**Microglial TREM2/DAP12 Signaling: A Double-Edged Sword in Neural Diseases**

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Microglia are activated after neuronal injury and in neurodegenerative diseases, and trigger neuroinflammation in the central nervous system (CNS). Microglia-derived neuroinflammation has both beneficial and detrimental effects on neurons. Because the timing and magnitude of microglial activation is thought to be a critical determinant of neuronal fate, understanding the molecular mechanisms underlying microglial activation is required to enable establishment of microglia-targeted therapies for neural diseases. Plasma membrane receptors play primary roles as activators of microglia and in this review, we focus on a receptor complex involving triggering receptor expressed on myeloid cells 2 (TREM2) and DNAX-activating protein of 12 kDa (DAP12), both of which are causative genes for Nasu-Hakola disease, a dementia with bone cysts. Recent transcriptome approaches demonstrated TREM2/DAP12 signaling as the principal regulator that transforms microglia from a homeostatic to a neural disease-associated state. Furthermore, animal model studies revealed critical roles for TREM2/DAP12 in the regulation of microglial activity, including survival, phagocytosis, and cytokine production, not only in Alzheimer’s disease but also in other neural diseases, such as Parkinson’s disease, demyelinating disease, ischemia, and peripheral nerve injury. Intriguingly, while TREM2/DAP12-mediated microglial activation is detrimental for some diseases, including peripheral nerve injury, it is beneficial for other diseases. As the role of activated microglia differs among disease models, TREM2/DAP12 signaling may result in different outcomes in different diseases. In this review we discuss recent perspectives on the role of TREM2/DAP12 in microglia and their contribution to neural diseases.

**Keywords:** damage, degeneration, inflammation, injury, ITAM, regeneration, Syk, TYROBP

**INTRODUCTION**

Microglia are macrophage-like myeloid cells in the central nervous system (CNS). Besides macrophage-related immunological functions, microglia play CNS-specific roles, such as maintenance of brain homeostasis and modulation of neural circuits (Wake et al., 2009; Paolicelli et al., 2011; Parkhurst et al., 2013; Ueno et al., 2013). Microglia exhibit a ramified morphology in the healthy adult brain and they survey their surrounding area with motile processes under physiological conditions (Davalos et al., 2005; Nimmerjahn et al., 2005; Hanisch and Kettenmann, 2007). However, upon neuronal injury and in neurodegenerative diseases, microglia become activated, and transform into a hypertrophic or ameboid shape (Lobsiger et al., 2013; Roth et al., 2014; Fernández-Arjona et al., 2017). Activated microglia are thought to have opposing functions...
They secrete a variety of neurotrophic factors to protect damaged neurons and phagocytose cellular debris to enable tissue regeneration (Nakajima and Kohsaka, 2004; Neumann et al., 2009); however, when microglia are excessively activated, they can damage neurons by secreting neurotoxic molecules, such as nitric oxide (NO) and reactive oxygen species (ROS), and eventually phagocytose injured neurons (Block et al., 2007; Brown and Neher, 2014; Fu et al., 2014). Thus, microglia may be critical determinants of neuronal fate and establishing a method to effectively control microglial activity would contribute to the treatment of neural diseases.

Receptors expressed on the microglial surface play roles in sensing environmental changes around microglia and regulate their activation (Kierdorf and Prinz, 2013). In this regard, recently there has been focus on a receptor complex, the triggering receptor expressed on myeloid cells 2 (TREM2), and the DNA-activating protein of 12 kDa (DAP12) [also known as TYRO protein kinase-binding protein (TYROBP) or killer cell activating receptor-associated protein (KARAP)]. As TREM2 is a strong risk factor for Alzheimer’s disease (AD) in humans and was recently demonstrated to be a critical regulator of microglial activity in mouse models of AD (Guerreiro et al., 2013; Jonsson et al., 2013; Jay et al., 2015; Wang et al., 2015; Keren-Shaul et al., 2017; Ulland et al., 2017), many articles have reviewed the recent progress of TREM2/DAP12 research in AD (Ma et al., 2015; Colonna and Wang, 2016; Mecca et al., 2018). However, TREM2/DAP12 have also been shown to control microglial activity and consequently affect the fate of damaged neurons after neuronal injury and in neurodegenerative diseases besides AD. In this review, we start with a brief introduction of the TREM2/DAP12 complex, shortly summarize the studies of TREM2/DAP12 in AD and then highlight the roles of TREM2/DAP12 in other animal models of neural disease.

THE TREM2/DAP12 COMPLEX

The immunoreceptor tyrosine-based activation (ITAM) motif in the intracellular domain of some transmembrane proteins generates an activation signal in leukocytes (Camberi, 1995).

