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Microglial TREM2 at the intersection of brain aging and Alzheimer's disease

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Abstract

As resident immune cells of the brain, microglia serve pivotal roles in regulating neuronal function under both physiological and pathological conditions, including aging and the most prevalent neurodegenerative disease, Alzheimer's disease (AD). Instructed by neurons, microglia regulate synaptic function and guard brain homeostasis throughout life. Dysregulation of microglial function, however, can lead to dire consequences, including aggravated cognitive decline during aging and exacerbated neuropathology in diseases. The triggering receptor expressed on myeloid cells 2 (TREM2) is a key regulator of microglial function. Loss-of-function variants of TREM2 are associated with an increased risk of AD. TREM2 orchestrates the switch of microglial transcriptome programming that modulates microglial chemotaxis, phagocytosis, and inflammatory responses, as well as microglial regulation of synaptic function in health and disease. Intriguingly, the outcome of microglial/TREM2 function is influenced by age and the context of neuropathology. This review summarizes the rapidly growing research on TREM2 under physiological conditions and in AD, particularly highlighting the impact of TREM2 on neuronal function.

Keywords

Microglia; TREM2; synaptic plasticity; cognitive function; aging; Alzheimer's disease

Introduction

Microglia are the resident immune cells of the brain that serve critical roles in regulating synaptic functions under both physiological and pathological conditions (Salter and Stevens, 2017). Under physiological conditions, microglia maintain a unique homeostatic gene expression signature (homeostatic microglia, also known as resting microglia or M0) (Keren-Shaul and others, 2017; Krasemann and others, 2017). Microglia are highly mobile and constantly survey the environment of the brain by extending and retracting

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processes. Once detecting an insult, microglia rapidly shorten processes and enlarge soma as they transform into a reactive state. This transformation alters microglial transcriptome programming that leads to functional subtypes of activation states, including the disease-associated microglia (DAM) (Keren-Shaul and others, 2017), similar to the microglial neurodegenerative phenotype (MGnD) and the activated response microglia (ARM) (Krasemann and others, 2017; Frigerio and others, 2019). DAM alters the gene network that is involved in enhancing chemotaxis, phagocytosis, and lysosomal degradation. The full activation of DAM requires functional triggering receptor expressed on myeloid cells 2 (TREM2), an immunoglobulin superfamily receptor.

As a key regulator of microglial function, TREM2 modulates microglial regulation of synaptic function throughout the lifespan in both health and disease. Loss-of-function variants of TREM2 or its signaling partner DNAX-activating protein of 12 kDa (DAP12; also known as KARAP and TYROBP) cause the Nasu-Hakola disease (NHD), a rare recessive disorder characterized by early-onset dementia and cystic bone lesions (Kaneko and others 2010). Genome-wide association studies (GWAS) have identified several loss-of-function variants of TREM2 as a strong risk for Alzheimer's disease (AD) (Guerreiro and others, 2013; Jonsson and others, 2013). AD patients carrying TREM2 loss-of-function variants also showed accelerated cognitive decline and shortened disease duration, indicating that TREM2 modifies the course of AD progression (Korvatska and others, 2015). AD is the most prevalent form of dementia in the elderly that affects millions of lives worldwide without a cure. Emerging evidence convincingly portrays an active role of microglia in modulating AD pathogenesis and supports TREM2 as a potential therapeutic target for AD. This review highlights recent insights into how TREM2 mediates the microglia-synapse crosstalk and its impact on cognitive function throughout life and on the pathogenesis of AD.

TREM2 expression, structure, and signaling pathways

TREM2 is an immunoglobulin superfamily receptor expressed by myeloid lineage cells including bone osteoclasts, resident tissue macrophages, and dendritic cells in the periphery (Turnbull and others, 2006). TREM2 is expressed exclusively by microglia in the brain parenchyma and the expression of TREM2 can also be modulated by inflammatory cytokines and environmental stimuli (Gratuze and others, 2018).

In healthy human brains, the *TREM2* mRNA expression depends on brain regions and increases with age, with higher expression in the white matter and hippocampus (Forabosco and others, 2013). However, microglia is more abundant in white matter than gray matter and microglial density increases during normal aging (Gefen and others, 2019), which may have contributed to elevated *TREM2* levels observed in certain brain areas and aged brains. Increased TREM2 expression has also been reported in human AD brains, with strong TREM2 immunoreactivity in amyloid plaques and neuritic tangle-associated microglia (Lue and others, 2015). However, transcriptomic analyses on bulk RNAseq or isolated microglia show no significant differences in *TREM2* expression between human AD brains and cognitively normal controls (Del-Aguila and others, 2019; Alsema and others, 2020). Single-cell RNAseq analysis on live microglia purified from human AD patients reveals high

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heterogeneity in the microglial population, and the expression of *TREM2* is increased in a subset of microglia (Olah and others, 2020).

Anionic molecules and bacteria were first identified as potential ligands for TREM2 that activate microglia to phagocytose various pathogens (Daws and others, 2003). Later studies have identified various putative ligands for TREM2, including amyloid-β (Aβ, apolipoproteins (including APOE, APOJ/clusterin, APOA-I, and APOB), galectin-3, TREM like 1 (TREML1), DNA, myelin sulfatide, phospholipids, sulfated proteoglycans, and bacterial components such as lipopolysaccharides (LPS) (Kober and Brett, 2017; Boza-Serrano and others, 2019). In addition to binding secreted molecules, TREM2 can also bind to astrocytes, neurons, and apoptotic cells, creating a cell-cell interaction and signaling between microglia and other cell types (Kober and Brett, 2017).

TREM2 consists of an extracellular immunoglobulin domain, containing positively charged arginine residues that interact with TREM2 anionic ligands and a stalk region followed by a transmembrane helix and a short intracellular cytosolic terminus with no known signaling or trafficking motif (Colonna and Wang, 2016). Because of the lack of an intracellular signaling domain, the TREM2 signaling cascade requires the binding of DAP12. DAP12 has a limited extracellular region with no ligand-binding capability and consists of an immunoreceptor tyrosine-based activation motif (ITAM), which is phosphorylated by Src family kinases upon TREM2 activation, generating a docking site for Src Homology 2 (SH2) domain-containing molecules to initiate signaling cascades (Figure 1) (Gratuze and others, 2018).

The main kinase recruited by DAP12 is Syk, which initiates several downstream signaling cascades including Vav guanine nucleotide exchange factors mediated actin remodeling and phagocytosis, phosphatidylinositol 3-kinase (PI3K)-Akt-mTOR mediated regulation of autophagy, phospholipase Cγ (PLCγ) mediated Ca^{2+} mobilization, and activation of protein kinase C (PKC), thereby regulating microglial phagocytosis of myelin, lipid metabolism, and survival (Figure 1) (Painter and others, 2015; Konishi and Kiyama, 2018; Andreone and others, 2020).

TREM2 signaling can crosstalk with other receptor-mediated pathways including the colony-stimulating factor 1 receptor (CSF1R) signaling to regulate microglial survival, the toll-like receptor 4 (TLR4) – JNK signaling to regulate inflammatory responses, and the Wnt/β-catenin pathways to regulate microglial survival and proliferation (Figure 1) (Zheng and others, 2017; Konishi and Kiyama, 2018). In addition to TREM2, DAP12 can also partner or interfere with the expression of other microglial immune receptors including CD33, CR3, and SIRPβ1, which are involved in the pathogenesis of AD (Haure-Mirande and others, 2017; Griciuc and others, 2019), underscoring the importance of TREM2/DAP12 signaling in regulating microglial function.

