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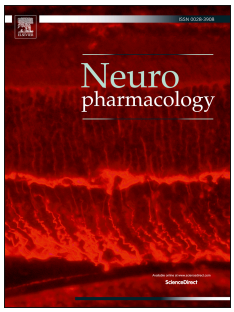

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Microglia and TREM2

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Abstract: TREM2 is a membrane receptor solely expressed on microglia in normal brain. In this review we outline recent advances in TREM2 biology and its implications for microglial function, with particular emphasis on findings from iPSC-derived microglia (iMG) expressing TREM2 loss-of-function mutations. Alterations in receptor proximal and distal signalling underlie T*REM2* risk variants linked to neurodegenerative disease, principally NH-linked FTD, and late-onset AD, but emerging data suggest roles for TREM2 in PD, MS and ALS. TREM2 downstream functions include phagocytosis of myelin debris, amyloid beta peptides, and phosphatidylserine-expressing cells (resulting from damage or stress). Microglial survival, migration, DAMP signalling, inflammasome activation, and intercellular signalling including tau spreading via exosomes, as well as roles for sTREM2 ain protection and as a biomarker are discussed. The role of TREM2 in metabolic homeostasis, and immunometabolic switching are discussed regarding microglial responses to damage and protection. The use of iPSC models to investigate the role of TREM2 in AD, PD, MS, ALS, and other neurodegenerative diseases could prove invaluable due to their ability to recapitulate human pathology, allowing a full understanding of TREM2 and microglial involvement in the underlying disease mechanisms and progression.

Abbreviations: Aβ, amyloid beta peptide; AD, Alzheimer's disease; AKT, protein kinase B; ADAMs, a disintegrin and metalloproteases; ApoE, apolipoprotein E; AVV, Adeno-Associated Virus; CSF, cerebrospinal fluid; CTF, c-terminal fragment; DAMP, damage-associated molecular patterns; DAP12, DNAX-activating protein of 12 kDa; ERK, extracellular-signal regulated kinase; FTD, frontotemporal dementia; IgG, immunoglobulin G; iMG, inducible pluripotent stem cell-derived microglia; iMAC, inducible pluripotent stem cell-derived macrophage; IP_3, inositol trisphosphate; ; LOAD, late-onset Alzheimer's disease; LPS, lipopolysaccharide; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; NFκB, nuclear factor kappa B; NHD, Nasu-Hakola disease; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; PAMP, pathogen associate molecular patterns; PC, phosphatidylcholine; PLCγ2, Phospholipase Cγ2; PS, phosphatidylserine; PS+, external phosphatidylserine expressing cells; SRC, proto-oncogene c-Src protein tyrosine kinase, SYK, spleen protein tyrosine kinase; sTREM2, soluble TREM2; TREM2, triggering receptor expressed on myeloid cells 2; TYROBP, transmembrane immune signalling adaptor.

Background: Up until approximately 10 years ago, most of the research on the immunological, cytological and molecular pathways in microglia was carried out using animal models, both *in vivo* and *in vitro*, predominantly rodent, with limited complementary studies on human microglia other than end-state postmortem tissue or isolated peripheral macrophages as models of human microglia. This was in part due to the problems of obtaining sufficient fresh human tissue combined with the technical resources available at that time. Advances in cell and molecular biology have allowed the development of new human models of microglia, particularly regarding the development of iPSC-derived microglial models (for review see Pocock and Piers 2018). Coupled with this are the advances in genetics and molecular biology which have led to the identification of gene variants linked to disease and the production of iPSC-derived cells from patients expressing the exact gene variant of interest (see Michalski and Wen 2023 for a review of their use in neurological and psychiatry disease). These

advances have allowed the production of powerful and relevant models with which to decipher the ramifications of disease-linked gene variants. Furthermore, development and refinement of CRISPR technologies and Custom Adeno-Associated Virus (AAV) methodologies have allowed the specific and stable manipulation of gene expression and more available cell lines. A framework for the clarification of iMG in terms of "signature" genes and proteins, particularly receptors, has allowed a relatively consistent approach to the culture of these cells (Haenseler et al., 2017, Garcia-Reitboeck et al., 2018; McQuade et al., 2018; Butovsky & Weiner 2018; Pocock & Piers 2018) and allows confidence in their use as models of human microglia.

TREM2 common variant/Wild-type signalling: Triggering receptor expressed on myeloid cells 2 (TREM2) is a transmembrane protein expressed on immune cells such as macrophages and microglia, as well as osteoclasts and dendritic cells (Colonna 2023). In the CNS microglia are the sole expressor of this protein. TREM2 is a type 1 (IgG) transmembrane protein consisting of 230 amino acids with an external immunoglobulin-like domain and a transmembrane sequence, and two N-linked glycans (Park et al., 2015). TREM2 is co-expressed with DNAX-activating protein of 12 kDa (DAP12)/ transmembrane immune signalling adaptor (TYROBP), (henceforth shortened to DAP12) which resides entirely within the cell **(Figure 1)**. The long ectodomain of TREM2 can be cleaved by sheddases, such as a disintegrin and metalloproteases (ADAMs) (Thornton et al., 2017). In humans, TREM2 is shed predominantly by ADAM17 but also by ADAM10 at the amino acid site H157-S158.

Until quite recently, the natural ligand of TREM2 was unknown. Lipid binding arrays with recombinant TREM2 revealed that TREM2 binds to anionic and zwitterionic lipids (Wang et al., 2015). These include anionic carbohydrates, anionic bacterial products and various phospholipids including aminophospholipid ligands, phosphatidylserine, phosphatidylethanolamine, and phosphatidylcholine, glycolipids, and apolipoproteins (notably ApoE) (Cannon et al., 2012; Atagi et al., 2015; Wang et al., 2015; Shirotani et al., 2019). TREM2 antibody crosslinking is also effective, suggesting receptor dimerization/clustering may play a role in signal transduction in different TREM2 expressing cells (Schlepckow et al., 2020; Ibach et al., 2021) including iMG (Cosker et al., 2021).

In human iMG, apoptotic cells (which flip phosphatidylserine to their external plasma membrane surface), are an effective ligand for activating downstream signalling pathways in iMG (Garcia-Reitboeck et al., 2018, Cosker et al., 2021) as well as in TREM2 overexpressing cell lines (Shirotani et al., 2019; Singh et al., 2021). Additionally, phosphatidylserine-enriched liposomes are effective at inducing down-stream signalling in iMg (Cosker et al., 2021) as are PS/phosphatidylcholine- (PS/PC) or PC-enriched liposomes (Hashioka et al., 2007; Boudesco et al., 2022).

