Role of triggering receptor expressed on myeloid cells 2 in neuroinflammation and neurodegeneration of the central nervous system

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Keywords
microglia; neurodegenerative disease; TREM2

Abstract
Triggering receptor expressed on myeloid cells 2 (TREM2) is a member of the TREM family of innate immune receptors. It is expressed on the cell membrane of myeloid lineage cells including osteoclasts and microglia. Since it was reported that rare TREM2 variants, such as R47H and R62H, increase the risk of late-onset Alzheimer's disease, it has been pointed out that many TREM2 variants relate to other neurodegenerative diseases, including amyotrophic lateral sclerosis, Parkinson's disease and frontotemporal dementia. Although there are still conflicting reports as to whether TREM2 promotes or suppresses neurodegenerative or neuroinflammatory diseases, TREM2 has recently been considered to play a key role in the concept of disease-associated microglia. In disease-associated microglia induction, TREM2 might have a role as a microglia-specific checkpoint.

TREM2
Triggering receptor expressed on myeloid cells 2 (TREM2) is a member of the TREM family, a class of innate immune receptors. It is expressed on the cell membrane of myeloid lineage cells, including osteoclasts and microglia. It is associated with the signaling molecule TYRO protein tyrosine kinase binding protein 12 kDa transmembrane protein (DAP12), and TREM2 ligands cause the phosphorylation of the immunoreceptor tyrosine-based activation motif in the cytoplasmic domain of DAP12 (Fig. 1). DAP12 is not only the co-receptor for TREM2, but also for many other receptors, including CD158, NKG2C, Ly49, signal regulatory protein beta 1 and translocating chain-associated membrane protein 1, which are expressed by natural killer cells, T cell subsets and myeloid lineage cells. TREM2/DAP12 signaling induces phosphorylation of the extracellular signal-regulated kinase. It is also known that TREM2 negatively regulates Toll-like receptor signaling. In the latter case, TREM2 signaling can inhibit the production of inflammatory cytokines, such as tumor necrosis factor-α, after Toll-like receptor and Fcγ receptor stimulation. As a most prevalent explanation of this multifaceted TREM2 signaling, a model of activating versus tonic receptor engagement by multivalent, high-affinity versus monovalent, low-affinity ligands is considered (Fig. 2).

TREM2 ligands
Various molecules have been reported as ligands for TREM2. In 2003, Gram-positive and Gram-negative bacteria, such as Escherichia coli, Staphylococcus aureus, Proteus mirabilis and Streptococcus pyogenes; fungus, such as Candida guilliermondii; and an astrocytoma cell line, as well as polyanionic molecules, were identified as TREM2 ligands. Furthermore, it has been reported that TREM2 can bind to various cells and cell-derived molecules, such as apoptotic neuronal cells; anionic molecules derived from apoptotic cells, such as phosphatidylethanolamine, phosphatidylinerine (PS) and cardiolipin; heat shock protein 60; and apolipoprotein (Apo) including ApoE. Among the various identified TREM2 ligands, the affinity between TREM2 and
phosphatidyserine is very high, whereas the affinity between TREM2 and heat shock protein 60 is very low (Fig. 2). Furthermore, the affinity between TREM2 and ApoE can be changed by TREM2 variants. The R47H variant has a weak ApoE binding, which leads to reduced TREM2 signaling compared with wild-type TREM2.

Figure 1 Scheme of the triggering receptor expressed on myeloid cells 2 (TREM2)/12 kDa transmembrane protein (DAP12) complex. Some disease-associated coding variants are shown on the right side. Syk, spleen tyrosine kinase; TYRO, protein tyrosine kinase binding protein.

Figure 2 Scheme of the multifaceted triggering receptor expressed on myeloid cells 2 (TREM2) signaling model. Multivalent, high-affinity binding between TREM2 and phosphatidyserine (PS) leads to an activating signal (left), whereas monovalent, low-affinity binding between TREM2 and HSP60 leads to an inhibitory signal (right). HSP60, heat shock protein 60.

