AD), the most common form of late-onset dementia. Moreover, TREM2 deficiency has been shown to alter microglial function in mouse models of AD (Ulrich et al., 2014; Jay et al., 2015; Wang et al., 2015). Here we review recent progress in our understanding of how TREM2 may control the microglial response to AD lesions and its impact on microglial senescence, as well as the interaction of TREM2 with other molecules encoded by gene variants associated with AD and the hypothetical consequences of its cleavage from the cell surface.

TREM2 Expression and Signaling

TREM2 is a transmembrane receptor that belongs to the TREM family of proteins, which are encoded by genes clustered on human chromosome 6p21.1 and mouse chromosome 17 (Klesney-Tait et al., 2006; Ford and McVicar, 2009). TREM2 is found in various tissue macrophages, such as CNS microglia (Paloneva et al., 2002; Schmid et al., 2002); bone osteoclasts (Cella et al., 2003; Paloneva et al., 2003; Humphrey et al., 2006); and alveolar (Wu et al., 2015), peritoneal (Turnbull IR et al., 2006) and intestinal (Seno et al., 2009) macrophages. TREM2 is also present on cultured bone-marrow-derived macrophages (Daws et al., 2001) and monocyte-derived dendritic cells (Bouchon et al., 2001). Its expression *in vitro* is induced by macrophage colony-stimulating factor 1 (CSF-1), granulocyte-macrophage colony-stimulating factor (GM-CSF, also known as CSF-2), and interleukin-4 (IL-4) and is inhibited by toll-like receptors (TLRs) (Cella et al., 2003; Turnbull IR et al., 2006; Ji et al., 2009). *Trem2* transcription is also regulated by retinoid X receptors (RXRs) in mouse macrophages (Daniel et al., 2014). Accordingly, treatment of mice with the RXR agonist bexarotene augmented the cortical expression of *Trem2* mRNA in an AD mouse model (Lefterov et al., 2015).

The extracellular region of TREM2 contains a single Ig superfamily domain and binds polyanionic ligands, such as bacterial lipopolysaccharides (LPS) and phospholipids (Fig. 1) (Cannon et al., 2012; Poliani et al., 2015; Wang et al., 2015; Daws et al., 2016). Upon ligand binding, TREM2 transmits intracellular signals through an adaptor, DAP12 (also known as TYRO protein tyrosine kinase–binding protein [TYROBP]), which is associated with the transmembrane region of TREM2 and recruits the protein tyrosine kinase SYK through its cytosolic immunoreceptor tyrosine-based activation motifs (ITAMs) (Fig. 1). SYK initiates a cascade of signaling events including protein tyrosine phosphorylation, phosphoinositide 3-kinase (PI3K) activation, Ca^{2+} mobilization, and mitogen-activated protein kinase (MAPK) activation (Fig. 1). TREM2 also signals through DAP10 (also known as hematopoietic cell signal transducer), a DAP12-related adaptor that recruits PI3K (Peng et al., 2010) (Fig. 1). Together, these signals promote survival (Otero et al., 2012; Wang et al., 2015), proliferation (Otero et al., 2012), phagocytosis (Takahashi et al., 2005), and secretion of cytokines and chemokines (Bouchon et al., 2001). TREM2-induced signals also augment the activation of integrins that induce remodeling of the actin cytoskeleton, which controls adhesion and migration (Takahashi et al., 2005; Melchior et al., 2010; Forabosco et al., 2013). However, TREM2-induced signals interfere with the function of TLRs and hence curtail macrophage inflammatory responses to various TLR ligands, such as LPS, lipoteichoic acid, and unmethylated CpG oligodeoxyribonucleotides (Hamerman et al., 2006; Turnbull IR et al., 2006). Thus, TREM2 can perform both activating and inhibitory functions in tissue macrophages.

Linking TREM2 and Dementia

Inactivating mutations of TREM2 were initially discovered in patients with a very rare form of autosomal recessive, inherited, early-onset dementia called Nasu-Hakola disease (NHD) (Paloneva et al., 2002; Klünemann et al., 2005). This disease causes brain and bone pathology consisting of sclerosing leukoencephalopathy and polycystic osteodysplasia, respectively (Paloneva et al., 2001). Based on these genetic studies and the observation that TREM2 is expressed in microglia and osteoclasts, it became apparent that these cells require TREM2 to perform their functions in the CNS and bone. More recently, Genome-wide association studies (GWAS) identified a low-frequency variant of *TREM2* as a genetic risk for nonfamilial AD. This variant, which results in an arginine-47-histidine (R47H) substitution in the extracellular Ig domain, significantly increased the risk for AD in two large cohorts of patients, a finding that was confirmed in other cohorts (Benitez et al., 2013; Bertram et al., 2013; Guerreiro et al., 2013a; Jonsson et al., 2013; Reitz et al. 2013; Ruiz et al., 2014; Slattery et al., 2014).