Abbreviations: Aβ, β-amyloid; AD, Alzheimer’s disease; ADAM, a disintegrin and metalloproteinase; ALS, amyotrophic lateral sclerosis; ApoE, apolipoprotein E; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CSF1R, colony-stimulating factor-1 receptor; DAP12, DNA-activating protein of 12 kDa; EAE, experimental autoimmune encephalomyelitis; ERK, extracellular signal-regulated protein kinase; IFN, interferon; IL, interleukin; ITAM, immunoreceptor tyrosine-based activation; KARAP, killer cell activating receptor-associated protein; KO, knockout; MPP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MMP, 1-methyl-4-phenylpyridinium; mTOR, mammalian target of rapamycin; NO, nitric oxide; NE, nuclear factor; 6-OHDA, 6-hydroxydopamine; PD, Parkinson’s disease; P3K, phosphatidylinositol 3-kinase; PLCγ, phospholipase Cγ; PLOS1, polycystic lipomembranous osteodysplasia with sclerosis leukoencephalopathy; ROS, reactive oxygen species; Siglec-H, sialic acid-binding immunoglobulin-like lectin H; SOD1, superoxide dismutase 1; sTREM2, soluble TREM2; TNF, tumor necrosis factor; TREM2, triggering receptor expressed on myeloid cells 2; TYROBP, TYRO protein kinase-binding protein; WT, wild-type.

DAP12 was identified as an ITAM-containing, disulfide bond-linked homodimer expressed on natural killer cells (Lanier et al., 1998). Because of its short extracellular domain, DAP12 itself is thought to have no ligand-binding capability. Instead, DAP12 forms complexes with some ligand-binding receptors (DAP12-associated receptors) and transduces signals from DAP12-associated receptors into the cytoplasm (Figure 1A). TREM2 was initially identified as a TREM1 homolog in an expressed sequence tag database (Bouchon et al., 2000) and was later shown to bind to DAP12 via oppositely-charged residues in their transmembrane domains (Bouchon et al., 2001; Daws et al., 2001). Upon ligand binding to TREM2, tyrosine residues within ITAM are phosphorylated, recruiting Syk kinase to activate downstream signaling molecules such as extracellular signal-regulated protein kinase (ERK), phosphatidylinositol 3-kinase (PI3K), phospholipase Cγ (PLCγ), and Vav (Takahashi et al., 2005; Otero et al., 2009; Peng et al., 2010; Wang et al., 2015; Colonna and Wang, 2016) (Figure 1A). Downstream signals from DAP12 and colony-stimulating factor-1 receptor (CSF1R) show crosstalk; for example Src tyrosine kinase, the main effector of CSF1R signaling, phosphorylates the ITAM motif of DAP12 (Zou et al., 2008; Otero et al., 2009) (Figure 1A).

Although ITAM is generally considered a signaling motif leading to cellular activation, TREM2/DAP12 complex can also induce inhibitory signals (Hamerman et al., 2006; Turnbull et al., 2006). This enigmatic function is hypothesized to result from the ligand affinity/avidity of DAP12-associated receptors (Turnbull and Colonna, 2007) (Figure 1B). When a low affinity/avidity ligand binds to a DAP12-associated receptor, the ITAM motif of DAP12 becomes partially, not fully, phosphorylated. The partial phosphorylation of ITAM recruits the SH2 domain-containing protein tyrosine phosphatase SHP-1, leading to dephosphorylation of downstream targets of Syk kinase, and inhibition of cellular activation (Peng et al., 2010).

TREM2/DAP12 IN NEURAL DISEASES

The functions of TREM2/DAP12 in neural diseases are summarized in Table 1 (excluding AD) and Figure 2.

TREM2/DAP12 in AD

After the discovery of the TREM2/DAP12 complex in the immune system, both molecules were sequentially identified as causative genes for Nasu-Hakola disease [also known as polycystic lipomembranous osteodysplasia with sclerosis leukoencephalopathy (PLOS1)], which is characterized by presenile dementia with bone cysts (Paloneva et al., 2000, 2002). Because TREM2 and DAP12 are predominantly expressed by microglia (Bakker et al., 2000b; Paloneva et al., 2001; Schmid et al., 2002), microglial dysfunction caused by TREM2/DAP12 impairment was assumed to be involved in the pathogenesis of Nasu-Hakola disease (Paloneva et al., 2000, 2001; Schmid et al., 2002). Almost a decade later, a breakthrough was made by studies demonstrating that a rare variant of TREM2 (loss-of-function mutation, R47H) is a risk factor for AD and frontotemporal dementia (Guerreiro et al., 2013; Jonsson et al., 2013). In the same period, DAP12 was also reported as a key regulator.
FIGURE 1 | Schematic representation of TREM2/DAP12 signaling in microglia. (A) Ligands and downstream signaling of TREM2/DAP12. Of the known TREM2 ligands, only ligands that highly correlate with neural diseases are shown. Upon ligand binding to TREM2, two tyrosine residues within the ITAM motif of DAP12 are phosphorylated, which recruits Syk kinase to activate downstream signaling molecules, such as ERK, PI3K, PLCγ, and Vav. Src, the main effector of CSF1R, is a kinase supposed to phosphorylate the ITAM tyrosine residues. The soluble form of TREM2, sTREM2, is generated by ectodomain shedding by ADAM 10 or 17, which activates PI3K, ERK, and NFκB via an unknown receptor. Note that parts of the signaling pathways are inferred from studies of other types of myeloid cells, such as macrophages and osteoclasts. (B) A putative mechanism by which TREM2/DAP12 generates opposing signals. Upon binding of high avidity ligands to TREM2, both tyrosine residues in the ITAM motif become phosphorylated and the recruited Syk kinase activates downstream signaling molecules, as shown in (A). Conversely, in the case of low avidity ligands, only partial phosphorylation occurs and then activated SHP-1 phosphatase dephosphorylates molecules downstream of Syk signaling to inhibit cellular activation.