Soluble form of TREM2

ADAM proteases can proteolytically cleave TREM2. Its extracellular domain is then released into the extracellular space as a soluble form (sTREM2), while the transmembrane and intracellular domain undergo degeneration by γ-secretases. sTREM2 is
detected in human samples, including blood plasma and cerebrospinal fluid, and has been implicated in the development of neuroinflammatory or neurodegenerative diseases, such as Alzheimer’s disease (AD) and multiple sclerosis (MS).\textsuperscript{17,18} It has been reported that sTREM2 promotes microglial survival in a phosphatidylinositol 3-kinase/protein kinase B-dependent manner, and stimulates the nuclear factor-kappa B-dependent production of inflammatory cytokines.\textsuperscript{19} Interestingly, sTREM2 derived from the rare variants, R47H and R62H (sTREM2-R47H and sTREM2-R62H), which are associated with AD, are less potent in both suppressing apoptosis and triggering pro-inflammatory responses.\textsuperscript{19}

\textbf{TREM2 and autoimmune diseases of the central nervous system}

MS is considered as a Th1-mediated demyelinating autoimmune disease of the central nervous system.\textsuperscript{20} As polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL), which is an autosomal recessive disease caused by loss of function of either DAP12 or TREM2, also shows demyelinating white matter lesions, TREM2/DAP12 gene mutations were examined in Finnish MS patients.\textsuperscript{21} However, there is no evidence of an association of TREM2/DAP12 polymorphisms with MS.\textsuperscript{21} Furthermore, PLOSL mutations detected in the general Finnish population were not more prevalent in Finnish MS patients.\textsuperscript{21} In contrast, studies have investigated the treatment of experimental autoimmune encephalomyelitis (animal model of MS) by TREM2 gene transfer.\textsuperscript{22} When TREM2-transduced bone marrow-derived myeloid precursor cells were injected intravenously into experimental autoimmune encephalomyelitis mice, these cells facilitated the repair within the experimental autoimmune encephalomyelitis lesions in the murine central nervous system through clearance of cellular debris.\textsuperscript{22} A relationship between sTREM2 and MS has also been reported.\textsuperscript{18,23} Compared with controls including patients with non-inflammatory neurologic diseases, sTREM2 levels in the cerebrospinal fluid were significantly higher in patients with relapsing–remitting MS, primary progressive MS and secondary progressive MS, as well as in patients with other inflammatory neurological diseases.\textsuperscript{18,23} Furthermore, after treatment with natalizumab or mitoxantrone, sTREM2 levels in the cerebrospinal fluid were significantly decreased to the levels of control participants.\textsuperscript{23}

\textbf{TREM2 and neurodegenerative diseases}

Recently, disease-associated microglia (DAM), a subset of microglia expressing unique surface markers and having unique functional signatures, were discovered in AD mice by using massively parallel single-cell RNA-seq and an index-sorting strategy that allowed for a retrospective analysis of single-cell surface marker combinations.\textsuperscript{36} Further studies led to the discovery of DAM-like phenotypes not only in other neurodegenerative diseases, such as amyotrophic lateral sclerosis\textsuperscript{37} and MS,\textsuperscript{38} but also in aging.\textsuperscript{38} Although DAM were primarily detected in regions such as those with amyloid $\beta$ ($\beta$) plaques in the central nervous system,\textsuperscript{36} DAM also appear