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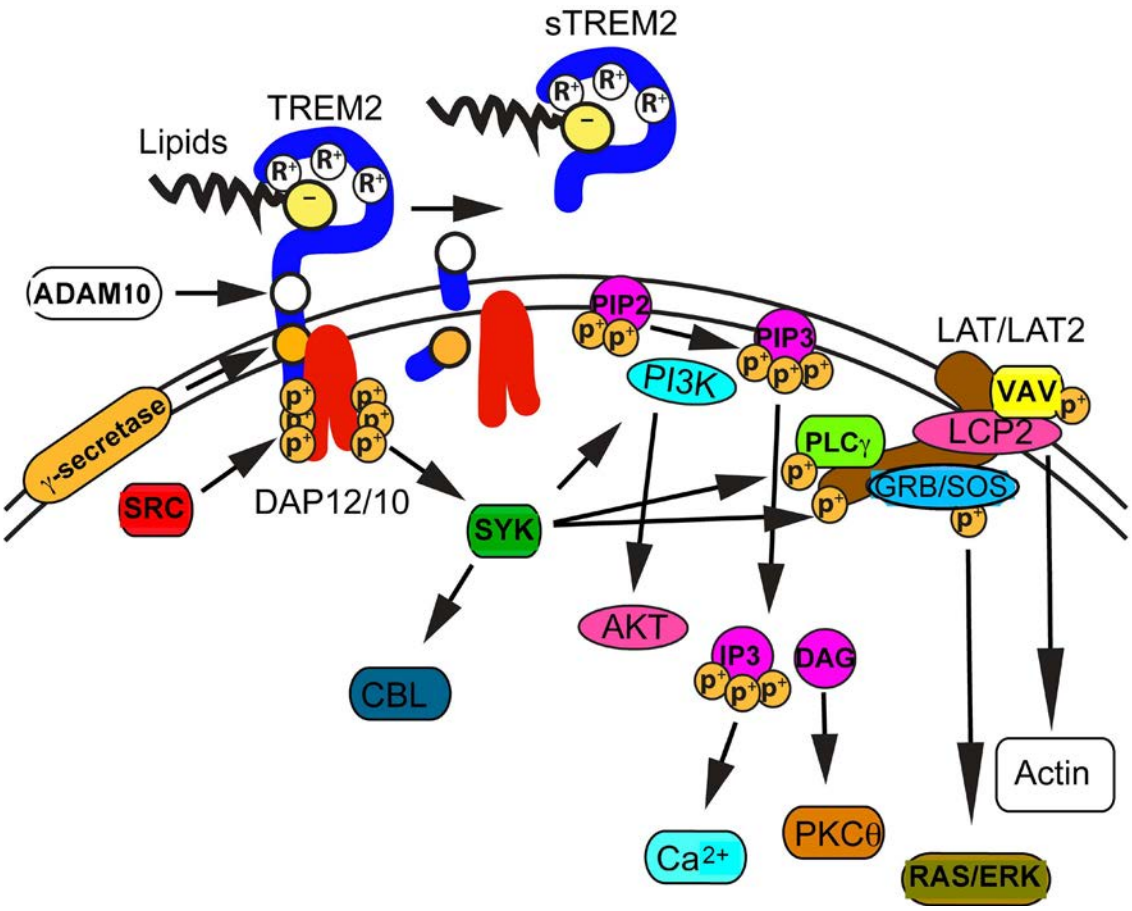

Figure 1. TREM2 signaling pathways. TREM2 binds negatively charged lipid ligands, most likely through the positively charged arginine residues (R^+) present in its extracellular domain. During ligand binding, the TREM2-associated adapter DAP12 is tyrosine phosphorylated by the protein kinase SRC and recruits the tyrosine-protein kinase SYK. SYK phosphorylates the adapters LAT (linker for activation of T-cells family member 1) and LAT2, which in turn recruit various signaling mediators and adapters, including phospholipase Cγ (PLCγ, which degrades phosphatidylinositol 3,4,5 trisphosphate [PIP3] into inositol trisphosphate [IP3] and diacylglycerol [DAG]); lymphocyte cytosolic protein 2 (LCP2, also known as SLP76); the proto-oncogene *vav* (VAV1); and growth factor receptor-bound protein 1 (GRB2) and/or son of sevenless homolog 2 (SOS2). Ultimately, these pathways lead to Ca^{2+} mobilization, activation of PKCθ, activation of the RAS/ERK pathway, and actin remodeling. SYK also activates the phosphoinositide 3-kinase (PI3K)–AKT pathway as well as the E3 ubiquitin-protein ligase CBL, which negatively regulates the TREM2 pathway. TREM2 also associates with DAP10, which recruits and activates PI3K. TREM2 can be cleaved from the cell surface by ADAM10 and γ-secretase, thereby releasing sTREM2. Modified with permission from Colonna M and Wang Y (2016), Figure 1. Copyright 2016, Nature Publishing Group