of late-onset AD by an integrative network-based approach (Zhang et al., 2013). AD model mice crossed with Trem2- or Dap12-deficient strains revealed that the TREM2/DAP12 complex is involved in microglial activation around amyloid plaques to prevent accumulation and diffusion of β-amyloid (Aβ) (Wang et al., 2015, 2016; Yuan et al., 2016; Keren-Shaul et al., 2017). TREM2/DAP12-mediated signals activate mammalian target of rapamycin (mTOR) to support microglial biosynthetic metabolism; Trem2 deficiency impairs cellular metabolism and promotes increased autophagy in microglia in an AD mouse model (Ulland et al., 2017). Transgenic overexpression of human TREM2 modified the morphological and functional responses of microglia, which resulted in amelioration of the pathology and memory deficits in an AD mouse model (Lee et al., 2018). Although overall, TREM2/DAP12-dependent cellular activation appears to be beneficial, Jay et al. suggested the possibility that the functional consequence of TREM2/DAP12 signaling depends on the stage of AD, with detrimental effects at the early stage and beneficial effects at the late stage (Jay et al., 2015, 2017).

Regarding TREM2 ligands, a variety of molecules including bacterial components have been identified (Kober and Brett, 2017). Among the known ligands, lipids such as phospholipids and glycolipids, and DNA, in particular, are predicted to be related to the pathology of dementia, as these molecules are thought to be released from or exposed on damaged cells (Cannon et al., 2012; Kawabori et al., 2015; Poliani et al., 2015; Wang et al., 2015). Apolipoprotein E (ApoE) is also considered an AD-associated ligand of TREM2 (Atagi et al., 2015; Bailey et al., 2015; Yeh et al., 2016) because the APOE genotype is a strong risk factor for late-onset AD (Corder et al., 1993). Very recently, Aβ oligomers were reported to bind directly to TREM2 and induce microglial activation with increased expression of pro-inflammatory cytokines (Zhao et al., 2018). Therefore, TREM2 recognizes multiple ligands in the extracellular milieu of the AD brain and generates intracellular activation signals via its signal transduction partner, DAP12.

In addition to its role as a receptor, the ectodomain of TREM2 can itself activate microglia (Figure 1A). As is the case with some receptor molecules, the ectodomain of TREM2 undergoes shedding by proteases in the “a disintegrin and metalloproteinase” (ADAM) family, including ADAM10 and ADAM17 (Kleinberger et al., 2014; Feuerbach et al., 2017; Schlepckow et al., 2017). The resulting soluble TREM2 (sTREM2) promotes survival and pro-inflammatory responses of microglia via the PI3K and nuclear factor (NF)-κB pathway, respectively (Zhong et al., 2017a). Another possible function of sTREM2 is as an inhibitor of TREM2; sTREM2 acts as a decoy receptor that competitively binds to TREM2 ligands (Piccio et al., 2008; Zhong
et al., 2017a). As the concentration of sTREM2 in cerebrospinal fluid increases in AD patients, sTREM2 could be a potential biomarker for AD (Heslegrave et al., 2016; Piccio et al., 2016; Suárez-Calvet et al., 2016).

**Parkinson’s Disease (PD)**

In addition to Alzheimer’s disease, R47H and other variants of TREM2 are reported to be risk factors for PD (Benitez et al., 2013; Rayaprolu et al., 2013; Liu et al., 2016), although this remains controversial (Jonsson and Stefansson, 2013; Lill et al., 2015). Neuroinflammation caused by activated microglia is assumed to be detrimental in PD pathology. Activated microglia in the substantia nigra of the PD brain proliferate and produce neurotoxic molecules, such as NO, ROS and pro-inflammatory cytokines, resulting in progressive degeneration of dopaminergic neurons in a non-cell autonomous manner (Wu et al., 2003; Hu et al., 2008). Therefore, suppression of microgliosis and microglia-derived neurotoxicity is expected to be a therapeutic strategy for PD (Subramaniam and Federoff, 2017).

DAP12 function in a mouse model of PD was studied by two groups using KA75 knock-in mice, in which downstream signal transduction of DAP12 is impaired because of deletion of the cytoplasmic domain including the second ITAM motif (Tomaselto et al., 2000). In the 6-hydroxydopamine (6-OHDA) model of PD in KA75 mice, microgliosis and neurodegeneration were suppressed (Virgone-Carlotta et al., 2013). The 1-methyl-4-phenylpyridinium (MPP)/1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model also revealed reduced in vitro neurotoxicity of microglia derived from KA75 mice; however, no alteration of neuropathology in KA75 mice was observed in vivo (Kinugawa et al., 2013). Although the in vivo consequence was different, both studies support the possibility that microglial neurotoxicity is suppressed in Dap12-deficient microglia. This is reminiscent of the finding that developmental apoptosis of hippocampal neurons is suppressed, possibly due to reduced neurotoxicity of KA75 microglia with lower levels of, for example, ROS production (Wakselman et al., 2008). The Trem2 knockout (KO) mouse also demonstrated that Trem2 deficiency results in reduced microglial numbers and decreased expression of pro-inflammatory cytokines, although the attenuated inflammation did not affect neuronal fate in the MPTP model (Belloli et al., 2017). Taken together, a TREM2/DAP12 signal likely promotes activation of microglia and subsequent neuroinflammation in the PD brain, occasionally leading to degeneration of dopaminergic neurons. However, a very recent study reported a conflicting result (Ren et al., 2018). The authors overexpressed Trem2 using an adeno viral vector and showed that TREM2 overexpression attenuates pro-inflammatory responses of microglia and protects dopaminergic neurons from damage in the MPTP mouse model. In this study, TREM2 was presumably also transduced in cell types other than microglia and the ectopic expression of TREM2 may cause different results.