TREM2 can be cleaved by disintegrin and metalloproteinase (ADAM) proteases and shed soluble TREM2 (sTREM2), which partially contribute to TREM2 surface expression decline upon microglial activation (Ulland and Colonna, 2018; Zhong and Chen, 2019). ADAM17/10 are the main TREM2 sheddases that cleave the H157-S158 peptide bond at

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the stalk region of TREM2. The remaining carboxy-terminus can be further cleaved by γ-secretase and release DAP12, which is important for PLCγ-mediated Ca^{2+} mobilization and microglial phagocytosis. sTREM2 can also be produced by alternative splicing that results in the lack of a transmembrane domain. Alternatively spliced sTREM2 transcript counts for 60% of the canonical transcript and codes for 25% of the sTREM2 protein (Del-Aguila and others, 2019). sTREM2 binds to unknown receptors and activates microglia, enhancing microglial viability via the PI3K/Akt pathway and promotes inflammatory cytokines production via the NF-κB pathway (Figure 1) (Zhong and others, 2017). sTREM2 can also act as a competitor for TREM2 ligands to suppress the canonical TREM2 signaling cascades. It is worth noting that many signaling studies were conducted *in vitro* and future studies are needed to validate these findings *in vivo*.

TREM2 in neurodevelopment and adulthood

The mRNA expression of *Trem2*/*Dap12* can be detected in the CNS as early as embryonic day 14 in mice (Thrash and others, 2009), the time when synaptogenesis emerges. During the early postnatal phase when developmentally programmed neuronal death and synaptic refinement occur, *Trem2* expression elevates in the brain (Jay and others, 2017b). At postnatal day zero or one (P0/P1), microglia are in close contact with apoptotic neurons, expressing DAP12, TREM2, and CD11b. The loss-of-function mutation of DAP12 reduces the microglial release of reactive oxygen species and prevents neuronal programmed cell death (PCD) in the hippocampus, through interaction with the CD11b pathway (Wakselman and others, 2008). During neurodevelopment, DAP12 also plays an important role in guiding cortical interneuron migration, axon outgrowth and facilitation, and myelinogenesis, acting in parallel with the CX3CR1/CR3 signaling (Squarzoni and others, 2014). The role of TREM2 in these neurodevelopmental events remains elusive (Figure 2a).

Notably, both DAP12 and TREM2 have been implicated in the regulation of synapses during the early postnatal period. Loss-of-function *Dap12* knock-in mice display enhanced hippocampal long-term potentiation/plasticity (LTP) in adolescent mice. The enhanced LTP is caused by an increase in the ratio of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) to N-methyl-D-aspartate receptor (NMDAR), the altered composition of AMPAR and NMDAR subunits, and a decrease in the neurotrophin brain-derived neurotrophic factor (BDNF)-tropomyosin receptor kinase B (TrkB) signaling in microglia (Roumier and others, 2008). Interestingly, DAP12 deficiency induces microglial overproduction of nitric oxide and pro-inflammatory cytokines during the prenatal phase, which has a delayed influence on glutamatergic synapse formation postnatally. Whether DAP12 deficiency has any impact on cognitive function and whether this modulation of synapses by DAP12 is mediated through TREM2 remain unclear.

The role of TREM2 in synaptic refinement has been investigated but the results across different studies are not consistent. *Trem2* knockout mice from the Colonna laboratory (Turnbull and others, 2006) show fewer and less active microglia in the hippocampal CA1 region during P18-20 compared with wild-type (WT) mice (Filipello and others, 2018). These *Trem2*-null microglia display reduced phagocytosis of synaptosomes *in vitro* and *in vivo*, resulting in higher pre- and postsynaptic contacts that contribute to higher

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miniature excitatory postsynaptic currents (mEPSCs) and brain connectivity defects. The altered synaptic function results in impaired repetitive and social behaviors that are parallel to autism symptoms but no changes in hippocampal learning and memory. Indeed, a negative correlation between TREM2 protein levels and the severity of autism symptoms has been reported in autistic patients (Filipello and others, 2018). There are some, but not all, overlapping phenotypes such as increased glutamatergic signaling between *Trem2* knockout and *Dap12* loss-of-function mice. Future studies investigating the role of TREM2 in neurotransmitter receptor properties and synaptic plasticity may shed light on other mechanisms of TREM2-DAP12 mediated signaling in shaping synaptic function during neurodevelopment (Figure 2a).

In another line of *Trem2* knockout mice (the Velocigene line, (Jay and others, 2015)), loss of *Trem2* results in a reduced number of synapses at one month of age (Jay and others, 2019), the age when the majority of developmental synapse formation and elimination is complete. The reduction of synapses is caused by increased synaptic engulfment by astrocytes rather than the interactions between microglia and neurons, leading to decreased mEPSCs of CA1 neurons. Intriguingly, these TREM2-dependent developmental changes are normalized in adulthood at four months of age but can be re-introduced by a high-fat diet. Consistent with this beneficial role of TREM2 at the synapse, adeno-associated virus (AAV)-mediated overexpression of TREM2 in the hippocampus of 8-week old mice leads to amelioration of high-fat diet-induced cognitive and synaptic impairment (Wu and others, 2020). These results indicate that TREM2 can restore neuronal function altered by environmental factors. It is noteworthy that the Velocigene *Trem2* knockout mice exhibit aberrant upregulation of *Treml1* (Kang and others, 2018), which may explain some of the discrepancies observed as TREML1 is also involved in regulating inflammatory response.

Two additional TREM2 loss-of-function mouse models, $Trem2^{Y38C/Y38C}$ and the Jackson Labs CRISPR/Cas9 *Trem2* knockout mouse model, have been characterized recently during development and adulthood (Jadhav and others, 2020). Neither mouse model displays altered pre- and post-synaptic protein levels at P20, suggesting normal neurodevelopment in these mice. Interestingly, both mouse models show decreased myelination, reduced synaptic protein expression, and impaired hippocampal LTP induced by high-frequency stimulation at six months of age, suggesting detrimental effects of TREM2 deficiency in young adults. However, studies using other TREM2 deficient mice have shown the impact of TREM2 at synapses is limited in young adults under physiological conditions. Studies in the Velocigene TREM2 knockout mice show that TREM2 deficiency does not alter anxiety, mobility, sociability, or amygdala/hippocampus-dependent learning and memory at 6 months of age (Kang and others, 2018). No defects in spatial learning and memory and working memory task are observed in the Colonna *Trem2* knockout mice at 3 months of age (Filipello and others, 2018). Recently, we have also reported no effects of TREM2 deficiency on anxiety level, locomotive habituation, and hippocampal-dependent spatial learning and memory in the Colonna *Trem2* knockout mice at 6 months of age (Qu and Li, 2020). These mice show an increase in dendritic spine density, likely a consequence of reduced synaptic pruning during development, but maintain normal short-term and long-term synaptic plasticity induced by theta-burst stimulation as well as a normal expression of synaptic proteins (Figure 2b). The discordant outcome in the literature might be related to different TREM2

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knockout mice models, experimental methods, and environmental factors. Transcriptomic analyses have shown that not all *Trem2*-null mice are created equal (Kang and others, 2018). LTP induction strategies could account for some discrepancies in electrophysiological experiments. Theta burst stimulation is more physiologically relevant and may produce different electrophysiological readouts compared with high-frequency stimulation (Larson and Munkácsy, 2015). Uncontrolled environmental factors, such as diet, may also be a confounding factor modifying cognitive and synaptic function in *Trem2* null mice (Jay and others, 2019; Wu and others, 2020).