The identification of TREM2 as a potential key molecule in AD pathogenesis was surprising, given the notable differences between NHD and AD. NHD is a rare form of early-onset dementia, whereas nonfamilial AD is the most common form of late-onset dementia (Holtzman et al., 2011). The pathological features of AD are also quite different from those of NHD: Whereas NHD consists of massive demyelination of the white matter of the frontal lobes (Paloneva et al., 2001), nonfamilial AD is characterized by the deposition of Aβ peptide and hyperphosphorylated tau aggregates in the gray matter, which are associated with neuronal cell death as well as activation of microglia and astrocytes (Holtzman et al., 2011). Although rare forms of autosomal dominant, inherited AD result from mutations in proteins involved in the Aβ processing pathway, such as amyloid precursor protein (APP) and presenilin 1 (PS1), the origin of nonfamilial AD is less well understood and may depend on a combination of genetic and nongenetic risk factors (Tanzi, 2012).

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The identification of a *TREM2* variant as a risk factor for AD supported the long-standing hypothesis that altered microglial function might significantly contribute to the pathogenesis of this disorder (Heneka et al., 2015; Meyer-Luehmann et al., 2015; Ransohoff and El Khoury, 2015). This hypothesis has also been corroborated by GWAS that have identified rare variants of other genes encoding immune receptors expressed by microglia as risk factors for AD. These include the inhibitory receptor myeloid cell surface antigen CD33 (CD33) (Bertram et al., 2008; Hollingworth et al., 2011; Naj et al., 2011; Bradshaw et al., 2013; Griciuc et al., 2013); the complement component (3b/4b) receptor 1 (CR1) (Lambert et al., 2009); the complement regulatory protein clusterin (Harold et al., 2009; Lambert et al., 2009); and the alternative activated macrophage marker *MS4A4A* (Hollingworth et al., 2011; Naj et al., 2011) (Table 1). Moreover, an integrated system approach has pinpointed immune-related gene networks as key regulators in AD. In particular, the role of TREM2, along with its associated adapter DAP12 and downstream signaling pathway, was highlighted (Zhang et al., 2013).

The identification of the R47H variant associated with AD has prompted extensive analyses of *TREM2* polymorphisms in the human population, leading to the identification of less frequent variants, such as the aspartic acid-87-asparagine (D87N) substitution (rs142232675 in Table 1) (Guerreiro et al., 2013). Variants of genes encoding other TREM family receptors, such as Trem-like transcript protein 2 (TREML2) (Benitez et al., 2014) and TREM1 (Replogle et al., 2015), have also been found to be associated with protection or susceptibility to AD, respectively, independent of their genetic linkage with TREM2 (Table 1). Although some variants were found in the exons encoding the extracellular portion of TREM receptors, others were found in intronic regions that may control gene expression and/or splicing. For example, a TREM1 risk allele was associated with a reduced ratio of TREM1:TREM2 expression (Chan et al., 2015). Further studies will be important to confirm these associations in various cohorts, determine the impact of these variants on TREM receptor expression and/or function, and assess their pathogenicity.

TREM2 Function During AD

Regulating microglial responses to Aβ plaques

Beyond GWAS, the mechanistic link between *TREM2* variants, microglial dysfunction, and neurodegeneration has remained elusive. An initial study investigated the function of TREM2 in microglia using overexpression and silencing approaches. In this *in vitro* study, microglia overexpressing TREM2 were more efficient in removing apoptotic neurons through phagocytosis, whereas silencing of TREM2 impaired this function (Takahashi et al., 2005). Thus, TREM2

Table 1. Genetic association of innate immune genes with AD.