**Amyotrophic Lateral Sclerosis (ALS)**

Shortly after the identification of the TREM2 variant R47H as a risk factor for AD, it was also reported to be a risk factor for sporadic ALS (Cady et al., 2014), although some studies showed no correlation (Rayaprolu et al., 2013; Lill et al., 2015). While TREM2 as a risk factor for ALS is under debate, the concentration of sTREM2 protein is higher in the cerebrospinal fluid of ALS patients, and TREM2 was shown to be a member of the immune network module of ALS (Cooper-Knock et al., 2017). Given that microglia-derived neuroinflammation is involved in ALS pathology (Mohand-Said et al., 2017; Liu and Wang, 2017), TREM2 is thought to play a role in the regulation of microglial activity in ALS. Although the ALS pathology of Trem2- or Dap12-deficient mice remains unknown, the molecular expression profile of microglia is significantly changed in Trem2 KO mice with the superoxide dismutase 1 (SOD1)G93A mutation (Krasemann et al., 2017). In the SOD1G93A mouse model, the gene expression pattern of spinal microglia is altered, with downregulation of homeostatic genes and upregulation of inflammatory genes (Shaul et al., 2017; Krasemann et al., 2017). However, these alterations in gene expression are suppressed in Trem2-deficient microglia, suggesting that TREM2 is a key switch that transforms microglia from homeostatic to an ALS-associated phenotype (Krasemann et al., 2017).

**Demyelinating Disease**

Demyelination is one of the hallmarks of Nasu-Hakola disease (Verloes et al., 1997; Kobayashi et al., 2000). Adult Dap12 KO and Dap12 loss-of-function KA75 mice show reduced myelin in the brain, likely due to impaired myelination rather than demyelination (Kaifu et al., 2003; Natäf et al., 2005). Kaifu et al. found ectopic oligodendrocytes with aberrant differentiation near the hypomyelinated area in Dap12 KO mice. They showed DAP12 expression in cultured oligodendrocytes in addition to microglia, raising the possibility that the hypomyelination might be a cell-autonomous phenotype of Dap12-deficient oligodendrocytes. However, given that DAP12 is predominantly expressed in microglia in vitro (Roumier et al., 2004; Trash et al., 2009; Kobayashi et al., 2016), microglial dysfunction is suggested to be the primary cause of the hypomyelination phenotype observed in Dap12-deficient mice (Natäf et al., 2005). Some studies have demonstrated that microglia promote oligodendrocyte differentiation during remyelination after demyelination in the adult, as well as myelinogenesis in the neonate (Miron et al., 2013; Wlodarczyk et al., 2017). Both Dap12 KO and KA75 mice have fewer microglia, with aberrant morphology, although the degree differs between the two strains (Natäf et al., 2005; Otero et al., 2009). This loss of functional microglia is suggested to lead to impaired differentiation of oligodendrocytes in Dap12-deficient mice.

In contrast to the two strains of Dap12-deficient mice described above, Trem2 KO mice show no spontaneous abnormalities in myelin, even in aged mice, although in aged Trem2 KO mice, the microglial number is smaller than age-matched wild-type (WT) mice and microglial morphology is dystrophic in restricted regions of the brain, including the corpus callosum (Poliani et al., 2015). However, after cuprizone-induced demyelination, myelin debris accumulated and axonal damage was augmented in Trem2 KO mice (Cantoni et al., 2015; Poliani et al., 2015). Under demyelinating
### TABLE 1 | Microglial TREM2/DAP12 function in neural diseases other than AD.