Binding of ligand to TREM2 induces proteolytic cleavage of the TREM2 ectodomain (Wunderlich et al., 2013; Glebov et al., 2016), subsequent interaction of the intracellular C-terminal fragment (CTF) of TREM2 with DAP12, which involves a gamma-secretase acting at the intra-cellular C terminal fragment of TREM2 (Glebov et al., 2016). This induces a downstream phosphorylation, mediated by SRC tyrosine kinase phosphorylation of the adaptor protein, DAP12, leading to spleen tyrosine kinase (SYK) phosphorylation. Downstream mitogen-activated protein kinase (MAPK) is phosphorylated, leading to extracellular-signal regulated kinase (ERK) and protein kinase B/serine-threoinine specific kinase (AKT) phosphorylation and induction of PI3Kinase signalling. The latter induces phagocytosis, by prompting the release of inositol trisphosphate (IP_3)-gated calcium stores, and subsequent calcium-dependent actin reorganisation. In iMG, following exposure to PS-expressing liposomes, apoptotic cells or TREM2 antibodies, SYK phosphorylation can be detected at 1 min but typically becomes maximal at 5 minutes, as does the phosphorylation of ERK and AKT (Cosker et al., 2021). Following antibody-induced activation of TREM2, cytoplasmic calcium is increased, mediated by Phospholipase Cγ2 (PLCγ2), which can subsequently modulate phagocytosis and survival, but not affect LPS signalling (Obst et al., 2021). Various proposed signalling pathways have been put forward which occur distal to the activation TREM2, and these are discussed in depth by Zing et al., 2015, although many of these have

yet to be confirmed in iMG/iMAC. Upon ligand binding, the TREM2 ectodomain undergoes proteolytic cleavage (Glebov et al., 2016), allowing the intracellular C-terminal fragment (CTF) of TREM2 to interact with DAP12, thereby activating SYK–PI3K/MAPK signalling and releasing IP_3-gated calcium stores to promote phagocytosis (Wunderlich et al., 2013; Glebov et al., 2016) (**Figure 1)**.

sTREM2: Soluble TREM2 (sTREM2) comprises the Ig-like domain and a portion of the stalk region of the TREM2 protein and is a constitutively shed soluble 17 kDa N-terminal cleavage fragment (Thornton et al., 2017). Shedding of sTREM2 can occur in response to external stimuli and can function independently of TREM2 to regulate interactions between other brain cells (Wunderlich et al., 2013). sTREM2 may be generated via two different mechanisms: (1) proteolytic shedding of the TREM2 ectodomain and (2) alternative splicing (Sheng et al., 2021). Proteolytic cleavage of membrane-bound TREM2, results in the shedding of the 17 kDa N-terminal ectodomain of TREM2 into the extracellular space (Feuerbach et al., 2017; Thornton et al., 2017). Following ADAM-mediated shedding of the TREM2 ectodomain, the remaining intramembrane C-terminal fragment (CTF) is cleaved by γ-secretase, thus releasing it from the membrane (Wunderlich et al., 2013). γ-secretase cleavage is essential for TREM2 signalling as inhibition of γ-secretase results in accumulation of TREM2 CTF at the membrane which traps DAP12, leading to reduced DAP12 phosphorylation (Wunderlich et al., 2013) and downstream TREM2 signalling (Glebov et al., 2016) **(Figure 1).**

At the cell surface, full-length TREM2 has a half-life of less than 1 h, due to the rapid receptor turnover (Thornton et al., 2017). Several different external stimuli have been shown to regulate sTREM2 shedding such as by acute (2 h) lipopolysaccharide (LPS) and IL-1β stimulation in primary mouse microglia (Zhong et al., 2019) and by Aβ oligomers in TREM2-overexpressing cells (Vilalta et al., 2021). A chronic 24 h TLR4 and IFNγ stimulation causes sTREM2 levels to fall in iMG (Vasilopoulou et al., 2024), and sTREM2 does not accumulate in cell culture medium. In iMG, stimulation with a TREM2 ligand, PS+ apoptotic cells, had no significant effect on sTREM2 levels, although it was also shown that PS+ apoptotic cells bind sTREM2 in the medium and may give the impression of reduced shedding in an ELISA (Cosker et al., 2021).

In human brain, four different TREM2 isoforms have been identified including ENST00000373113 which encodes the 230 amino acid (aa) full-length TREM2, as well as the alternatively spliced isoforms ENST00000373122, ENST00000338469 (Jin et al., 2014) and a TREM2 isoform lacking exon 2 encoding the Ig-like V-type domain (Kiianitsa et al., 2021; Shaw et al., 2022). Interestingly, the alternatively spliced ENST00000373122 (222 aa) contains a different protein sequence after exon 3 compared with full-length TREM2 and ENST00000338469 (219 aa) completely lacks exon 4 which encodes the transmembrane domain of the receptor (Jin et al., 2014). These two isoforms have been found to be translated and secreted as sTREM2 into the extracellular space of transfected HEK-293T cells (Moutinho et al., 2023). While full-length TREM2 is the most highly expressed isoform, the alternatively spliced 219 aa sTREM2 have been found to constitute 25% of total TREM2 mRNA levels in human cortex suggesting that up to 25% of sTREM2 could be due to secretion of alternatively spliced sTREM2 rather than shedding (Del-Aguila et al., 2019). The function of sTREM2 remains poorly understood. One hypothesis is that sTREM2 may act as a decoy receptor, competing for endogenous ligands with membrane-bound TREM2. Support for a protective role for sTREM2 in AD includes the findings that sTREM2 binds Aβ oligomers, inhibits Aβ aggregation (Vilalta et al., 2021; Sheng et al., 2021; Belsare et al., 2022) and protects against Aβ-induced neurotoxicity in primary glia-neuron co-cultures (Vilalta et al., 2021); such findings were less prominent in the AD risk variant $TREM2^{R47H}$ expressing microglia (Vilalta et al., 2021; Belsare et al., 2022). In contrast to a protective role of sTREM2, Moutinho et al. (2023) demonstrated that certain splice variant generated sTREM2 isoforms inhibited long-term potentiation (LTP) in mouse brain slices, an effect which was abolished by inhibition of the $GABA_A$ receptor. Soluble TREM2 CSF levels are modified by colocalisation of TREM2 at the membrane with membrane-spanning 4-domains subfamily A (MS4A4A), and variants in the gene

MS4A4A associated with lower AD risk enhanced CSF sTREM2 concentrations whilst the opposite is true for variants associated with increased AD risk (Deming et al., 2019).
The lack of sTREM2 shedding in FTD and NHD TREM2 variants also infers a critical role for sTREM2 in limiting pathogenesis. AD patients with elevated CSF sTREM2 are predicted to demonstrate slower disease progression, promoting the suggestion that sTREM2 levels attenuate cognitive and clinical decline (Ewers et al., 2019). Furthermore, microglia expressing TREM2 may corral Aβ into plaques, limiting neurotoxicity (Basha et al., 2023).