TREM2 in normal brain aging

The developmental and early-life regulation of TREM2 at the synapses sets a stage for its impact on cognitive function during aging and in neurodegenerative diseases.

A key contributor to age-related cognitive decline is myelin degeneration. Myelin debris is continuously generated but fails to be phagocytosed by microglia during aging, resulting in accumulated lipid droplets in microglia that lead to their dysfunction (Shobin and others, 2017; Nugent and others, 2020). *TREM2* or *DAP12* loss-of-function variants cause NHD, and one of the pathological characteristics of NHD is demyelination (Kaneko and others 2010). TREM2 is required for microglial expansion during normal aging in mice, especially in the white matter and hippocampus (Poliani and others, 2015). Aged *Trem2* deficient microglia display dystrophic morphology with reduced ramifications compared with aged WT microglia. Similar phenotypes of microglia also have been reported in *Dap12* knockout mice (Otero and others, 2009), suggesting the importance of the TREM2-DAP12 pathway in mediating age-related microglial expansion and morphology, likely driven by microglial innate gene network changes. In the Colonna *Trem2* null mice, microglia fail to adopt the transcriptional programming for myelin debris removal and remyelination in the cuprizone-induced demyelination model (Poliani and others, 2015). Normally, the sulfatide of myelin debris binds to TREM2 that triggers microglial phagocytosis and promotes myelin debris clearance (Nugent and others, 2020). The cuprizone demyelination model induces the DAM phenotype of microglia, and *Trem2* deficient microglia isolated from the CRISPR/Cas9 *Trem2* knockout mice fail to respond to cuprizone and display attenuated transition to DAM, with a reduced expression level of *Apoe*. APOE is the main cholesterol/lipid transporter in the brain and the human variant *APOE4* is the strongest genetic risk factor for AD. Reduced microglial *Apoe* results in accumulated lipid droplets consisting of myelin cholesterol-derived cholesteryl ester, causing metabolic abnormality and stress in microglia (Nugent and others, 2020).

The role of TREM2 in aging under physiological conditions has also been investigated. As loss-of-function variants of *TREM2* or *DAP12* increase the risk of developing age-related dementia including AD and NHD, TREM2 deficiency is expected to exacerbate neuronal dysfunction and cognitive decline during normal aging. A study using an undisclosed line of *Trem2* knockout mice reports that the lack of TREM2 leads to a tendency toward defects in spatial learning and memory while *Trem2* overexpressing transgenic mice display enhanced learning capacity compared with WT at 12 months of age (Kim and others, 2017). In contrast, another study shows AAV-mediated overexpression of *Trem2* in the cortex and

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hippocampus of WT mice causes markedly activated microglia at 12 months of age (Sheng and others, 2019). The activated state of microglia leads to impaired synaptic function including suppressed hippocampal LTP, reduced pre- and postsynaptic markers, decreased spine density, and impaired spatial learning and memory, indicating a detrimental role of TREM2 during neuronal aging.

Of note, the age of 12 months in mice is considered as middle age, and microglia are known to have a low AAV transfection rate (Maes and others, 2019). To elucidate the role of TREM2 in normal aging, we used the well-charactered Colonna *Trem2* knockout mice to investigate the hypothesis that TREM2 deficiency and aging act synergistically to impair neuronal function and cognition. Unexpectedly, we found that TREM2 deficiency confers resilience to synaptic and cognitive impairment in aged (19-months) mice (Qu and Li, 2020). The neuroprotective effect of TREM2 deficiency is attributed to normal dendritic spine density maintained during normal aging, resulting in enhanced hippocampal LTP and elevated expression of synaptic markers in aged mice. The prevention of age-related neuron loss in both hippocampus and substantia nigra has also been reported in the Colonna *Trem2* knockout mice, accompanied by enhanced synaptic density and reduced microglial activation, at 24 months of age (Linnartz-Gerlach and others, 2019). Whole-brain transcriptome analysis of these mice reveals that aged *Trem2* knockout mice display overall reduced oxidative stress and attenuated complement activation in the brain. Despite changes in microglial abundance in *Trem2* null mice might be a confounding factor, the overall reduction in oxidative stress and complement activation is expected to confer beneficial outcomes to synaptic and cognitive function during normal aging in mice (Figure 2c). Since TREM2 deficient microglia show reduced phagocytosis and TREM2 favors mediating the phagocytosis of stressed yet viable neurons (Gabande-Rodriguez and others 2020), reduced engulfment of synapses in aged neurons likely constitutes one of the mechanisms underlying TREM2 deficiency-induced neuroprotective effects. Effects of TREM2 deficiency on cognitive and synaptic function in normal aging in different mouse models are summarized in Table1. Further studies are needed to determine whether these effects are unique in mouse models or applicable to humans.

Transcriptome analysis of microglia isolated from aged *Trem2* knockout mice shows that TREM2 deficient microglia fail to adopt DAM genes induced by aging and maintain a homeostatic phenotype under physiological conditions (Nugent and others, 2020). Whether maintaining a DAM state is detrimental or beneficial appears to depend on the context of neuropathology. In the presence of overwhelming myelin debris or pathology, microglial DAM status helps to clear harmful debris and limit the damage to neurons. However, demyelination is limited in mouse brains during normal aging compared with primates, and TREM2 deficiency in aged mice is not sufficient to drive the pathological changes equivalent to human NHD brains (Poliani and others, 2015). This difference may separate the beneficial effects of TREM2 deficiency in aged mouse brains from pathology-driven detrimental effects of TREM2 deficiency in human brains. Indeed, emerging evidence shows that in the presence of limited demyelination and pathology, maintaining microglial DAM status during normal aging might be harmful. It has been shown that blocking a canonical B cell receptor, CD22 that is a negative regulator of phagocytosis and is upregulated in aged microglia, improves microglial phagocytosis and prevents the adoption of DAM

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phenotype in microglia (Pluvinage and others, 2019). Furthermore, restoring the hemostatic state of microglia by chronic anti-CD22 treatment enhances cognitive function in aged mice, suggesting potential detrimental effects of persistent microglial DAM state during normal aging. Improving phagocytosis while maintaining the homeostatic state of microglia might be key to develop effective therapeutic strategies for age-related cognitive disorders.

TREM2 in Alzheimer's disease

TREM2 deficiency locks microglia in a homeostatic status, leading to a failed immune response to environmental insults, and has been acknowledged for its complex role in neurological disorders. Homozygous loss-of-function variants in *TREM2* cause NHD. The *TREM2* hypomorphic variant, R47H, increases the risk of developing AD by several folds. The penetrance is less for other *TREM2* mutations including R62H and D87N (Ulland and Colonna, 2018). Interestingly, an activity-enhancing variant of PLCγ2, downstream of TREM2, reduces the risk of developing AD (Takalo and others, 2020).