| Disease model       | Manipulation tool                                      | Phenotype (↑: Increase, ↓: Decrease, → : No change) | Effect on neuronal fate | References                  |
|---------------------|---------------------------------------------------------|-----------------------------------------------------|-------------------------|-----------------------------|
| PARKINSON’S DISEASE |                                                          |                                                     |                         |                             |
| MPP (Mix culture)   | DAP12 loss-of-function mouse (KΔ75)                     | Loss of dopaminergic neuron ↓                       | DAP12: detrimental      | Kinugawa et al., 2013       |
| MPTP                | DAP12 loss-of-function mouse (KΔ75)                     | Microglial number → Loss of dopaminergic neuron →   | DAP12: No effect        |                             |
| 6-OHDA              | DAP12 loss-of-function mouse (KΔ75)                     | Microglial number ↓ Loss of dopaminergic neuron ↓   | DAP12: detrimental      | Virgone-Carlotta et al., 2013|
| MPTP                | TREM2 KO mouse                                          | Microglial number ↓ [11C]PK11195 uptake by microglia↑| TREM2: No effect        | Beliol et al., 2017         |
| MPTP                | TREM2 overexpression by adenovirus                      | Microglial number ↓ Pro-inflammatory molecule (IL-1β, TNF-α) ↓| TREM2: beneficial       | Ren et al., 2018            |
| DEMYELINATING DISEASE |                                                          |                                                     |                         |                             |
| EAE                 | DAP12 loss-of-function mouse (KΔ75)                     | Activation marker of microglia (MHCII) ↓ Number of infiltrating leucocytes ↓ EAE Severity (Clinical score) ↓ | DAP12: detrimental      | Bäkler et al., 2000a        |
| EAE                 | Transplantation of TREM2-transduced bone marrow-derived myeloid cells | Number of phagocytic cells ↑ Clearance of myelin debris ↑ Pro-inflammatory molecule (IL-1β, TNF-α, IFN-γ) ↓ Anti-inflammatory molecule (IL-10) ↑ Tissue damage of spinal cord ↓ EAE Severity (Clinical score) ↓ | TREM2: beneficial       | Takahashi et al., 2007      |
| EAE                 | TREM2 functional blocking antibody                      | Leucocytic infiltration ↑ Demyelination ↑ EAE Severity (Clinical score) ↑ | TREM2: beneficial       | Picco et al., 2007          |
| Cuprizone           | TREM2 KO mouse                                          | Microglial number ↓ Dystrophic morphology of microglia Pro-inflammatory molecule (IL-1β, IL-6, etc.) ↓ Phagocytic molecule (Axl) ↓ Molecules for lipid transport and metabolism (ApoE etc.) ↓ Clearance of myelin debris ↓ Axonal damage ↑ Remyelination ↓ | TREM2: beneficial       | Poliani et al., 2015        |
| Disease model                           | Manipulation tool | Phenotype (↑: Increase, ↓: Decrease, →: No change)                                                                                   | Effect on neuronal fate | References                   |
|----------------------------------------|-------------------|----------------------------------------------------------------------------------------------------------------------------------|------------------------|-----------------------------|
| Cuprizone                              | TREM2 KO mouse    | Microglial number ↓  
Less activated morphology of microglia  
Activation marker of microglia (Mac-3, MHCII) ↓  
Pro-inflammatory molecule (iNOS) ↓  
Molecules for lipid metabolism (Lipoprotein lipase) ↓  
Clearance of myelin debris ↓  
Axonal damage ↑  
Neurological deficit ↑ | TREM2: beneficial | Cantoni et al., 2015 |
| ISCHEMIA                               |                   |                                                                                                                                  |                        |                             |
| Transient middle cerebral artery occlusion | TREM2 KO mouse    | Microglial number ↓  
Pro-inflammatory molecule (IL-1α, IL-1β, TNF-α) ↓  
Phagocytic marker (CD68) ↓  
Infarct size → | TREM2: No effect | Sieber et al., 2013 |
| Permanent middle cerebral artery occlusion | TREM2 KO mouse    | Number of IB4+ activated microglia ↓  
Number of CD68+ phagocytic microglia ↓  
Contact of microglia with apoptotic cells ↓  
Infarct size ↑  
Neurological deficit ↑ | TREM2: beneficial | Kawabori et al., 2015 |
| Transient middle cerebral artery occlusion | TREM2 siRNA       | Pro-inflammatory molecule (IL-1β, TNF-α) ↑  
Anti-inflammatory molecule (IL-10) ↓  
NF-κB phosphorylation ↑  
Number of apoptotic neuron ↑  
Infarct size ↑ | TREM2: beneficial | Wu et al., 2017 |
| Transient middle cerebral artery occlusion | TREM2 siRNA       | Pro-inflammatory molecule (iNOS) ↑  
Anti-inflammatory molecule (Arg-1) ↓  
Number of apoptotic neuron ↑  
Infarct size →  
Neurological deficit → | TREM2: beneficial | Zhai et al., 2017 |
| Trem2 overexpression by lentivirus      |                   | Pro-inflammatory molecule (iNOS) ↓  
Anti-inflammatory molecule (Arg-1) ↑  
Number of apoptotic neuron ↓  
Infarct size ↓  
Neurological deficit ↓ |                        |                             |
| Disease model                        | Manipulation tool     | Phenotype (↑: Increase, ↓: Decrease, →: No change)                                                                 | Effect on neuronal fate | References                   |
|-------------------------------------|----------------------|------------------------------------------------------------------------------------------------------------------|-------------------------|------------------------------|
| **PERIPHERAL NERVE INJURY**         |                      |                                                                                                                 |                         |                              |
| Motor nerve injury                  | DAP12 KO mouse       | Microglial number ↓<br>Pro-inflammatory molecule (IL-1β, IL-6, TNF-α, IRF8, etc.) ↓<br>Neuronal damage ↓        | DAP12: detrimental      | Kobayashi et al., 2015      |
| Neuropathic pain (Sensory nerve injury) | DAP12 KO mouse     | Microglial proliferation →<br>Activation marker of microglia (CD11b) ↓<br>Pain-related molecule (Cathepsin S, BDNF) ↓<br>Neuropathic pain ↓ | DAP12: detrimental for pain | Guan et al., 2016            |
| Neuropathic pain (Sensory nerve injury) | DAP12 KO mouse   | Microglial number ↓<br>Pro-inflammatory molecule (IL-1β, IL-6, TNF-α, IRF8, etc.) ↓<br>Pain-related molecule (Cathepsin S, P2RX4) ↓<br>Neuropathic pain ↓ | TREM2/DAP12: detrimental for pain | Kobayashi et al., 2016      |
|                                      | TREM2 agonistic antibody | Pro-inflammatory molecule (IL-1β, TNF-α, IRF8) ↑<br>Neuropathic pain ↑ |                         |                              |
| Motor nerve injury                  | TREM2 KO mouse       | Neuronal damage ↓                                              | TREM2: detrimental      | Krasemann et al., 2017      |
| **Epilepsy**                        |                      |                                                                                                                 |                         |                              |
| TREM2 KO mouse                      |                      | Microglial number ↓<br>Less activated morphology of microglia                                                |                         | Zheng et al., 2017           |
| **Traumatic brain injury**          |                      |                                                                                                                 |                         | Saber et al., 2017           |
| TREM2 KO mouse                      |                      | Lesion site: Number of microglia/macrophages ↑<br>Away from lesion: Number of macrophages ↓<br>Away from lesion: Pro-inflammatory molecule (TNF-α) ↓<br>Away from lesion: Hippocampal damage ↓<br>Neurological deficit ↓ | TREM2: detrimental      |                              |
| **Focal laser injury**              |                      |                                                                                                                 |                         | Mazaheri et al., 2017        |
conditions, myelin lipids trigger TREM2 to induce microglial activation, including upregulation of some genes involved in pro-inflammatory responses and myelin clearance (Cantoni et al., 2015; Poliani et al., 2015). Thus, Trem2-deficient microglia show a less-activated or dystrophic morphology, decreased proliferative activity, and dysfunction of myelin clearance (Cantoni et al., 2015; Poliani et al., 2015). As a TREM2-mediated signal contributes to reprogramming of microglia for appropriate myelin clearance, which is thought to be required for remyelination (Lampron et al., 2015), TREM2 is a neuroprotective molecule in the cuprizone model.