TREM2 Variants linked to Dementia: Neurodegeneration and neuroinflammation are multicomplex disorders. However, until recently very few were linked primarily to microglial dysfunction as a possible starting point. One such disease is Nasu-Hakola disease (NHD), the first disease linked to *TREM2* variants. Nasu–Hakola disease is a rare but fatal brain and bone disorder (Hakola, 1972), caused by homozygous inheritance of null or hypomorphic variants of the *TREM2* gene (Klünemann et al., 2005). NHD, also known as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL), is a genetic disorder characterized by progressive presenile dementia and bone cysts (Bianchin et al., 2004; Chouery et al., 2008; Paloneva et al., 2001, 2003). Patients with NHD develop early onset frontotemporal dementia and cyst-like bone lesions. Histologically, the disease manifests mainly in the white matter of the frontotemporal lobe and basal ganglia, and NHD brains show neuronal loss, astrocyte proliferation and hypertrophy. There is also extensive microglial activation in the cerebral white matter, and this finding alerted researchers to the possibility that this disease might be driven by microglial dysfunction. *TREM2* variants linked to NHD/FTD encode mutations in the TREM2 protein; Q33X, Y38C, T66M and W50C, and whilst extremely rare, their study helped revealed the role TREM2 plays in the CNS.

One of the first studies that TREM2 might be driving neurodegeneration was the finding that knock-down of TREM2 prevented apoptotic cell clearance (Takahashi et al., 2005), leading to suggestions this receptor may play an important role in tissue homeostasis (Neumann and Takahaski 2007). Subsequently, there was an explosion of interest in this receptor, when two papers, published back-to-back, and using genome, exome, and Sanger sequencing, described 22 variants in *TREM2.* The most common risk variant, rs75932628 (encoding R47H), was linked to late onset Alzheimer's disease, (LOAD), the most pervasive form of AD (Guerreiro et al., 2013, Jonson et al., 2013), and although rare at a prevalence of 0.3-0.6% of the population, it confers a risk of developing LOAD to carriers 2 to 11-fold above the general population (Finelli et al., 2015). There was a concomitant interest in the role of this receptor in mouse models of AD and a recent review eloquently highlights some of the confounding findings regarding this research when compared with predicted human outcomes (Gandy and Ehrlich 2023). We have also recently highlighted the complexities of these models regarding their replication of human TREM2 genetics (Xiang et al., 2018).

Patient fibroblasts with the NHD/FTD TREM2 mutations $T66M^{hom}$ and $W50C^{hom}$ and non-affected $T66M^{het}$ were used to derive iMG and to subsequently assess the impact of these variants on microglial function (Garcia-Reitboeck et al., 2018). At basal, there was no detectable sTREM2 shedding in the homozygous hypomorphs and in addition, the expression of TREM2 was absent at the surface of the cells and showed reduced maturation and glycosylation within the Golgi, absence of the C-terminal fragment, impaired phagocytosis of apoptotic cells, but no reduction in the phagocytosis of ligands linked to toll-like receptor TLR2 or TLR4 function or any obvious effects on cytokine secretion (ether basal or LPS-evoked). The homozygous LoF variants also displayed lower survival following growth factor withdrawal, as well as reduced migration. These findings suggest that when a human microglial cell is devoid of TREM2 at its surface, there is a reduced ability in its response to a specific TREM2-recognised DAMP (such as apoptotic cells) but no effect on their ability to respond to PAMPS (bacteria, fungi and viruses, classical PAMP ligands of TLR4 and TLR2). Their lowered survival and migrational ability also point to crucial roles of TREM2 down-stream signalling in these processes. Subsequent

analysis of these NHD variants compared with iMg derived from patient fibroblasts expressing the LOAD TREM2 variant R47H^{het} show quite distinct differences in their deficits.

In iMG, The R47H^{het} variant, linked to LOAD, showed no significant reduction in basal sTREM2, likewise a CRISPR-Cas9 R47H^{hom} iMG line showed no significant reduction in sTREM2 shedding compared with parental isogenic control (Cosker et al., 2021). Clinical studies revealed that sTREM2 levels are elevated in cerebrospinal fluid (CSF) of AD patients (Heslegrave et al., 2016, Ewers et al., 2019), and positively correlated with the levels of classical CSF biomarkers of neural injury, t-tau and p-tau, indicating that it is a reliable predictor of early-stage AD (Heslegrave et al., 2016; Yang et al., 2020) before Aβ pathology (Suárez-Calvet et al., 2017). sTREM2 builds up in tissue culture medium at basal conditions, supporting constitutive production; however following stimulation of TLR4, sTREM2 levels are reduced, suggesting that either it is degraded, or internalisation of TREM2 prevents this shedding. Proximal signalling to TREM2/DAP12, SYK, ERK and AKT all show decreased phosphorylation in R47H^{het} iMG following exposure of TREM2 ligands including apoptotic cells, liposomes and TREM2 antibody (Cosker et al., 2021). Furthermore, whilst the activation of the inflammasome is regarded as a pathological response in AD, in R47H expressing iMG, inflammasome activation is attenuated as is the activation of Caspase 1 and the production of IL-1β.

As well as T66M^{hom} and W50C^{hom}, other TREM2 mutations show loss of TREM2 shedding, including Q33X, Y38C and W38C (Schlepckow et al., 2017). These mutations are located in the Ig-like domain of the TREM2 protein. One TREM2 AD variant, H157Y, which is located in the stalk region of the protein, shows increased sTREM2 shedding (Thornton et al., 2017; Yang et al., 2020). Interestingly the increased shedding observed in this variant reduced phagocytosis of *E.coli* (Schlepckow et al., 2017). How this mutation affects phagocytosis of recognised TREM2 ligands has not yet been ascertained, and the effect of this mutation on iMG functions has also not yet been examined.