Since the discovery of the strong association of TREM2 variants with AD, much research effort has been drawn to understand the role of TREM2 in AD. In the presence of Aβ, *Trem2* complete deficiency affects the initial formation of Aβ plaques, impairs plaque compaction, and mediates neurite dystrophy. *Trem2* haplodeficiency does not affect Aβ pathology but alters the morphology of plaque-associated microglia and worsens axonal dystrophy (Ulrich and others, 2014; Yuan and others, 2016). In the presence of both Aβ and tau pathology, TREM2 deficiency accelerates tau pathology spreading and exacerbates tau-mediated neurodegeneration enhanced by Aβ (Leyns and others, 2019; Lee and others, 2021). In the presence of tau pathology alone, complete loss of TREM2 exacerbates tau hyperphosphorylation but rescues tau-mediated neurodegeneration at a later stage, whereas TREM2 haplodeficiency aggravates tau pathology and exacerbates brain atrophy (Bemiller and others, 2017; Leyns and others, 2017; Sayed and others, 2018; Gratuze and others, 2020). In terms of the DAM state transition, only *Trem2*-null microglia, not WT or *Trem2* haplodeficient microglia, fail to adopt the DAM state upon demyelination treatment (Nugent and others, 2020). Collectively, these data portray a complex role of TREM2 in the pathogenesis of AD and suggest that the outcomes of TREM2 signaling-mediated DAM are influenced by the stage of the disease development, the context of neuropathology, and the gene dosage of loss-of-function TREM2. In the following section, recent key findings regarding the role of TREM2 in AD are summarized, particularly emphasizing the influence of TREM2 on neuronal function and cognition.

Impact of TREM2 deficiency in the context of Aβ and tau pathology

Microglia adopt the DAM phenotype near Aβ plaques and TREM2 is required for the switch to the full activation of the DAM state. Without a functional TREM2, microglia fail to respond and cluster around Aβ (Shi and Holtzman, 2018). Aβ can bind to TREM2 directly, and the other two TREM2 ligands, APOE and galectin-3, which are upregulated DAM genes, can also interact with Aβ to modulate microglial response through TREM2 (Boza-Serrano and others, 2019; Parhizkar and others, 2019). Galectin-3 is required for Aβ oligomerization and APOE facilitates the deposition and compaction of fibrillar plaques

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(Ulrich and others, 2018; Tao and others, 2020). Therefore, TREM2 deficiency-induced lack of microglial interactions with APOE and galectin-3 would lead to impairment in the initial formation of Aβ plaques, which may explain reduced plaque load in some TREM2 deficient mouse models at the early stage of β-amyloidosis (Figure 3a) (Jay and others, 2017a).

After the formation of plaques, the clustering of microglia around plaques promotes Aβ clearance and creates a physical barrier to limit the spread of toxic Aβ, protecting nearby neurites from dystrophy in a TREM2-dependent manner (Wang and others, 2016; Yuan and others, 2016). Complete deletion or haplodeficient *Trem2* or *Dap12* in AD mice and human *TREM2 R47H* variant carriers all show abolished microglial envelopment of Aβ fibrils, resulting in less compacted plaques and increased surface exposure and neurotoxicity to nearby neurites (Figure 3a). Interestingly, complete deletion but not haplodeficiency of *Trem2* or *Dap12* in AD mice impairs microglial phagocytosis, indicating that establishing an effective microglial barrier around the plaques is more important than microglial phagocytosis of Aβ for controlling neuropathology (Yuan and others, 2016). Increased microglial compaction of diffused plaques into fibrillar amyloidosis positively correlates with improved cognitive function and preserved synaptic density (Deussing and others, 2019).

Intriguingly, single-nucleus RNAseq analysis has revealed that microglia from human TREM2 mutation carriers display less evident reactive gene signature than those of AD mouse models (Zhou and others, 2020). Microglial transcriptome in the human AD brain only partially overlaps the DAM signature in mouse models, indicating species-specific changes in microglial response to AD pathology. Transcriptomic and functional analysis of human induced pluripotent stem cells (iPSC)-derived microglia confirms that TREM2 deficiency reduces microglial survival, phagocytosis, and chemotaxis migration towards Aβ (McQuade and others, 2020). Notably, transplanting human *TREM2* knockout or WT iPSC-derived microglia in a mouse model of AD has revealed that human *TREM2* deficient microglia exhibit a similar impairment in clustering around plaques as murine microglia and show a deficit in transition from homeostatic to the human DAM subtype (McQuade and others, 2020). Interestingly, human microglia-like, iPSC-derived macrophages that harbor homozygous R47H mutation of TREM2 show similar gene network signature changes but do not show dysregulation in survival, phagocytosis, and motility as the *TREM2* knockout microglia, suggesting partial loss-of-function effects of the R47H mutation (Hall-Roberts and others, 2020). Since human iPSC-derived microglia maintain a functional identity in the chimeric mouse brains (Xu and others, 2020), future studies characterizing AD pathology and neuronal function in the chimeric AD mouse model transplanted with human microglia that harbors disease-associated mutations should provide more translational potential for therapeutic development.

Impairment of plaque-associated microgliosis is very consistent across all studies in the brains of AD patients with TREM2 variants as well as animal models. Because TREM2 is involved in microglial recognition, compaction, and clearance of Aβ, the accumulation of Aβ accelerates and peaks early in *Trem2* deficient AD mice but reduces in aged animals (Parhizkar and others, 2019; Meilandt and others, 2020). Despite a reduced rate of amyloid accumulation, aged *Trem2* deficient AD mice display increased $A\beta_{42}$:$A\beta_{40}$

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ratios and Aβ oligomers, exacerbating neuronal damage (Meilandt and others, 2020). Due to this complicated relationship between Aβ deposition and TREM2, the effects of TREM2 on amyloid burden evaluated at specific pathology stages are inconsistent across different studies (Jay and others, 2015; Wang and others, 2015; Wang and others, 2016; Jay and others, 2017a). However, several reports consistently showed that TREM2 deficiency exacerbates neurite dystrophy and dendritic spine loss at middle to late stage of β-amyloidosis (Figure 3a) (Wang and others, 2016; Yuan and others, 2016; Meilandt and others, 2020). Evaluating spine density near and far from plaques at the middle stage in an Aβ mouse model further reveals that TREM2 is not required but protects against microglia-mediated spine loss near plaques (Meilandt and others, 2020). In AD brains, dendritic spine loss and neuronal signaling dysfunction are contributed by a combination of neurotoxic Aβ exposure and reactive gliosis. TREM2 is necessary for microglial compaction and containment of Aβ fibrils that protect neurites from dystrophy. However, in the early disease stage when plaques are limited in the brain, TREM2 deficiency might be protective against spine loss. Pre- and peri-adolescent *TREM2 R47H* KI rats expressing physiological levels of human Aβ show elevated pro-inflammatory cytokines, including TNF-α, and display augmented glutamatergic synaptic transmission and suppressed LTP of the hippocampus without altering Aβ levels (Ren and others, 2020). The increased glutamatergic transmission has also been reported in *Trem2* null mice under physiological conditions due to synaptic pruning defects (Filipello and others, 2018). In another study with an Aβ mouse model, systemic *Trem2* deletion and AAV-mediated *Trem2* knockdown are found to enhance hippocampal LTP, increase synaptic spine density, and elevate pre- and post-synaptic markers at the early stage of AD, but the effects are reversed at the middle to late stage of AD (Sheng and others, 2019). These results suggest that TREM2 mediates the phagocytosis of synapses as well as amyloid plaques. However, direct evidence of TREM2 meditated microglial phagocytosis of synapses across different pathology development stages has yet to be shown. Such information will be critical for determining the optimal timing of TREM2 based interventions in AD.