In another model of demyelination, experimental autoimmune encephalomyelitis (EAE), excessive activation of microglia is thought to be detrimental for regeneration (Chu et al., 2018). Two types of study have addressed the role of TREM2 in EAE. Inflammation was promoted and the EAE clinical score and demyelination were worsened by intraperitoneal injection of a TREM2 functional blocking antibody (Piccio et al., 2007). Other studies transplanted TREM2-overexpressing bone marrow-derived myeloid cells (in which phagocytic activity was enhanced and pro-inflammatory gene expression was downregulated upon TREM2 stimulation) intravenously into mice with EAE (Takahashi et al., 2005, 2007). The transplanted TREM2-transduced myeloid cells successfully migrated to EAE lesions. The removal of degenerated myelin was promoted and expression of pro-inflammatory molecules such as Il1b, Tnfa, and Ifng [encoding interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, respectively] was suppressed, resulting in reduced damage of not only remaining myelin but also axons. Although this transplantation study targeted bone marrow-derived myeloid cells and not microglia, taken together these studies indicate that the TREM2-mediated signal reduces neurotoxicity by suppressing pro-inflammatory responses in an EAE model. However, an apparently controversial result was obtained in Dap12 KO mice with EAE (Bakker et al., 2000a). Dap12 KO mice were shown to be highly resistant to EAE; disease onset was delayed and the clinical score was significantly better than WT mice. Thus, DAP12 is a neurotoxic molecule in the EAE model, while TREM2 is neuroprotective as described above. One possible reason for this discrepancy may be the variety of DAP12-associated receptors. As described in a later section, sialic acid-binding immunoglobulin-like lectin H (Siglec-H) is expressed by microglia as a DAP12-associated receptor, and signals derived from Siglec-H/DAP12 and TREM2/DAP12 complexes may oppositely regulate microglial activity in a mouse model of sensory nerve injury (Konishi et al., 2017). In addition to microglia, dendritic cells, which play a pivotal role as antigen-presenting cells in EAE pathogenesis (Mohammad et al., 2012), also express several DAP12-associated receptors.

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**FIGURE 2** | Summary of consequences of microglial TREM2/DAP12 in neural diseases. (A) Alzheimer’s disease. (B) Parkinson’s disease. (C) Demyelinating disease (cuprizone and EAE models). (D) Ischemia. (E) Peripheral nerve injury (cranial motor nerve injury and sensory nerve injury models).
besides TREM2 (Lanier, 2009). As TREM2 is one of the DAP12-associated receptors, the activation state of microglia or dendritic cells may be different between Trem2- and Dap12-deficient strains. Although the functional consequences of TREM2/DAP12 signaling in the EAE model are enigmatic, the role of TREM2/DAP12 may involve modulation of toll-like receptor signaling in microglia and/or dendritic cells (Ito and Hamereman, 2012; Kobayashi et al., 2015; Zhong et al., 2017b) because EAE development is dependent on toll-like receptors (Marta, 2009; Miranda-Hernandez and Baxter, 2013).