SNP number	Locus	Odds ratio	Functional impact on the protein	Susceptibility to AD	References
rs75932628	TREM2	4.5, 4.66	Loss of function	Increased	Guerreiro et al., 2013; Jonsson et al., 2013; Kleinberger et al., 2014; Wang et al., 2015
rs142232675	TREM2	NA	ND	Increased	Guerreiro et al., 2013; Jonsson et al.
rs3826656	CD33	NA	ND	Increased	Bertram et al., 2008
rs3865444^{T}	CD33	0.89, 0.91	Reduced expression	Decreased	Hollingworth et al., 2011; Naj et al., 2011; Griciuc et al., 2013
rs3865444^{C}	CD33	NA	Increase expression	Increased	Bradshaw et al., 2013; Hollingworth et al., 2011; Naj et al., 2011
rs6701713	CR1	1.16	ND	Increased	Lambert et al., 2009
rs6656401	CR1	1.21	ND	Increased	Lambert et al., 2009
rs3747742	TREML2	0.89	ND	Decreased	Benitez et al., 2014
rs6910730	TREM1	NA	Reduced expression	Increased	Replogle et al., 2015

NA, not applicable; ND, not determined; SNP, single nucleotide polymorphism.
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was proposed to be a phagocytic receptor. This view was supported by studies showing that TREM2 contributes to macrophage phagocytosis of bacteria (N'Diaye et al., 2009) and that overexpression of TREM2 in a microglia cell line increases its capacity to phagocytose Aβ (Melchior et al., 2009; Jiang et al., 2014). TREM2 was also found to curb myeloid cell secretion of pro-inflammatory cytokines (Takahashi et al., 2005; Hamerman et al., 2006; Turnbull et al., 2006). Thus, it was initially hypothesized that TREM2 might protect from neurodegeneration by promoting phagocytosis and clearance of apoptotic neurons while controlling detrimental inflammation (Fig. 2).

Recent studies analyzed the impact of TREM2 deficiency or haploinsufficiency on the microglial response to Aβ deposition in two mouse models of AD: *APPPS1-21* and *5XFAD* mice. These mice carry three or five mutations, respectively, in human transgenes encoding proteins involved in the Aβ processing pathway, including APP PS1 (Ulrich et al., 2014; Jay et al., 2015; Wang et al., 2015). All studies found that Aβ deposition induced robust microgliosis in TREM2-sufficient mice: that is, there was activation and accumulation of microglia around Aβ plaques. In contrast, microglia failed to cluster around Aβ plaques in TREM2-deficient or haploinsufficient mice, indicating a defective response to Aβ accumulation. Moreover, gene expression analyses of microglia demonstrated that TREM2 deficiency reduced the expression of genes associated with microglial activation in response to Aβ deposits, including phagocytic receptors, costimulatory molecules, inflammatory cytokines, and trophic factors (Ulrich et al., 2014; Jay et al., 2015; Wang et al., 2015). These results indicate that TREM2 promotes a broad array of microglial functions in response to Aβ deposition, rather than just phagocytosis.

Impact of TREM2 deficiency on Aβ accumulation

Although the results from all the mouse studies described above demonstrated the importance of TREM2 in microgliosis, their findings on the impact of TREM2 deficiency on Aβ accumulation were contradictory, which led to disparate interpretations of the mechanisms through which TREM2 deficiency impacts Aβ-reactive microgliosis.

In the *5XFAD* model, TREM2-deficient microglia did not became activated or proliferate in response to Aβ deposition, but rather underwent apoptosis (Wang et al., 2015). This defect resulted in Aβ accumulation at 8 months of age. A partial increase in Aβ1-40 and Aβ1-42 deposition was also evident in TREM2 haploinsufficient *5XFAD* mice. Moreover, this study found that TREM2 binds anionic and zwitterionic phospholipids that may become exposed during Aβ accumulation owing to neuronal and glial apoptosis, myelin degradation, and the formation of aggregates between Aβ and phospholipids. In contrast, microglia expressing the R47H variant of TREM2 associated with AD had a reduced capacity to bind phospholipids (Wang et al., 2015). The model that emerged from this study is that TREM2 senses changes in the lipid microenvironment that result from Aβ accumulation and neuronal degeneration, and this response triggers signals that activate microglial capacity to limit Aβ accumulation (Fig. 2). Consistent with this model, virally induced overexpression of TREM2 ameliorated neuropathology and rescued cognitive impairment in another mouse model of AD (Jiang et al., 2014).

In the *APPPS1-21* model, TREM2 was found to be expressed on plaque-associated myeloid cells that lack phenotypic features of microglia, such as low expression of CD45 and high expression of the purinoceptor P2RY12 (Jay et al., 2015). Based on these results, Jay and colleagues proposed that the myeloid cells that cluster around Aβ plaques originate from peripheral blood monocytes that are recruited to the brain rather than from resident microglia, and that TREM2 is required for such recruitment (Fig. 2). Interestingly, in this study, lack of TREM2 resulted in reduced accumulation of Aβ in 4-month-old mice (Jay et al., 2015). Therefore, the authors posited a detrimental role for TREM2 in AD pathology, through a yet undefined mechanism.