In addition to amyloid deposition, another pathological hallmark of AD is the formation of neurofibrillary tangles (NFTs). Amyloid deposition creates a favorable environment for early tau seeding in dystrophic neurites and forming tau aggregates surrounding neuritic plaques (NPs), which trigger the spread and expansion of hyperphosphorylated tau and secondary seeding and formation of NFTs (He and others, 2018). The level of TREM2 expression correlates positively with tau phosphorylation in postmortem human AD brains, and total tau and hyperphosphorylated tau levels are elevated in the CSF of TREM2 R47H carriers (Lill and others, 2015; Lue and others, 2015). The R47H variant of TREM2 aggravates tau hyperphosphorylation and neurite dystrophy in human AD brains (Yuan and others, 2016). Exacerbated axonal dystrophy and hyperphosphorylation of tau have also been observed in TREM2 deficient Aβ mouse models (Wang and others, 2016; Yuan and others, 2016). However, most of the Aβ mouse models do not develop tau pathology seen in human AD cases. To investigate the role of TREM2 in the combination of Aβ and tau aggregation, tau isolated from human AD brains was injected into *Trem2* null or *TREM2 R47H* Aβ mouse models (Leyns and others, 2019). At the initial tau seeding stage, loss of TREM2 or TREM2 R47H mutation reduces microgliosis and increases Aβ42 around plaques, which

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leads to exacerbation of pathological tau spreading and Aβ-associated neurite dystrophy (Figure 3b). Since neurons that bear tau pathology can be phagocytosed by microglia and TREM2 signaling affects the phagocytic ability of microglia (Vogels and others, 2019), whether exacerbated tau spreading in dystrophic neurites is due to more exposure to less compact Aβ fibrils or reduced phagocytosis by microglia remains to be investigated.

To imitate the chronic progression of both Aβ and tau pathology in human AD brains, a slow progression tauopathy mouse model (pR5-183) was crossed with an Aβ mouse model (Lee and others, 2021). Aβ pathology intensifies tau pathology, heightens microglial DAM activation, and contributes to brain atrophy (Figure 3b). Importantly, TREM2 deficiency accelerates tau-mediated neurodegeneration, and this effect depends on the presence of Aβ pathology, indicating that Aβ and tau pathology provides a neurotoxic environment that triggers TREM2 deficient microglia to favor neurodegeneration. These findings provide important molecular insights into the role of TREM2 deficiency in human AD cases and inspire future studies to investigate the role of TREM2 in models that closely mimic the pathogenic process of human AD so that discoveries from animal studies can be translated to develop therapeutic strategies for humans.

In the presence of pathological tau alone, microglial phagocytic activity and neuroinflammatory response play dual roles (Vogels and others, 2019). Removal of stressed but viable neurons disrupts neuronal network, which leads to cognitive decline but helps limit the spread of pathological tau to healthy neurons. Despite exacerbated pathology at the early stage of tauopathy in a humanized tau mouse model (Bemiller and others, 2017), complete *Trem2* or *Dap12* deletion or transgenic expression of human *TREM2 R47H* prevents neurodegeneration at the late stage in an aggressive tauopathy model, PS19 (Figure 3c) (Leyns and others, 2017; Audrain and others, 2019; Gratuze and others, 2020). The neuroprotective effects of TREM2 deficiency might be due to reduced complement-mediated phagocytosis of synapses. However, the connection between TREM2 signaling and the complement cascade remains to be investigated. Interestingly, *Trem2* haplodeficiency and complete deletion differently regulate the microglial transcriptome, especially the expression of inflammatory genes, and neuropathology. In a mouse model of tauopathy, whereas complete *Trem2* deletion attenuates hippocampal atrophy, *Trem2* haplodeficiency exacerbated tau pathology and neurodegeneration (Sayed and others, 2018). Since most AD patients with TREM2 variants carry only one copy of the mutant *TREM2* gene, this might be one of the reasons for detrimental effects seen in humans with partial loss of TREM2 versus beneficial effects observed in mouse tauopathy models with complete loss of TREM2. Another possibility is that the role of TREM2 in tauopathy depends on the presence of Aβ as discussed in the previous paragraph. Animal studies that investigated the effects of TREM2 deficiency on neuropathology in the different contexts of Aβ and tau pathology are summarized in Table 2.

Modulation of TREM2 as a therapeutic approach for AD

Recent efforts have been dedicated to developing TREM2 activating antibodies. TREM2 proximal singling activation antibodies rescue survival defects and modulate migration and cytokine expression in *Trem2*^{R47H} expressing microglia and macrophages *in vitro*

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(Cheng and others, 2018). A TREM2 stalk region binding antibody, 4D9, competes with ADAM protease-mediated shedding of sTREM2 to prolong TREM2 receptor surface expression levels and increase TREM2 signaling (Schlepckow and others, 2020). This TREM2-modulating antibody promotes microglial transition to DAM, improves microglial phagocytosis of myelin debris and Aβ *in vitro*, and ameliorates amyloid burden *in vivo*. Another TREM2-activating antibody, AL002, binds to the extracellular region of TREM2 and increases the phosphorylation of Syk (Ray and Buggia-Prevot, 2021). The mouse TREM2 recognizing variant of AL002, AL002a, stimulates microglia activation, reduces amyloid deposition, and improves learning and memory (Price and others, 2020). Of note, since both microglial anti-inflammatory and pro-inflammatory cytokines, including TNF-α and IL-1β are elevated in the hippocampus with this antibody treatment, possibly caused by increased microglial activation and proliferation, the long-term effects of these antibody treatments on neuronal function should be assessed as prolonged activation and release of pro-inflammatory cytokines can be neurotoxic. The human TREM2 agonistic variant of AL002, AL002c, activates both the common variant hTREM2 and the R47H hTREM2 variant *in vitro* and *in vivo* (Wang and others, 2020). Single-nuclei RNAseq analysis reveals that the AL002c promotes the transition of microglia from homeostatic to the DAM state and induces microglial metabolic activation and proliferation. Sustained systemic administration of AL002c in an Aβ mouse model expressing human R47H TREM2 increases microglia surveillance and phagocytosis of Aβ. Counteracting reduced plaque compaction caused by TREM2 deficiency, the treatment with AL002c converts harmful diffused plaques to less harmful compacted plaques, subsequently ameliorating plaque-associated neurite dystrophy and rescuing exploratory and anxiety behavior. Encouragingly, in the phase I clinical trial AL002c administration is well tolerated in humans, in which sTREM2 and CSF1R fragments are increased in the CSF, suggesting increased microglia proliferation as shown in mice. Another novel TREM2-activating antibody, Ab-T1, has been reported recently to enhance microglial phagocytosis of Aβ and alleviate cognitive deficits in an Aβ mouse model (Fassler and others 2021). Interestingly, Ab-T1 antagonizes sTREM2 and attenuates chronic neuroinflammation. Taken together, these results provide a promising therapeutic potential of activating TREM2 for treating AD. However, TREM2 plays a complex role in AD pathogenesis. Future studies evaluating the efficacy of TREM2-activating antibodies in the presence of both Aβ and tau pathology are required. Furthermore, since AD-associated variants of TREM2 are heterogeneous and rare in the human population, the safety and efficacy of TREM2 activation should be evaluated in not only individuals carrying TREM2 variants but also other sporadic and familial AD cases at different disease stages. In addition, as TREM2 activation triggers the phagocytic activity of microglia, which also plays an important role in synapse engulfment and neurite severing, future studies are needed to evaluate the safety of TREM2 activation on synaptic structure and neuronal function.