Ischemia
Recent studies have revealed that microglial activation is spatiotemporally regulated and activated microglia play a biphasic role (Guruswamy and ElAli, 2017; Ma et al., 2017). Microglia are thought to enhance inflammation by releasing pro-inflammatory molecules and recruiting leukocytes in the acute phase. However, in the recovery phase, microglia may secrete anti-inflammatory cytokines to attenuate the inflammation and promote tissue repair.

Several reports analyzed TREM2 function in the mouse middle cerebral artery occlusion model of ischemia, in which the microglial number significantly increases in the ischemic hemisphere. Two different groups revealed that the increase in microglial number after ischemia was suppressed in Trem2 KO mice (Sieber et al., 2013; Kawabori et al., 2015). Trem2-deficient microglia exhibited decreased expression of the phagocytic marker CD68 and reduced association with apoptotic cells (Sieber et al., 2013; Kawabori et al., 2015). The attenuated proliferation and phagocytic activity of Trem2-deficient microglia is consistent with the demyelination model induced by cuprizone described above (Cantoni et al., 2015; Poliani et al., 2015). Clearance of cellular debris is thought to be required for tissue reconstruction after injury (Neumann et al., 2009), and Kawabori et al. demonstrated a worsened neurological score in Trem2 KO mice (Kawabori et al., 2015), suggesting a neuroprotective role for microglial TREM2 in ischemia. Regarding inflammatory responses of microglia, genes encoding pro-inflammatory cytokines such as IL-1β and TNF-α were downregulated in Trem2 KO mice (Sieber et al., 2013), suggesting that TREM2 stimulates pro-inflammatory responses of microglia. In contrast, by overexpression or knockdown of Trem2, two other papers showed TREM2 is an inducer of anti-inflammatory responses (Wu et al., 2017; Zhai et al., 2017). The differences may arise from differences between the ischemic model or the timing of the analysis. However, it should be noted that TREM2 was consistently shown to be neuroprotective in all the studies (Kawabori et al., 2015; Wu et al., 2017; Zhai et al., 2017).

Peripheral Nerve Injury
Motor nerve injury causes microglial activation around the cell bodies of injured motor neurons. Activated microglia change their shape to an amoeboid morphology and adhere to and enwrap cell bodies of injured neurons (Graeber et al., 1988). Although the function of activated microglia remains unclear, the adhesion or enwrapping is assumed to affect the fate of injured motor neurons (Yamada and Jinno, 2011). In the case of sensory nerve injury, in the peripheral branch of dorsal root ganglion neurons, for example, microglia become activated in the ipsilateral dorsal horn of the spinal cord. Activated microglia proliferate, secrete various pain-related molecules such as brain-derived neurotrophic factor (BDNF), and augment neuropathic pain (Inoue and Tsuda, 2018).

In a mouse model of motor nerve injury, microglial neurotoxicity was attenuated in both Trem2 KO and Dap12 KO mice (Kobayashi et al., 2015; Krasemann et al., 2017). TREM2 drives transformation of homeostatic microglia into a neurodegenerative phenotype, with upregulation of some inflammatory molecules (Krasemann et al., 2017). Dap12 KO mice showed reduced microgliosis and lower expression of pro-inflammatory molecules (Kobayashi et al., 2015), which is reminiscent of the Trem2 KO mice with cuprizone-induced demyelination described above (Cantoni et al., 2015; Poliani et al., 2015). Taken together, TREM2/DAP12-mediated microglial neuroinflammation enhances neurotoxicity to injured motor neurons (Kobayashi et al., 2015).

TREM2/DAP12 function was also addressed in a sensory nerve injury model (neuropathic pain model) (Guan et al., 2016; Kobayashi et al., 2016). Kobayashi et al. showed that microglial numbers as well as expression of pro-inflammatory molecules were decreased in the ipsilateral dorsal horn of Dap12 KO mice compared with WT, leading to attenuated neuropathic pain. The study further revealed, using an agonistic antibody for TREM2, that TREM2 was the counterpart receptor of DAP12 in microglia involved in the DAP12-mediated inflammatory response (Kobayashi et al., 2016). Guan et al. also demonstrated that DAP12 leads to microglial activation as the downstream associated receptor of CSF1R after sensory nerve injury (Guan et al., 2016). Dap12 KO mice demonstrated suppressed pain behavior and decreased expression of microglial pain-related genes (Guan et al., 2016), which is in line with the results reported by Kobayashi et al. (2016). However, the study showed normal proliferation of Dap12-deficient microglia in the dorsal horn (Guan et al., 2016), while Kobayashi et al. demonstrated fewer microglia in Dap12 KO mice (Kobayashi et al., 2016). Although further confirmatory studies are needed for the DAP12-mediated proliferative activity of microglia, the TREM2/DAP12 complex, by cross-talking with CSF1R, would stimulate microglial activation after sensory nerve injury and exacerbate neuropathic pain (Inoue and Tsuda, 2018).