\begin{table}[h]
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\textbf{Disease} & \textbf{TREM2 form} & \textbf{Possible role of TREM2} & \textbf{References} \\
\hline
Nasu–Hakola disease & Complete lack of TREM2 signal (E14X, etc.) & Impaired osteoclast differentiation and inefficient clearance of apoptotic neuronal and myelin debris by microglia & 2,24,25 \\
 & K186N & Defect of signal transduction due to loss of the conserved lysine residue & 26 \\
Alzheimer’s disease & R47H & Impaired interaction of TREM2 with neurons and plaques during amyloid-beta accumulation & 27 \\
 & R62H & AD risk factor – reduced ligand affinity and signaling response & 28,29 \\
 & T96K & AD risk factor – increased ligand affinity and signaling response & 28,29 \\
 & H157Y & AD risk, TREM shedding by cleavage & 30 \\
 & L211P & AD risk, unknown, low level of soluble TREM2 in CSF & 31 \\
Parkinson’s disease & & & 32,33 \\
Amyotrophic lateral sclerosis & R47H & ALS risk factor – reduced ligand affinity and signaling response & 28,29,34,35 \\
Essential tremor & R47H & ET risk factor – reduced ligand affinity and signaling response & 28,29,35 \\
Multiple sclerosis & Soluble TREM2 & Inhibition of anti-inflammatory function of membrane-bound TREM2 & 18 \\
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\caption{Role of triggering receptor expressed on myeloid cells 2 as a risk factor for neurodegenerative diseases}
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AD, Alzheimer’s disease; ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; ET, essential tremor; TREM2, triggering receptor expressed on myeloid cells 2.
under conditions characterized by the accumulation of apoptotic neuronal cells and myelin debris in regions affected by conditions such as amyotrophic lateral sclerosis, AD and demyelinating diseases. These results show that DAM plays a protective role against neuronal damage. It is believed that at an early stage, DAM protects against disease progression, whereas at a late stage, they become dysregulated and accelerate the disease progression.39 DAM express microglial markers, such as ionized calcium-binding adapter molecule 1 and TREM2, and downregulate “homeostatic” microglial markers, such as transmembrane protein 119, cluster of differentiation 33, CX3C chemokine receptor 1 and purinergic receptor P2Y12.36,38 Although M1 microglia, another activation form of microglia, also downregulate homeostatic microglial markers, M1 microglia suppress ApoE expression, whereas DAM induce ApoE expression.38 DAM-like cells are also found in post-mortem brains of AD patients.36 A recent study reported that TREM2 plays an important role in the induction of DAM.38 The TREM2–ApoE signaling pathway mediates a switch from homeostatic resting (ramified) microglia to DAM.38 DAM are considered to be induced by a two-step signal (Fig. 3).36,39 Although the signals to stage 1 DAM are still unknown, the signals to stage 2 DAM are dependent on TREM2 (Fig. 3).38,39 Knockout of TREM2 abolishes the TREM2–ApoE signaling pathway and restores homeostatic microglia by suppressing the induction of DAM, which leads to an attenuation of neurodegenerative diseases.38

**TREM2 variants and neurodegenerative diseases**

Since it was reported that rare TREM2 variants, such as R47H and R62H, increase the risk of late-onset AD,40,41 it has been pointed out that many TREM2 variants relate to other neurodegenerative diseases, including amyotrophic lateral sclerosis,34 Parkinson’s disease42 and frontotemporal dementia (Table 1).43 Although the variant 140C>T in exon 2 of the TREM2 gene (protein, R47H) is involved in neurodegenerative diseases and essential tremor,35 it lies within a region that forms a basic patch on the surface of TREM2 that is thought to be critical for association with anionic ligands.44 TREM2 variants associated with neurodegenerative diseases can occur in almost every exon constructing the protein motifs; for example, the PLOSL-associated 40G>T variant in exon 1 of the TREM2 gene (protein, E14X; signal sequence peptide region),25 the AD-associated 469C>T variant in exon 3 of the TREM2 gene (protein, H157Y), the PLOSL-associated 588G>A variant in exon 4 of the TREM2 gene (protein, K186N; transmembrane domain)26 or the AD- and frontotemporal dementia-associated 632C>T variant in exon 4 of the TREM2 gene (protein, L211P; intracellular domain; Fig. 1).43,45 These neurodegenerative disease-associated TREM2 variants show either an enhanced or attenuated TREM2 signaling compared with the TREM2 wild type.28 For example, the R47H variant, the most famous AD-associated variant, does not change the surface expression of TREM2, but reduces ligand affinity, signaling response, phagocytosis and microgliosis.44 In contrast, the T96K variant increases ligand affinity and signaling response.44 Interestingly, R47H and T96K have the opposite effect on the TREM2 signaling pathway, but both are risk factors for AD.

**Conclusion**

Although there are still conflicting reports as to whether TREM2 promotes or suppresses neurodegenerative or neuroinflammatory diseases, TREM2 has recently been considered to play a key role in the concept of DAM. In DAM induction, TREM2 might have a function of a microglia-specific checkpoint, which provides a new therapeutic approach for many neurodegenerative diseases similar to programmed cell death 1 inhibitors for many cancers.

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Conflict of interest
None declared.

References