In the third of these studies, haploinsufficiency of TREM2 in the *APPPS1-21* model had no effect on Aβ pathology in 3-month-old mice (Ulrich et al., 2014). Thus, although there is a consensus that TREM2 is required for microgliosis, the origin of the microglia surrounding Aβ plaques and their impact on Aβ accumulation remain controversial (Tanzi, 2015).

It is possible that, although the microglial response to Aβ occurs very early in the progression of disease in these models, Aβ accumulation itself may require much longer. Therefore, discrepancies in the effects of TREM2 deficiency on Aβ accumulation may be the result of varied timing of the analyses performed in the different studies (8, 4, and 3 months in Wang et al., 2015; Ulrich et al., 2014; and Jay et al., 2015, respectively). A time-course analysis of

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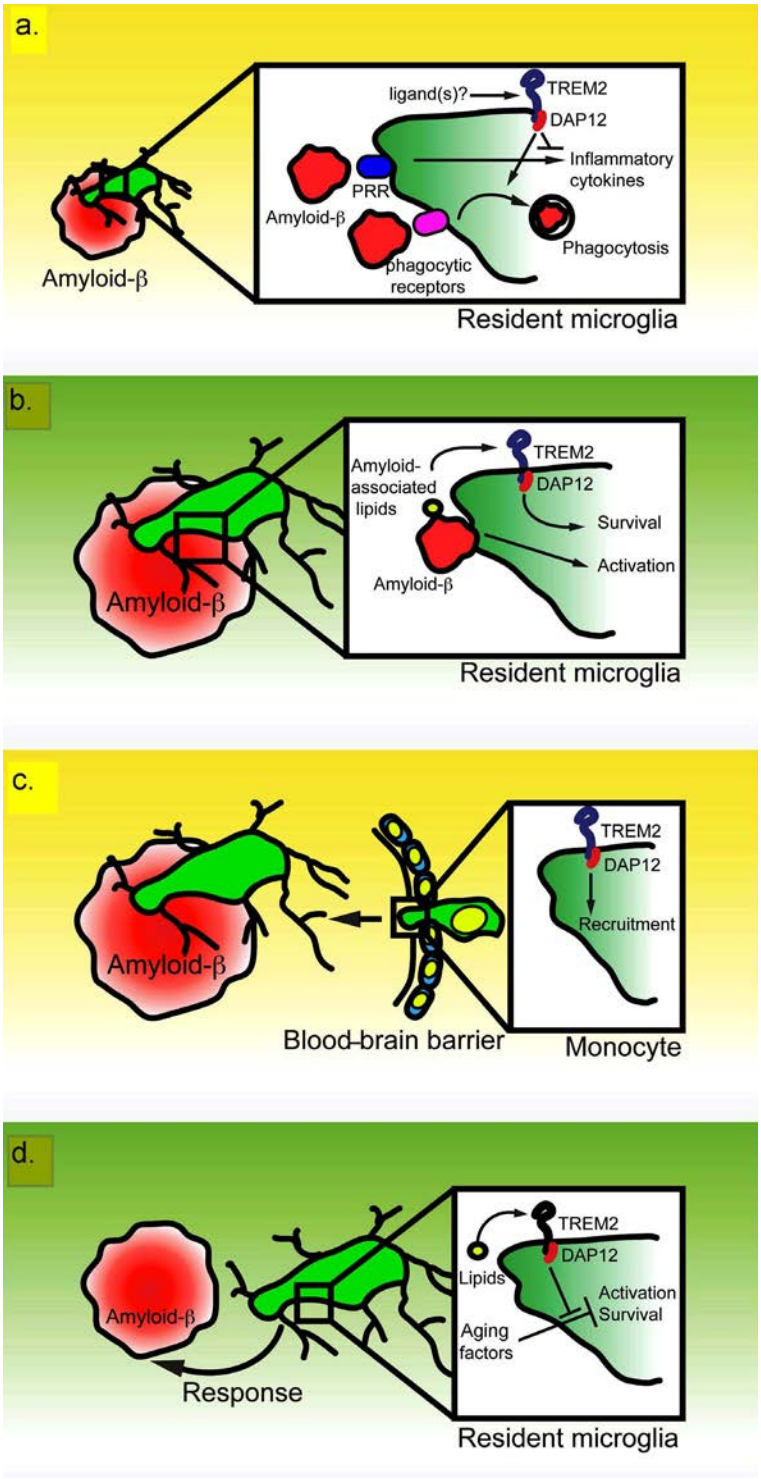