TREM2 and other neurodegenerative diseases – PD, MS, ALS: While the primary focus of research on TREM2 lies within AD, missense mutations of TREM2 have also been associated with an increased risk for neurodegenerative diseases other than AD, including Parkinson's disease, multiple sclerosis, (MS) and amyotrophic lateral sclerosis (ALS) by some studies (Cady et al 2014; Rikos et al., 2019; Peplonska et al., 2018; Dardiotis et al., 2021). Whilst we discuss here the role of iMG for investigating TREM2 in disease, further reviews of the relevance of iPSC

Liang et al., (2024) showed that TREM2 facilitates iPSC differentiation into dopaminergic neurons via TGF-β pathway activation, and stereotaxic injection of iPSC overexpressing TREM2 into the brains of 6-OHDA lesioned mice promoted neuronal repair, further suggesting a protective role of TREM2 in PD. Interestingly, TREM2 deficiency attenuated an α-Synuclein induced inflammatory response in BV2 microglia and exacerbated dopaminergic loss in response to α-Synuclein overexpression *in vivo* (Guo et al 2019). Moreover, CSF sTREM2 is increased in PD patients and positively correlated with CSF total α-Synuclein (Peng et al., 2020; Gu et al., 2023), further corroborating a link between TREM2 with PD; however exact mechanisms are still underexplored.

Regarding MS, increased TREM2 expression was detected in active demyelinating MS lesions, and TREM2-/- and TREM2+/- mice, following CPZ-induced demyelination, demonstrated impaired clearance of myelin debris (Cantoni et al., 2015; Cignarella et al., 2020). Consistent with this, Wang et al., (2023) showed that microglia isolated from TREM2-/- and MDMs from R62H LoF carriers display impaired myelin phagocytic capacity and migration, and suggested these deficiencies, as well as impaired cholesterol metabolism, may contribute to impaired remyelination observed in TREM2-/- mice. In turn, potentiating TREM2 function by an activating antibody (AL002a) increased myelin uptake and intracellular degradation in TREM2 deficient *in vitro* and *in vivo* models and positively impacted axonal health after CPZ-induced demyelination in vivo (Cignarella et al., 2020).

The TREM2^{R47H} variant is a risk gene for the development of ALS (Cady et al., 2014). Mechanistically, Xie et al., (2022) provided evidence suggesting that TDP-43, an ALS-related protein linked to neurodegeneration, may be a ligand for TREM2, and consistent with this, TREM2 deficient microglia displayed an inability to phagocytose TDP-43 inclusions. Furthermore, TREM2 transcripts in postmortem ALS spinal cord are deregulated, and suggested blood and CSF sTREM2 as a putative ALS biomarker (Jerico et al., 2023). Using iPSC models for investigating the role of TREM2 in PD, MS, ALS, and other neurodegenerative diseases could prove invaluable in better recapitulating human pathology and understanding TREM2 involvement in the underlying disease mechanisms and progression.

TREM2 and NLRP3 inflammasome activation in microglia: The NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) is the best studied inflammasome, and is activated upon exposure to pathogens, such as Aβ (Wang et al. 2017), leading to cleavage and activation of caspase-1 and release of the proinflammatory cytokines IL-1beta and IL-18 (reviewed in Liang et al. 2022). Using iPSC-derived microglia from patient lines expressing the TREM2^{R47H} mutation, Cosker et al., (2021) showed that TREM2^{R47H} cells exhibited impaired NLRP inflammasome activation that was dependent on SYK signalling, resulting in reduced ASC speck formation, reduced Caspase-1 activation, and reduced IL-1beta production. Similar findings were observed in TREM K/O mice (Jung et al., 2022).

TREM2 might also impact on the NLRP3 inflammasome through *PLCG2*, another late onset Alzheimer's risk factor gene (Andreone et al., 2020). PLCγ2 is required for TREM2 functions in iPSC-derived microglia, such as cell survival, phagocytosis, and processing of neuronal debris. Interestingly, TREM2^{R47H} cells having increased accumulation of cholesterol esters in response to incubation with myelin debris *in vitro* (Andreone et al., 2020). In SIM-A9 microglial cells, a high cholesterol load resulted in activation of the inflammasome leading to a protective microglial phenotype (de Dios et al., 2023) and there is speculation that TREM2 itself might act as a sensor for lipids such as cholesterol associated with Aβ (Wang et al., 2015). Another late onset Alzheimer's risk factor gene that might link TREM2 to the NLRP3 inflammasome is *INPP5D,* which encodes SHIP1. Studies in human iPSC microglia have shown that reduced INPP5D activity induces the formation of the NLRP3 inflammasome (Chou et al., 2023, Terzioglu et al., 2023). INPP5D is a scaffolding protein, that binds to DAP12, the signalling partner of TREM2 (Peng et al., 2010) and SHIP1 has been shown to regulate TREM2 signalling (Obst et al., 2020).

TREM2 and microglial metabolism: TREM2 can modify metabolic pathways, including oxidative phosphorylation, glycolysis and lipid metabolism, regulating microglia activation states and functions. In a normal homeostatic state, microglia mostly rely on oxidative phosphorylation for ATP production, but they reprogram their metabolism toward glycolysis when activated (Lynch et al., 2020). This immunometabolic switch is essential in disease context since it drives microglia immune response, enabling them to rapidly meet their energy demands and perform functional responses. Several studies have highlighted the crucial role of TREM2 in maintaining microglia metabolic fitness and enabling the transition of microglia towards a disease-associated microglial (DAM) profile (Ulland et al., 2017, Keren-Shaul et al., 2017). DAM state is characterised by the transcriptional alteration of genes that control metabolic processes (Lauro & Limatola 2020), implying that it is the immunometabolic shifts that draw a link between TREM2 dysregulation and DAM profile in disease.