Conclusion

Mounting evidence reinforces the vital role of microglia in health and disease. As a critical immune receptor exclusively expressed by microglia, TREM2 orchestrates microglial immune homeostasis by sensing extracellular signals and regulates microglia

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proliferation, phagocytosis, and neuroinflammatory responses. Therefore, TREM2 facilitates the microglial regulation of synaptic and cognitive function throughout life under both physiological and pathological conditions (Figure 4). Loss of functional TREM2 locks microglia in a homeostatic state, which is less responsive to environmental stimuli. Since loss-of-function variants of TREM2 are associated with increased risk of AD, extensive efforts have been put to illuminate the role of TREM2 in AD pathogenesis, yet results are not consistent across different studies, revealing a complex relationship between TREM2 and synaptic function that depends on the disease stage and the pathological environment. Several questions remain to be addressed in future studies to better understand the biological function of TREM2 under both physiological and pathological conditions. For example, the molecular mechanisms by which TREM2-DAP12 signaling in shaping synaptic refinement and neuronal plasticity during neurodevelopment are unclear. It is also not known whether TREM2 plays any active roles in maintaining neuronal function during normal aging without developmental complication, which calls for inducible/conditional TREM2 knockout models. The inducible/conditional TREM2 models can also help clarify the disease-stage dependent roles of TREM2 in AD. The modulation of TREM2 signaling on disease pathology has been extensively investigated but the cognitive outcomes and neuronal structural and functional consequences remain to be explored. In humans, partial loss of TREM2 function exerts detrimental effects, whereas in Aβ and tau mouse models, studies on TREM2 gene dosage effects show discordant results. Replicating findings from AD mouse models in human cellular and organoid models may provide more translational insights. TREM2 induces APOE signaling in microglia and this interaction regulates microglial phenotypes. How TREM2 interacts with different isoforms of APOE in the progression of AD remains to be investigated. Emerging evidence supports TREM2 activation as a promising therapeutic avenue for AD. Further studies are required to elucidate the optimal timing and duration of TREM2 intervention to maximize neuroprotective effects and minimize neurotoxic outcomes.

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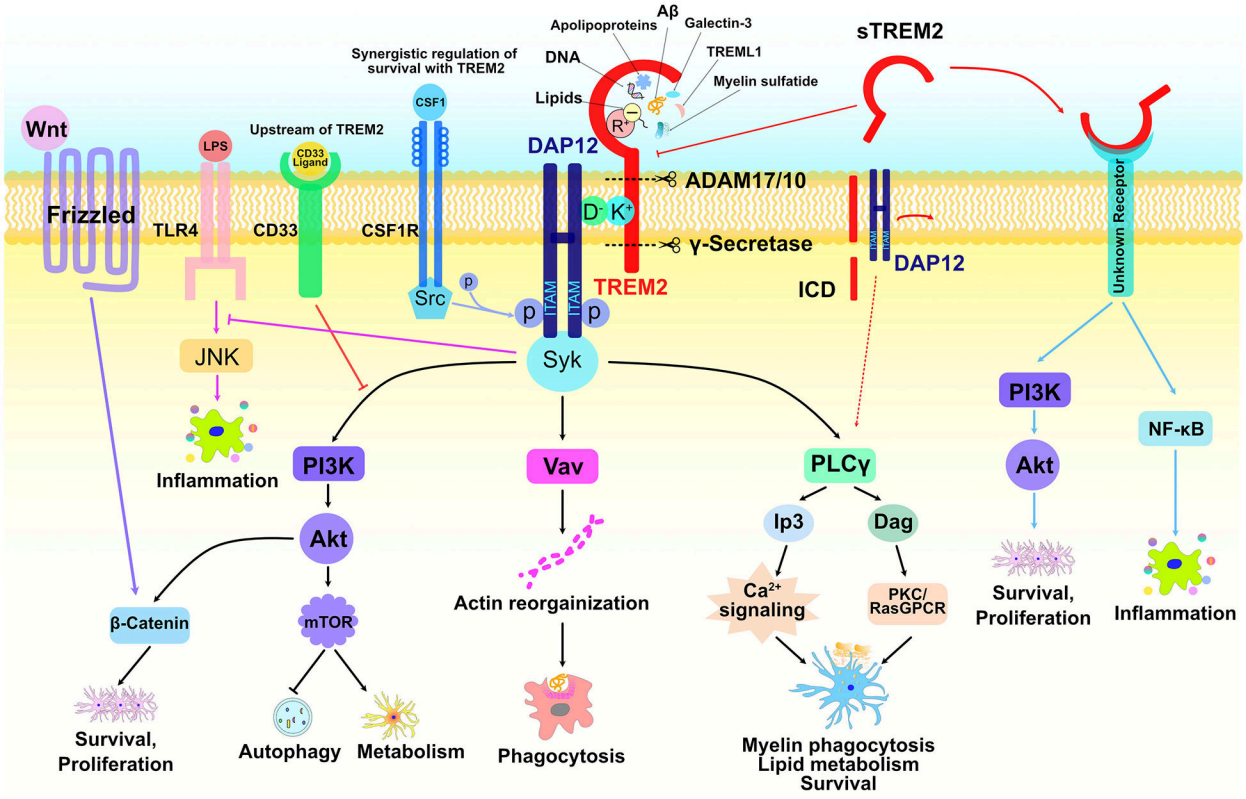

Figure 1. TREM2 signaling mediates microglial immune function.

TREM2 binds to various ligands including lipids, DNA, apolipoproteins, Aβ, galectin-3, TREML1, and myelin sulfatide. Upon ligand binding of TREM2, the ITAM motifs of DAP12 are phosphorylated and recruit Syk that activates signaling mediators including PI3K, Vav, and PLCγ. The downstream signaling of these mediators regulates microglial survival, proliferation, autophagy, phagocytosis, myelin debris removal, and lipid metabolism. TREM2 signaling can crosstalk with other microglial immune receptors including the CSF1R signaling to regulate microglial survival, the toll-like receptor 4 (TLR4) – JNK signaling to regulate inflammatory responses, and the Wnt/β-catenin pathways to regulate microglial survival and proliferation. TREM2 has been shown to act downstream of CD33 in mediating microglial phagocytosis. TREM2 can be cleaved by ADAM17/10 to shed sTREM2, which binds to an unknown receptor and regulates microglial survival and inflammation. The remaining carboxy-terminus can be further cleaved by γ-secretase to generate the intracellular domain (ICD) and release DAP12. which regulates the PLCγ pathway.