Figure 2. Potential models of TREM2 function in microglial response to AD. ***a,*** According to one model, TREM2 in resident microglia promotes phagocytosis and removal of apoptotic cells. Moreover, TREM2 limits inflammation by interfering with the ability of pattern recognition receptors (PRRs) to transmit pro-inflammatory signals at amyloid recognition; ***b,*** A second model suggests that TREM2 signals sustain the long-term survival of microglia in response to lipids that may become exposed during AD due to cell death, myelin degradation, and generation of Aβ complexes with phospholipids. Thus, TREM2 enables and sustains activation of microglia by PRRs or other receptors that sense Aβ deposition; ***c,*** A third model suggests that TREM2 expression on peripheral monocytes promotes their recruitment through the BBB to the Aβ plaque; ***d,*** a fourth model suggests that, on sensing brain lipid components, TREM2 delivers a tonic signal that delays aging of microglia by contrasting yet undefined aging risk factors. Modified with permission from Colonna M and Wang Y (2016), Figure 2. Copyright 2016, Nature Publishing Group.

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Aβ accumulation may be helpful to settle these discrepancies. Furthermore, in these studies Aβ accumulation was examined in two distinct *Trem2*$^{-/-}$ mouse lines in which the mutations targeted different regions of the *TREM2* gene. It is therefore possible that the discrepancies may be related to yet undefined disruptions of the *Trem* locus engendered during targeting, which may affect the expression of other TREM family members that are also involved in AD. Deriving the complete sequence of the targeted *Trem* locus will be necessary to address this possibility.

It is noteworthy that, beyond the discrepancies in the findings on Aβ accumulation, all studies demonstrated pathological changes that occurred preferentially in the hippocampus, perhaps suggesting a region-specific role for TREM2 that should be further investigated. In addition to Aβ pathology, it will be important to determine the impact of TREM2 deficiency on aggregates of hyperphosphorylated tau and neurite dystrophy. Behavioral studies may also be beneficial for evaluating the overall impact of TREM2 deficiency on Aβ and tau–mediated neuronal damage (Rivest, 2015).

Origin of Aβ-reactive microglia

During embryogenesis, microglia progenitors develop in the yolk sac and migrate into the primitive brain, where they expand and differentiate into mature microglia that self-renew by slowly dividing throughout life (Gomez Perdiguero et al., 2013; Greter and Merad, 2013). However, in inflammatory conditions, microglia-like cells can be generated from circulating monocytes that cross the blood–brain barrier (BBB). It is unclear whether the Aβ-reactive microgliosis that has been observed involves cells derived from resident microglia or infiltrating monocytes. This has been difficult to resolve for various reasons. In particular, surface marker–based identification of cellular origin has proven unreliable. Peripheral blood monocytes have unique phenotypic features, such as C-C chemokine receptor type 2 (CCR2) expression; however, once they infiltrate the brain, they quickly downregulate CCR2 and undergo molecular reprogramming to adopt features similar to those of resident microglia. These features include morphology, plaque association, and expression of allograft inflammatory factor 1 (AIF1, also known as IBA1) and TREM2 (Varvel et al., 2012). Additionally, although several novel microglia-specific markers have recently been identified (Hickman et al., 2013; Butovsky et al., 2014; Zhang et al., 2014), it is possible that their expression may be altered after activation or influenced by inflammatory stimuli, as shown for P2RY12, which is downregulated during LPS-induced inflammation and in the *SOD1* model of amyotrophic lateral sclerosis (ALS) (Haynes et al., 2006; Butovsky et al., 2015).

Other techniques to distinguish between the contributions of brain resident microglia and bone-marrow-derived cells to reactive microgliosis are based on bone marrow grafts, which replace monocytes but not resident microglia. However, whole-body irradiation before bone marrow grafts increases permeability of the BBB, inducing an artificial influx of blood monocytes into the brain (Mildner et al., 2011). To overcome these obstacles, parabiosis experiments can be performed in which TREM2-sufficient and TREM2-deficient strains developing Aβ accumulation are surgically joined to facilitate exchange of peripheral blood, leaving the BBB unaltered. Preliminary data suggest that, in these settings, myeloid cells clustered around Aβ plaques derive from resident microglia (Wang et al., 2016). Two very recent studies examined an experimental model in which resident microglia are depleted by intracranial administration of gangliocyclovir and replaced with blood monocytes. These studies showed that the blood monocytes that repopulate the brain after microglial depletion express TREM2 and cluster around Aβ deposits only after a long period of time. Moreover, these myeloid cells fail to modify the Aβ load, despite adopting features of microglia (Prokop et al., 2015; Varvel et al., 2015). Thus, peripheral monocytes may be incapable of becoming fully functional microglia or may require a yet undefined process of maturation.