In iMG from AD patients carrying TREM2 LoF variants, including R47H, W50C and T66M variants, deficits in oxidative phosphorylation and mitochondrial respiratory capacity were observed (Garcia-Reitboeck et al., 2018; Piers et al., 2020), which also seemed to be the case in complete absence of TREM2 (Reich et al., 2020). Additionally, TREM2 LoF variant iMG presented glycolytic deficiencies and an inability to perform the expected immunometabolic switch towards glycolysis upon pro-inflammatory insult, which was consistent with the observed impairments in glycolytic-dependent functional responses due to TREM2 LoF (Piers et al, 2020). For example, Aβ1-42 phagocytosis was

impaired in TREM2 LoF iMG, but it was restored upon activation of PPAR-γ (Piers et al., 2020), a glitazone receptor involved in glucose metabolism and mitochondrial biogenesis, further supporting a straightforward connection among TREM2, metabolism and functional responses, which, when "broken", can be detrimental and even contribute to disease progression. Indeed, recently published metabolomic and transcriptomic analysis in APP/PS1 mice lacking TREM2 demonstrated significant abnormalities associated with glucolipid metabolism, suggesting that TREM2-dependent metabolic dysregulation contributes to AD development (Wang et al., 2023). Conversely, boosting TREM2 signaling by an agonistic antibody enhanced microglial energetic capacity by increasing mitochondrial metabolic pathways, lipid catabolism and glucose oxidation in iMG (van Lengerich et al., 2023). In a familial AD mouse model expressing human TREM2, antibody-mediated TREM2 activation ameliorated glucose metabolism, induced transcriptional changes related to metabolic pathways, and increased brain glucose uptake by FDG-PET imaging, which notably, had been previously reported to be reduced in TREM2 pT66M loss of function knock-in mice (Kleinberger et al., 2017). Tagliati et al., (2024) extended the TREM2 role in shaping microglia bioenergetics to neurons by uncovering a non-cell-autonomous regulation of neuronal mitochondrial metabolism by TREM2 during development.

The involvement of TREM2 in microglial metabolism encompasses its intimate association with lipid metabolism of cholesterol, myelin and phospholipids, with implications for neurodegenerative and demyelination diseases. This association, at least partly, arises from the TREM2 capacity to bind to lipid-associated ligands, including the apolipoprotein E (apoE). ApoE, a risk gene for AD, mediates the endocytosis and efflux of lipids and cholesterol; thus, it is possible that the effect of TREM2 on lipid-related pathways is linked to this cholesterol transporter, in which uptake is regulated by TREM2 (Yeh et al., 2016). When microglia are exposed to apoptotic cells or myelin debris, lipids can serve as signalling molecules to initiate phagocytosis (Nadjar 2018), affecting at the same time microglia metabolic performance by supplying lipids that feed into the metabolic pathway. Indeed, PS+ cells, upon binding to TREM2, increase metabolic performance in common variant iMG, and rescue metabolic deficits in R47H variant iMG, possibly acting as an energy source (Cosker et al., 2021). Accumulating evidence indicates that TREM2 absence leads to impaired lipid metabolism in microglia. Lipidomic, transcriptome analyses and *in vitro* cell biological studies (iMG and BMDMs) showed that TREM2 deficiency results in cholesterol efflux defects characterized by intracellular accumulation of cholesterol esters (CE) in models characterized by demyelination-induced lipid overload (cuprizone treatment) (Nugent et al., 2020). Likewise, myelin-exposed TREM2$^{-/-}$ iMG was shown to present increased levels of several types of lipids compared to WT iMG, processes that seem to occur in a PLCγ2 dependent manner (Andreone et al., 2020). This was also shown to be the case in R47H expressing iMG, consistent with the increase in CE levels in AD patients (Chan et al., 2020). However, the role of TREM2 in lipid metabolism and the reported lipid accumulation seems to be more complicated, possibly context- or variant- dependent. Recent data show that iMG from NHD patients carrying the TREM2 LoF pQ33X mutation presented lysosomal dysfunction, downregulation of cholesterol genes and reduced lipid droplets compared to control iMG, and these deficits were rescued by enhancing lysosomal biogenesis through mTOR dependent and independent pathways (Filipello et al., 2023). Similarly, upon demyelinating injury, TREM2 deficient mice exhibited an inability to respond efficiently to cholesterol exposure, presented reduced formation of lipid droplets and development of ER stress (Guna et al 2021). Work from our group has shown that R47H and TREM2$^{-/-}$ iMG display decreased lipid droplet content compared with common variant iMG, and this could be normalised to control levels when supplementing microglia with TCA substrates (Vasilopoulou et al., 2024). The identified link between TREM2 and microglial metabolism highlights TREM2 as a promising target for therapeutic interventions in conditions marked by metabolic dysfunction and lipid metabolism dysregulation, including neurodegenerative and demyelinating diseases.

Exosomal secretion from TREM2 Lof microglia: Microglia provide neuronal support through mechanisms often involving reciprocal neuron-microglia communication or interaction with astrocytes (Szepesi et al. 2018; Lana et al. 2021). Several studies have highlighted a role for TREM2 in

microglia-neuronal interactions during development and in a disease context, maintaining proper synaptic balance and influencing neuronal wiring and brain connectivity (Qu and Li 2021; Fracassi et al. 2023; Tagliatti et al., 2024). Besides direct microglia-to-neuron contact, TREM2 dysregulation could result in an altered secretome, which in turn would differentially alter neuronal trajectories. Exosomes are extracellular vehicles with a diameter of 40-120 nm, released from all CNS cells, and containing mitochondrial and cytosolic proteins, metabolic enzymes, microRNA, mRNA and cell surface receptors, which are taken into recipient cells, to influence their behaviour (Beatriz et al., 2021). TREM2 is found in exosomes and thus may influence microglia intercellular signalling (Mallach et al. 2021a; Mallach et al. 2021b;). Exosomes secreted by iMG expressing $TREM2^{R47H}$ display reduced secretion levels and altered content compared with $TREM2^{CV}$ exosomes (Mallach et al., 2021a; Mallach et al., 2021b). Whilst $TREM2^{CV}$ exosomes support the survival of stressed neurons, and enhance neuronal development, these functions were compromised by R47H. Interestingly, $TREM2^{R47H}$ exosomal content was enriched in proteins involved in negative regulation of transcription and metabolic processes, indicating that exosome signalling for metabolism is decreased in TREM2 LoF iMG, and, importantly, suggesting reduced metabolic support of neighbouring neurons (Mallach et al 2021a; Mallach et al., 2021b). Indeed, as mentioned above, $TREM2^{-/-}$ microglia affected neuronal metabolic fitness *in vivo* (Tagliati et al 2024). TREM2 also appeared to influence microglia-microglia interactions via exosomes, and subsequent functions such as phagocytosis. Zhu et al., (2022) showed that exosomes can bind to Aβ in a TREM2-dependent manner promoting Aβ phagocytosis by microglia, which was reduced when exosomal TREM2 was defective.