Amongst the known DAP12-associated receptors, Siglec-H is also expressed in microglia (Kobayashi et al., 2016; Konishi et al., 2017). A sensory nerve injury model showed enhanced pain behavior and increased expression of microglial pro-inflammatory cytokines in Siglech knockout mice (Konishi et al., 2017). Thus, a Siglec-H/DAP12-mediated signal seems to act as a suppressor of microglial activation, which is in line with the anti-inflammatory role of Siglec-H in plasmacytoid dendritic cells in the immune system (Blasius et al., 2006; Takagi et al., 2011, 2016). By making a complex with either TREM2 or Siglec-H, DAP12 induces opposing signals in microglia in the injured dorsal horn. This paradoxical function of DAP12 is also suggested...
in the immune system (Blasius and Colonna, 2006; Turnbull and Colonna, 2007; Linnartz-Gerlach et al., 2014).

**Other Injury Models**

In a kainic acid-induced epilepsy mouse model, microglia become activated and proliferate, particularly in the hippocampus (Zheng et al., 2011). Trem2 KO mice had microglia with a less activated morphology (Zheng et al., 2017). The increase in microglial number after seizure was also suppressed in Trem2 KO mice, which was suggested to result from both the attenuated proliferative activity and reduced viability of microglia in these mice. Other groups found downregulation of TREM2 expression in cortical tissues of patients with refractory epilepsy and in kainic acid-injected hippocampi in mice, which might be associated with alteration of microglial phagocytic activity in epileptic conditions (Abiega et al., 2016; Wyatt et al., 2017).

After traumatic brain injury, microglia, and infiltrating monocytes/macrophages trigger long-term neuroinflammation, which significantly affects the pathological, and functional outcome (Ziebell and Morganti-Kossmann, 2010). In the acute phase of traumatic brain injury, the numbers of microglia/macrophages are increased near the injury site in Trem2 KO mice compared with WT (Saber et al., 2017). Conversely, the number of macrophages and expression of Tnfa are reduced at the periphery of the injury site in Trem2 KO mice. The attenuated inflammatory response at the periphery of the injury results in reduced hippocampal atrophy and cognitive decline in Trem2 KO mice. Thus, at least at the periphery of the lesion, TREM2 promotes pro-inflammatory responses that damage brain tissue.

Mazaheri et al. found downregulation of some chemotaxis-related genes in Trem2-deficient microglia and consequently investigated changes in microglial chemotactic activity in the absence of TREM2 expression (Mazaheri et al., 2017). Migration toward injected apoptotic neurons and process extension toward a miniature laser-induced lesion site was impaired in the brains of Trem2 KO mice, suggesting that TREM2 is required for an appropriate microglial chemotactic response to neuronal injury.

**CONCLUDING REMARKS**

A TREM2/DAP12-mediated signal promotes proliferation, phagocytosis, and migration of microglia by induction and maintenance of microglial activation. However, it remains unclear whether TREM2 is a pro- or anti-inflammatory molecule. Initial studies of microglial TREM2 found that it promoted phagocytosis of apoptotic neurons and suppressed expression of pro-inflammatory molecules such as TNF-α (Takahashi et al., 2005, 2007). Although some studies reported TREM2 as an anti-inflammatory molecule, others proposed a pro-inflammatory role (Table 1). One of the reasons for this controversy may be microglial classification. The microglial phenotype is more complicated than previously thought. Microglia used to be classified into M1 (pro-inflammatory) or M2 (anti-inflammatory) phenotypes according to the expression pattern of marker molecules, as defined in macrophages (Arcuri et al., 2017). However, microglia are distinct from macrophages in terms of their molecular expression profile (Gautier et al., 2012; Hickman et al., 2013; Butovsky et al., 2014). Furthermore, microglia are highly adapted to the CNS environment and have CNS-specific roles (Gosselin et al., 2014; Sierra et al., 2014), suggesting that this simple classification is not appropriate (Mittelbronner, 2014; Ransohoff, 2016). The concepts “disease-associated microglia” or “microglia with neurodegenerative phenotype” have emerged recently (Keren-Shaul et al., 2017; Krasemann et al., 2017) and their molecular expression patterns are related to microglia in the aged brain (Krasemann et al., 2017). Importantly, TREM2 was shown to be the principal inducer of this phenotype, at least in mouse models of AD and ALS (Keren-Shaul et al., 2017; Krasemann et al., 2017). Because the TREM2/DAP12-mediated signal is a dominant switch that transforms microglia from a homeostatic to a disease-associated state, it is likely that dysregulation of TREM2/DAP12 signaling contributes to the pathogenesis of neurodegenerative diseases, including AD. A TREM2/DAP12-targeted strategy could provide new therapies for neurodegenerative diseases.

**AUTHOR CONTRIBUTIONS**

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

**ACKNOWLEDGMENTS**

This work was partly supported by KAKENHI (16K07055 to HKo; 16H05117 and 17H05743 to HKi) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan and grants from Japan Foundation for Applied Enzymology to HKi. We are grateful to Dr. M. Kobayashi at Osaka City General Hospital for his previous works with us and Ms. A. Asano for secretarial works. We also thank Ann Turnley, Ph.D., from Edanz Group for editing a draft of this manuscript.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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