TREM2 expression in blood monocytes during AD

Early work in healthy donors detected TREM2 only in tissue macrophages as well as dendritic cells and macrophages cultured *in vitro*, but not in appreciable quantities in blood monocytes (Bouchon et al., 2001; Cella et al., 2003). However, more recent studies reported increased TREM2 expression on blood monocytes from some AD patients (Hu et al., 2014) as well as a decrease in the TREM1:TREM2 expression ratio in these cells (Chan et al., 2015). The mechanisms by which TREM2 expression may be controlled during AD remains unclear. TREM2 could be induced on human monocytes by CSF-2 and IL-4 (Bouchon et al., 2001; Cella et al., 2003) and/or RXR ligands (Daniel et al., 2014; Lefterov et al., 2015). Moreover, a recent study proposed that CD33 signaling can promote TREM2 expression in monocytes (Chan et al., 2015). Whether these mechanisms are active in AD and the pathogenetic impact of altered TREM2 expression on blood monocytes remain to be investigated.

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TREM2's role in preventing microglial aging

Aging is the most important risk factor for AD. It has been proposed that microglial dysfunction is part of the normal aging process and contributes to AD pathology (Streit, 2006; Streit et al., 2009; Hefendehl et al., 2014). Can TREM2 deficiency accelerate senescence by progressively disabling the capacity of microglia to respond to degenerative processes? A recent study revealed that aged TREM2-deficient mice have significantly reduced numbers of microglia in the white matter (Poliani et al., 2015). Moreover, microglia of aged TREM2-deficient mice acquire a dystrophic morphology that is reminiscent of senescent microglia in humans (Streit, 2006; Poliani et al., 2015). A similar phenotype was also observed in aged DAP12-deficient mice (Otero et al., 2009). These studies suggest that the TREM2–DAP12 complex, stimulated by the lipid-rich environment of the brain, may deliver a continuous tonic signal that sustains microglial survival and preserves normal microglial function over time (Fig. 2).

A possible role for soluble TREM2

One intriguing feature of TREM2 biology is that the extracellular portion of TREM2 is shed by proteases like ADAM10 (a disintegrin and metalloproteinase domain-containing protein 10) and γ-secretase (Wunderlich et al., 2013; Kleinberger et al., 2014). This has two consequences. First, a soluble form of TREM2 (sTREM2) is released into the CNS, which can then be detected in the cerebrospinal fluid (Piccio et al., 2008; Kleinberger et al., 2014). Second, a C-terminal fragment of TREM2 remains inserted in the microglial plasma membrane in association with DAP12. This C-terminal fragment is cleaved by γ-secretase, releasing bound DAP12 (Wunderlich et al., 2013). It has been observed that the concentration of sTREM2 in the cerebrospinal fluid correlates with the levels of tau in the cerebrospinal fluid (Lill et al., 2015). Thus, sTREM2 may be an effective biomarker of microglial activation in response to neurodegeneration and neuronal injury. Whether sTREM2 and/or the C-terminal fragment has any biological function remains unclear. It is possible that sTREM2 acts as a decoy or scavenger receptor, binding phospholipids and/or apoptotic cells. Cleavage of the C-terminal fragment may increase the bioavailability of DAP12 for native TREM2 or other DAP12-associated receptors (Wunderlich et al., 2013). Failure of this cleavage may lead to sequestration of DAP12 at the cell surface, altering DAP12 signaling. Thus, it is important to investigate the biological significance of TREM2 shedding and whether AD-associated *TREM2* variants affect this process.

TREM2 and Other AD Risk Factors

Because TREM2 is one of multiple immune-related genes expressed in microglia and implicated in the pathogenesis of AD, it is possible that some of these genes are functionally connected and belong to common pathways that may be targeted for future therapeutic intervention. Using network analysis, highly preserved immune and/or microglia modules in normal and AD human brains have been detected in which TREM2, DAP12, CD33, and the gamma chain of Fc receptors are key nodes (Forabosco et al., 2013; Zhang et al., 2013). More recent data provide some experimental support for this systems biology data. CD33 is an inhibitory receptor expressed on microglia that recruits protein tyrosine phosphatases through cytoplasmic tyrosine-based inhibitory motifs (ITIMs). A variant that confers enhanced expression of CD33 is associated with increased risk for AD (Bertram et al., 2008; Hollingworth et al., 2011; Naj et al., 2011; Bradshaw et al., 2013; Griciuc et al., 2013). This CD33 variant was shown to be associated with increased expression of TREM2 and antibody-mediated suppression of CD33-moderated TREM2 expression on blood monocytes (Chan et al., 2015). Thus, TREM2 may lie downstream of CD33 (Chan et al., 2015). Alternatively, because TREM2 sustains microglial activation through ITAM signaling, and CD33 inhibits microglial activation through ITIM signaling, either impaired TREM2 function or increased CD33 function may result in altered intracellular tyrosine phosphorylation that facilitates microglial dysfunction and AD. In addition to TREM2 and CD33, TREM1 has been linked to AD (Replogle et al., 2015). Because TREM2 and TREM1 share DAP12 as a signaling adapter, it is possible that variants affecting the expression of TREM1 may impact the expression and signaling properties of TREM2 and vice versa.