Exosomes can also propagate the spreading of pathological proteins among CNS cells, and TREM2 has been recently shown to affect this process in the context of tau pathology. Indeed, microglia-derived exosomes contribute to the spreading of tau (Asai et al., 2015), and $TREM2^{-/-}$ mice exhibit exacerbated tau spreading in the hippocampus, consistent with synaptic loss and cognitive impairment (Leyns et al 2019; Zhu et al., 2022). As TREM2 is implicated in other neurodegenerative diseases marked by accumulation and spreading of pathological proteins such as α-synuclein in PD models (Guo et al 2019}, it is possible that the role of TREM2 in these diseases entails perturbed microglia exosomal secretion and function in a similar way to that shown for pathological tau, an aspect that deserves future exploration. Taken together, TREM2 exosomal signalling plays a pivotal role in microglial support of neighbouring CNS cells with implications for neurodevelopmental and neurodegenerative diseases.

Therapeutic targeting of microglial TREM2: Given the critical role of TREM2 in neurodegeneration, it is no surprise that targeting TREM2 is being sought as a therapeutic strategy for late-onset AD. Studies using direct over or under expression of TREM2 have shown that this is not a particularly successful strategy with caveats and contradictions to each approach, and overall this approach does not mimic adequately the subtleties of TREM2 variants (eg. Jay et al., 2015; Sheng et al., 2019; Zhao et al., 2022; Jain et al., 2023; see review by Gandy and Erhlich 2023).

In terms of pharmacological interventions, the first evidence of antibody-mediated manipulation of TREM2 was described by Takahashi et al. (2005), where antibody-mediated crosslinking of Flag-tagged TREM2 resulted in activation of downstream signalling pathways such as ERK and improved phagocytosis of apoptotic neurons in transduced primary microglia cultures. Further supporting the hypothesis that TREM2 crosslinking enhances receptor activation is the finding that a tetravalent TREM2 targeted antibody induced a stronger TREM2 activation, and improved microglial migration and phagocytosis compared with its bivalent form in mouse neonatal microglia. The same tetravalent antibody was also able to reduce amyloid pathology and rescue synaptic and neuronal loss in 5xFAD mice (Zhao et al., 2022). Other groups have also reported effects with TREM2 targeted antibodies (Sheng et al., 2019 Wang et al., 2020; Fassler et al., 2021; Ibach et al., 2021; Schlepckow et al., 2020; Szykowska et al., 2021).

The TREM2-targeted monoclonal antibody 4D9, induces cross-lining of TREM2, and binds to the stalk region of TREM2, close to the sTREM2 cleavage site, thereby inhibiting shedding and stabilising the receptor at the surface (Schlepckow et al., 2020), to enhance phospho-SYK signalling, phagocytosis of myelin and Aβ, and increase survival in primary microglia and BMDMs, as well as reduce plaque burden in the Alzheimer's disease (AD) APP knock-in mouse model (Schlepckow et al., 2020). Interestingly, this antibody also enhanced TREM2 expression and reduced the expression of the homeostatic marker P2RY12, explained as a shift from a homeostatic state to a DAM state (Schlepckow et al., 2020). This antibody was also found to bind to CSF sTREM2. Further improvement of this TREM2 antibody by bioengineering it with a monovalent transferrin-receptor binding site, termed an antibody transport vehicle (ATV) facilitates its transfer into the brain (ATV:TREM2). This was further shown to induce microglial proliferation and improve metabolism in human iPSC-derived microglia (van Lengerich et al., 2023).

The AL002c antibody, a mouse IgG1 anti-hTREM2 monoclonal antibody that was generated using the recombinant hTREM2 extracellular domain as an immunogen, binds human TREM2 between S112 and S17 (Wang et al., 2020). This antibody reduced neuritic dystrophy but did not increase the number of microglia round plaques or decrease plaques in the 5xFAD mouse model (Wang et al., 2020). The antibody was well tolerated in phase I clinical trials (Wang et al., 2020), where it lowered CSF sTREM2. The clinically modified version of this humanized monoclonal IgG1 antibody is being developed in a partnership between Alector and AbbVie; AL002 is the first TREM2 targeted antibody to have entered phase II clinical trials for treatment of AD. The therapeutic potential of TREM2 modulation may not be restricted to late-onset AD but also in other neurodegenerative diseases. The mouse TREM2 specific antibody AL002a enhanced microglial phagocytosis and clearance of myelin debris, increased oligodendrocyte precursor accumulation and maturation as well as improved remyelination in the cuprizone model of CNS demyelination (Cignarella et al., 2020). However, in contrast to the beneficial effects of TREM2 activation regarding amyloid and myelin, a recent study reported that chronic TREM2 activation by AL002a exacerbated tau pathology and enhance neuritic dystrophy in a 5xFAD mice seeded with AD-tau (Jain et al., 2023).

With regard to small molecule agonists of TREM2, VigilNeuro report development of VG-3927, as well as a monoclonal antibody VGL101 (Iluzanebar), targeting TREM2 (https://www.vigilneuro.com/pipeline). The antibody binds to an external site on the TREM2 protein, causing TREM2 clustering (Ellwanger et al., 2021; Meier et al., 2023) and prevents sTREM2 shedding in commercial iMG, presumably expressing Cv TREM2 (Tchessalova et al., 2022). Whilst there is pharmaceutical interest in generating small molecules, "monoclonal antibodies (mAb) have a potential advantage over small molecules as they can engage specific epitopes within TREM2 without penetrating the cells thus avoiding unpredictable side effects" as stated by George (2023). Furthermore, tagging human TREM2-activating antibody with a monovalent transferrin receptor (TfR) binding site, termed antibody transport vehicle (ATV), facilitates blood–brain barrier transcytosis in animal models (van Lengerich et al., 2023).

Overall, many of these drugs seem to work by inducing receptor clustering and in turn prevent the shedding of sTREM2, which, given the findings that sTREM2 seems to have beneficial properties, does pose the question of how this might interfere with microglial functions. On the other hand, there is strong genetic evidence linking accelerated sTREM2 shedding with an increased risk for late-onset AD (H157Y variant), suggesting that the potential beneficial functions of sTREM2 may not outweigh the loss of membrane-bound TREM2 on microglia. Upstream targets to modulate TREM2 including iRhom2, MS4A and ApoE (alzforum.org) are also being considered to modulate TREM2 in neurodegenerative disease. Other approaches include targeting of multiple sites on TREM2.