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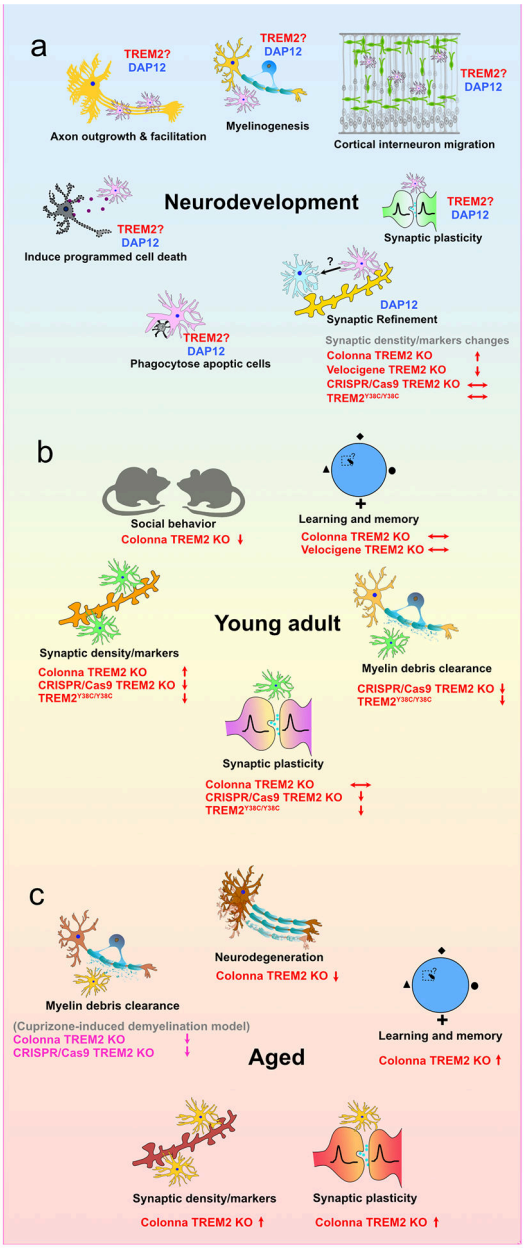

Figure 2. TREM2/DAP12 signaling regulates neuronal function throughout life.

a. During neurodevelopment, DAP12 plays important roles in modulating programmed cell death, phagocytosis of apoptotic cells, axon outgrowth and facilitation, myelinogenesis, cortical interneuron migration, and synaptic plasticity, whereas the role of TREM2 in these events remains elusive. TREM2 is involved in synaptic refinement but the results on the impact of TREM2 deficiency on synaptic density/markers are inconsistent across different mouse models.

b. TREM2 continues to modulate synaptic and cognitive function in healthy adult brains but results from different lines of TREM2 deficient mice are not consistent.

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c. During normal physiological aging, TREM2 deficiency confers protection against neurodegeneration and synaptic/cognitive decline. However, in the cuprizone-induced demyelination, TREM2 deficiency leads to impaired clearance of myelin debris.

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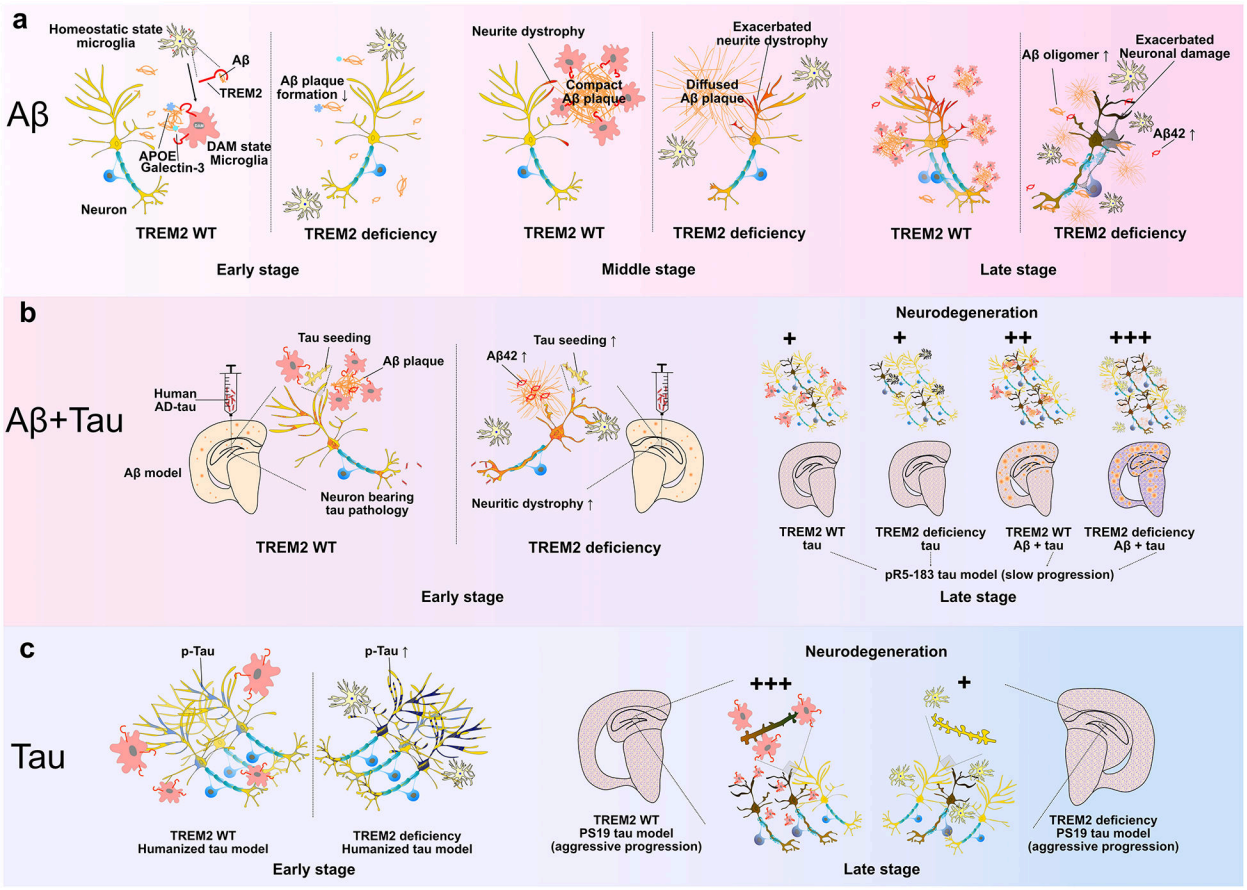

Figure 3. TREM2 acts as a double-edged sword in a disease stage-dependent manner in the context of Aβ and tau pathology.

a. Role of TREM2 in the context of Aβ pathology. Upon detecting Aβ by TREM2, microglia adopt the DAM phenotype and regulate the initial formation of amyloid plaques at the early stage of β-amyloidosis, and TREM2 ligands including APOE and galectin-3 are involved in this process. TREM2 is required for microglia to compact amyloid as the disease progresses to the middle stage. Neurite dystrophy is found near plaques and amyloid compaction limits the amyloid spread and preserves neurites of nearby neurons. In the late stage of the pathology, TREM2 deficiency leads to increased Aβ oligomers, Aβ42, and exacerbated neuronal damage.

b. Role of TREM2 in the context of Aβ and tau pathology. Aβ deposition creates a favorable environment for tau seeding of experimentally injected human AD-tau in dystrophic neurites near plaques. TREM2 deficiency exacerbates tau seeding, increases Aβ42, and worsens neurite dystrophy near plaques. In the late stage, TREM2 has negligible impact on neurodegeneration in a slow progression tau mouse model but is required for ameliorating neuron loss in a mouse model that harbors both Aβ and tau pathology.

c. Role of TREM2 in the context of tau pathology. TREM2 deficiency exacerbates phosphorylated tau early on in a humanized tau mouse model but prevents neurodegeneration later on in an aggressive tauopathy model, PS19.