Given that TREM2 is a lipid sensor, it is possible that TREM2 interacts with AD risk factors involved in lipid metabolism, such as apolipoprotein E (ApoE). The ε4 allele of ApoE is a major risk factor for non–autosomal dominant forms of early-onset AD (Corder et al., 1993; Strittmatter et al., 1993). Moreover, ApoE is the most abundant lipoprotein in the brain for lipid transport and can aggregate with amyloid plaques (Namba et al., 1991; Wisniewski and Frangione, 1992). Thus, the association of both *TREM2* and *APOE* polymorphisms with AD may reflect a functional interface. Accordingly, recent biochemical approaches have shown interactions between TREM2 and ApoE *in vitro* (Atagi et al., 2015; Bailey et al., 2015), suggesting that ApoE may act as a ligand to stimulate microglial function through

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TREM2. Future *in vivo* studies will be important to determine whether functional deficiencies of ApoE and TREM2 have similar impact on AD pathology.

TREM2 in Other Diseases

In addition to AD, *TREM2* variants have been found to be associated with other neurodegenerative diseases, such as frontotemporal lobar degeneration (FTD) (Guerreiro et al., 2013b,c; Lattante et al., 2013; Borroni et al., 2014; Cuyvers et al., 2014; Le Ber et al., 2014; Ruiz et al., 2014), ALS (Cady et al., 2014; Lill et al., 2015), and Parkinson's disease (Rayaprolu et al., 2013; Lill et al., 2015), suggesting that TREM2 deficiency may be a general risk factor for microglial dysfunction and neurodegeneration. However, the precise impact of TREM2 in these human pathologies is not clear because *TREM2* variants are extremely rare and the analysis of small cohorts has generated conflicting results (Thelen et al., 2014; Lill et al., 2015).

Studies of a mouse model of demyelination caused by administration of cuprizone, a toxic agent that kills oligodendrocytes, showed that TREM2 deficiency impairs the ability of microglia to remove damaged myelin and hinders subsequent remyelination (Cantoni et al., 2015; Poliani et al., 2015). TREM2 deficiency in mouse models of stroke also resulted in reduced inflammatory response (Sieber et al., 2013) as well as reduced microglial activation and phagocytosis of injured neurons, impaired neurological recovery, and ultimately, less viable brain tissue (Kawabori et al., 2015). Finally, clinical symptoms in an experimental mouse model of autoimmune encephalitis improved after adoptive transfer of myeloid cells expressing TREM2 but became worse after TREM2 blockade with a monoclonal antibody (Piccio et al., 2007; Takahashi et al., 2007). These *in vivo* studies support a general role for TREM2 in controlling the microglial response to pathological changes in the CNS.

Future Perspectives

Although it is now well established that TREM2 binds lipids and that the R47H mutation impairs this capacity, it remains to be determined whether the other *TREM2* variants found in AD patients are also hypofunctional. These variants might also affect protein expression or folding, as reported for the glutamine-33-stop (Q33X) and threonine-66-methionine (T66M) mutations associated with NHD and FTD (Kleinberger et al., 2014). Elucidating the crystal structure of TREM2 will provide a structural basis for the involvement of particular amino acid residues, such as R47, in lipid binding. In addition to TREM2–lipid interactions, several studies have indicated that TREM2 may bind to nonlipidic ligands, such as heat shock protein 60 (Stefano et al., 2009) or act in concert with PlexinA1 as a coreceptor for the transmembrane semaphorin Sema6D (Takegahara et al., 2006). Moreover, it was shown that soluble fusion proteins containing the TREM2 extracellular domain can bind to the surface of multiple cells, especially in regions immediately surrounding amyloid plaques (Hsieh et al., 2009; Melchior et al., 2010). Future investigation will determine whether TREM2 recognizes alternative ligands and whether these interactions impact microglial function and AD pathogenesis. Finally, the identification of TREM2 as a potential protective factor in AD has prompted the design of drugs that may promote microglial responses to Aβ. It is likely that agonistic antibodies and activating ligands of TREM2 will contribute to therapeutic strategies in AD.

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