Together, these findings suggest that therapeutic targetting of TREM2 could improve microglial functions and potentially slow down the progression of AD. However, further research is required to better understand the effects of chronic TREM2 stimulation in humans, the time points at which TREM2 stimulation may be beneficial during disease progression, and what patient population could best benefit from such therapeutics. There is also the confounding problem of antibody-based therapeutics inducing Amyloid-Related Imaging Abnormalities (ARIA) with haemorrhage (ARIA-H) or oedema (ARIA-E) as has been reported for anti-amyloid therapies (Withington and Turner 2022) and for the Alector/AbbVie TREM2 antibody AL002 (https://www.alzforum.org/therapeutics/al002).

Conclusions:

- TREM2 is a membrane receptor expressed on microglia, the immune cell of the brain, and loss of function mutations in this receptor are linked to increased risk of developing neurodegenerative diseases, including late-onset Alzheimer's disease.
- Here we have discussed the biology of this receptor, focussing on studies in human iMG. The ramifications of TREM2 loss-of-function mutations on human microglia depends on where the mutation is located in the protein, whether the variant is heterozygous or homozygous, and can affect a number of pathways, including phagocytosis, metabolism, shedding of soluble TREM2, inflammasome activation, survival, migration and exosome secretion.
- Novel TREM2 antibody-based therapeutics are now under investigation as well as the development of small molecule compounds. These compounds aim to promote activation of TREM2 to overcome the consequences of loss of function variants linked to AD, providing promise for potential treatments for AD.

Figure Legends

Figure 1

TREM2 ligand-induced pathway activation in microglia. See main text for references.

Figure 2

Location of TREM2 variants linked to NHD and LOAD in TREM2 protein. See main text for references.

Table 1

Reported effects of TREM2 variants and Knock-outs on function in iPSC-derived microglia or macrophages. See main text for references.

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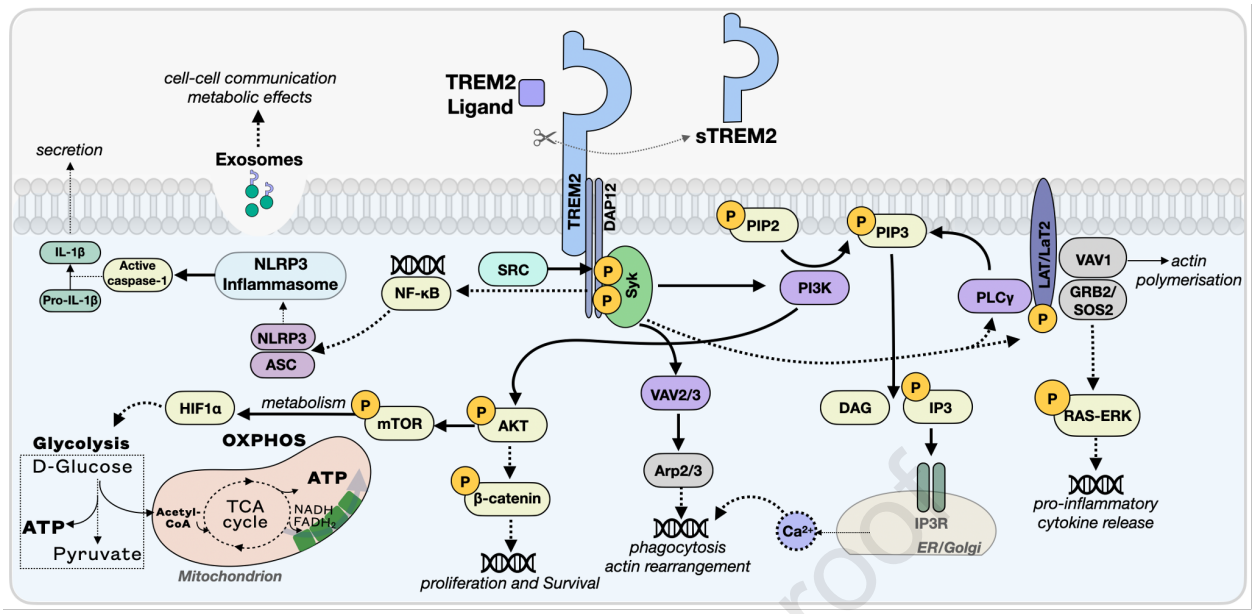
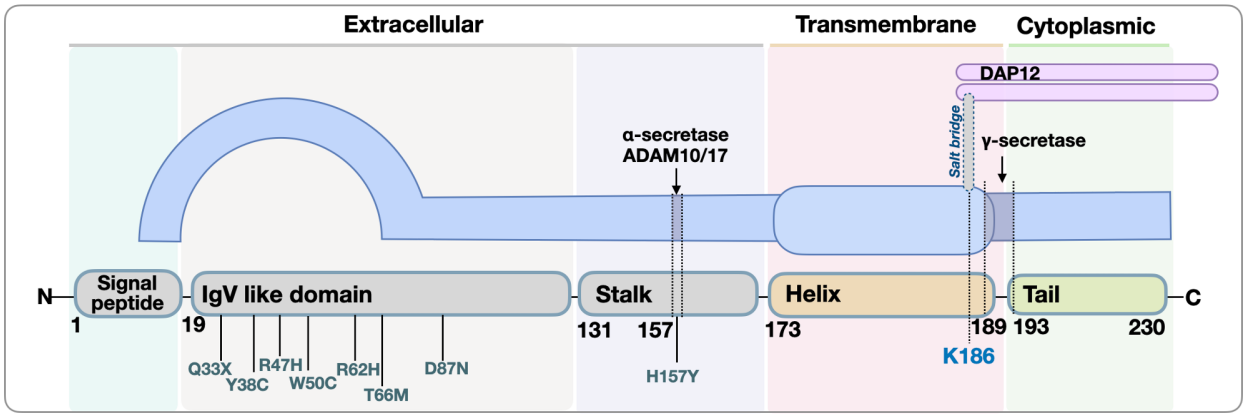
Variant	Function	Allele	Impact	Model	Reference
R47H	**Inflammatory response/ cytokine secretion**	Heterozygous	Increased	iMG	Penney et al., 2024
			Decreased	iMG	Piers et al., 2020; Cosker et al., 2021
		Homozygous	Decreased	iMG // iMac	Piers et al., 2020; Hall Roberts et al., 2020
			No change	iMG // iMac	Hall Roberts et al., 2020; Vasilopoulou et al., 2024; Cosker et al., 2024
	Metabolic performance (OXPHOS, glycolysis)	Heterozygous	Decreased	iMG	Piers et al., 2020; Cosker et al., 2021; Vasilopoulou et al., 2024
		Homozygous	Decreased	iMG	Piers et al., 2020; Vasilopoulou et al., 2024
	Lipid metabolism (accumulation)	Homozygous	Decreased	iMG // x-iMG	Claes et al., 2021; Vasilopoulou et al., 2024
		Overexpression	Increased	iMG	Andreone et al., 2020
	pSyk signalling upon activation	Heterozygous	Decreased	iMG	Cosker et al., 2021
		Homozygous	Decreased	iMG	Cosker et al., 2021
			Increased	iMG	Popescu et al., 2023
			No change	iMac	Hall Roberts et al., 2020
	Aβ uptake	Heterozygous	Decreased	iMG	Penney et al., 2024; Piers et al., 2020
		Homozygous	Decreased	iMG	Piers et al., 2020; Vasilopoulou et al., 2024
			No change	iMG	Cosker et al., 2024
	Myelin uptake	Heterozygous	Decreased	iMG	Penney et al., 2024
	Apoptotic cells phagocytosis	Heterozygous	No change	iMG	Cosker et al., 2021
		Homozygous	No change	iMac	Hall Roberts et al., 2020
	Synaptosome phagocytosis	Heterozygous	Increased	iMG	Popescu et al., 2023
			Decreased	iMG	Penney et al., 2024
		Homozygous	Increased (number)	iMac	Hall Roberts et al., 2020
			No change (spot area)	iMac	Hall Roberts et al., 2020
	Synaptic density	Heterozygous	Decreased	x-iMG	Penney et al., 2024
	sTREM2 shedding	Heterozygous	Increased	iMG	Penney et al., 2024
			No change	iMG	Cosker et al., 2021
		Homozygous	Increased	iMac	Hall Roberts et al., 2020