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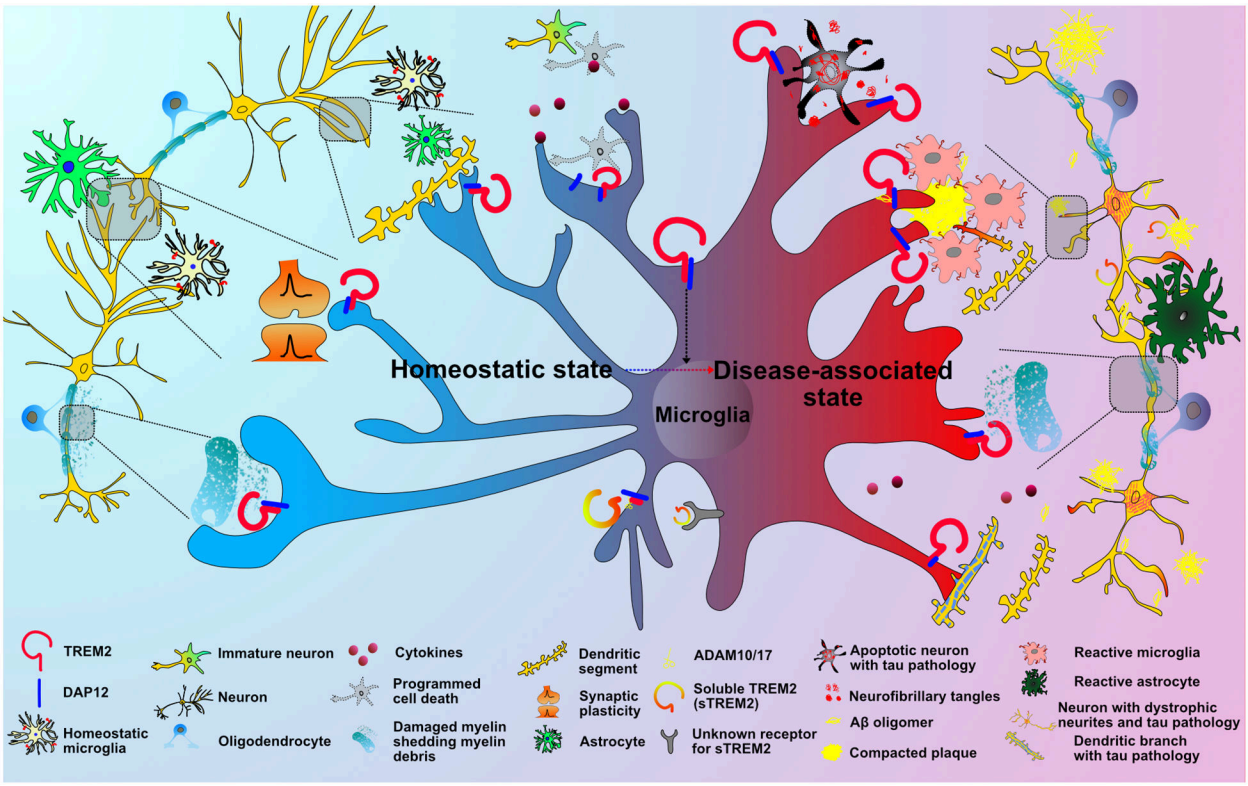

Figure 4. Schematic overview of TREM2/DAP12 mediated microglial function in health and disease.

TREM2 is required for microglia to switch from the homeostatic state to the disease-associated state defined by their gene expression signatures. Under the physiological condition, TREM2/DAP12 signaling mediates programmed cell death during neurodevelopment, modulates synaptic pruning, regulates synaptic plasticity, and clears myelin debris. TREM2 can be cleaved and shed soluble TREM2 that mediates microglial signaling. During the pathogenic process of AD, microglia adopt the disease-associated state. TREM2/DAP12 signaling regulates neurodegeneration, encompasses amyloid plaques to protect neurite dystrophy, mediates myelin debris removal, and limits the spread of pathological tau.

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Table 1.

Effects of TREM2 deficiency on cognitive and synaptic function in normal aging in mouse models

Models	Conditions	Major effects of TREM2 deficiency	References
Colonna *Trem2* KO	Neurodevelopment	↑Synaptic density	(Filipello and others, 2018)
	Young adulthood	↑Synaptic density ↓Social behavior	(Filipello and others, 2018; Qu and Li, 2020)
	Aged	↑Synaptic density ↑Synaptic plasticity & learning and memory ↓ Neuron loss	(Qu and Li, 2020) (Linnartz-Gerlach and others, 2019)
Velocigene *Trem2* KO	Neurodevelopment	↓Synaptic density	(Jay and others, 2019)
CRISPR/Cas9 *Trem2* KO & TREM2$^{Y38C/Y38C}$	Young adulthood	↓Myelin debris clearance ↓Synaptic markers and plasticity	(Jadhav and others, 2020)
Cuprizone-induced demyelination	Young adulthood/aged animals	↓Myelin debris clearance	(Poliani and others, 2015; Nugent and others, 2020)

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Table 2.

Effects of TREM2 deficiency on Neuropathology in AD mouse models

Pathology	Stage	Major effects of TREM2 deficiency	References
Aβ	Early stage	↓Initial amyloid plaque formation ↑ Pro-inflammatory cytokines ↑Synaptic spine density	(Jay and others, 2017a; Sheng and others, 2019; Ren and others, 2020)
	Middle stage	↑Plaque associated neurite dystrophy ↓Amyloid plaque compaction	(Wang and others, 2016; Yuan and others, 2016; Parhizkar and others, 2019; Meilandt and others, 2020)
	Late stage	↓ Aβ plaque accumulation ↑Aβ42:Aβ40 ratio and Aβ oligomers ↑Neuron damage	(Parhizkar and others, 2019; Meilandt and others, 2020)
Aβ+Tau	Early-Middle stage	↑Tau seeding and spreading ↑Plaque associated neurite dystrophy ↓Microgliosis	(Leyns and others, 2019; Lee and others, 2021)
	Late stage	↑Neurodegeneration	(Lee and others, 2021)
Tau	Early stage	↑Tau pathology	(Bemiller and others, 2017)
	Late stage	↓Neurodegeneration	(Leyns and others, 2017; Gratuze and others, 2020)