			Decreased	iMG	Vasilopoulou et al 2024; Cosker et al., 2024
	Inflammasome activation	Heterozygous	Decreased	iMG	Cosker et al., 2021
	Ca^{2+} response	Homozygous	No change	iMac	Hall Roberts et al., 2020
	Exosome secretion	Heterozygous	Altered	iMG	Mallach et al., 2021a, Mallach et al., 2021b
T66M	**Proinflammatory signature and cytokine secretion**	Homozygous	Decreased	iMG	Piers et al., 2020
			No change	iMG	Garcia-Reitboeck et al., 2018; Brownjohn et al., 2018
		Heterozygous	No change	iMG	Garcia-Reitboeck et al., 2018; Brownjohn et al., 2018
	Metabolic performance	Homozygous	Decreased	iMG	Piers et al., 2020
	Aβ uptake	Homozygous	Decreased	iMG	Piers et al., 2020
	Apoptotic cells uptake	Heterozygous	Decreased	iMG	Garcia-Reitboeck et al., 2018
		Homozygous	Decreased	iMG	Garcia-Reitboeck et al., 2018
	E.coli uptake	Heterozygous	No change	iMG	Garcia-Reitboeck et al., 2018; Brownjohn et al., 2018
		Homozygous	No change	iMG	Garcia-Reitboeck et al., 2018; Brownjohn et al., 2018
	acLDL uptake	Homozygous	No change	iMG	Brownjohn et al., 2018
	sTREM2 shedding	Heterozygous	Decreased	iMG	Garcia-Reitboeck et al., 2018
		Homozygous	Decreased	iMG	Garcia-Reitboeck et al., 2018
W50C	**Proinflammatory signature and cytokine secretion**	Homozygous	No change	iMG	Brownjohn et al., 2018; Garcia-Reitboeck et al., 2018
			Decreased	iMG	Piers et al., 2020
	Metabolic performance	Homozygous	Decreased	iMG	Piers et al., 2020
	Aβ uptake	Homozygous	Decreased	iMG	Piers et al., 2020
	Apoptotic cells uptake	Homozygous	Decreased	iMG	Garcia-Reitboeck et al., 2018
	E.coli phagocytosis	Homozygous	No change	iMG	Brownjohn et al., 2018; Garcia-Reitboeck et al., 2018
	acLDL uptake	Homozygous	No change	iMG	Brownjohn et al., 2018
	sTREM2 shedding	Homozygous	Decreased	iMG	Garcia-Reitboeck et al., 2018
p.Q33X	**Lipid metabolism (accumulation)**	Homozygous	Decreased	iMG	Filipello et al., 2023
	Lysosomal function	Homozygous	Decreased	iMG	Filipello et al., 2023
	sTREM2 shedding	Homozygous	Decreased	iMG	Filipello et al., 2023

KO	**Proinflammatory signature and cytokine secretion**		No change	iMG // iMac	Vasilopoulou et al., 2024; Cosker et al., 2024; Hall Roberts et al., 2020
	Metabolic performance		Decreased	iMG	Reich et al., 2021
			No change	iMG	Vasilopoulou et al., 2024
	Lipid metabolism (Accumulation)		Increased	iMG	Nugent et al., 2020; Andreone et al., 2020
			Decreased	iMG	Vasilopoulou et al., 2024
	pSyk signalling upon activation		Decreased	iMG // iMac	Hall Roberts et al., 2020; McQuade et al., 2020; Budesco et al., 2022
	Aβ uptake		Decreased	iMG	McQuade et al., 2020; Reich et al., 2021
			No change	iMG	Vasilopoulou et al., 2024; Cosker et al., 2024
	Apoptotic cells phagocytosis		Decreased	iMG	Hall Roberts et al., 2020
	Myelin uptake		Decreased	iMG	Nugent et al., 2020
	Zymosan uptake		No change	iMG	McQuade et al., 2020
	Synaptosome phagocytosis		Decreased (number)	iMac	Hall Roberts et al., 2020
			No change (spot area)	iMac	Hall Roberts et al., 2020
	Ca^{2+} response		Decreased	iMG	McQuade et al., 2020; Jairaman et al., 2022
			Differences observed depend on stimulus	iMG	Reich et al., 2021

Abbreviations: iPSC-microglia (iMG); iPSC-macrophages (iMac); acetylated low-density lipoprotein (acLDL); amyloid beta (Aβ); soluble TREM2 (sTREM2); xenotransplanted iMG (x-iMG); phosphorylated Syk (pSyk)





Microglia and TREM2

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Highlights

- TREM2 is a membrane receptor expressed on microglia, the immune cell of the brain.
- Focussing on human iMG, we discuss the biology and role of TREM2.
- The impact of TREM2 loss-of-function mutations on microglia is examined.
- The implications of TREM2 variants in neurodegenerative diseases are reviewed.
- We discuss the state of current pharmacological research targeting TREM2.

Declaration of Interests

All authors confirm they have no declaration of interest

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