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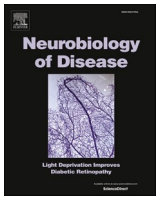

Review

Soluble TREM2: Innocent bystander or active player in neurological diseases?

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ABSTRACT

Triggering receptor expressed on myeloid cells 2 (TREM2) is an innate immune receptor expressed by macrophages and microglia in the central nervous system (CNS). TREM2 has attracted a lot of interest in the past decade for its critical role in modulating microglia functions under homeostatic conditions and in neurodegenerative diseases. Genetic variation in *TREM2* is sufficient to cause Nasu-Hakola disease, a rare pre-senile dementia with bone cysts, and to increase risk for Alzheimer's disease, frontotemporal dementia, and other neurodegenerative disorders. Beyond the role played by *TREM2* genetic variants in these diseases, TREM2 engagement is a key step in microglia activation in response to different types of tissue injury (e.g. β-Amyloid deposition, demyelination, apoptotic cell death) leading to enhanced microglia metabolism, phagocytosis, proliferation and survival. TREM2 also exists as a soluble form (sTREM2), generated from receptor shedding or alternative splicing, which is detectable in plasma and cerebrospinal fluid (CSF). Genetic variation, physiological conditions and disease status impact CSF sTREM2 levels. Clinical and preclinical studies suggest that targeting and/or monitoring sTREM2 could have clinical and therapeutic implications. Despite the critical role of sTREM2 in neurologic disease, its function remains poorly understood. Here, we review the current literature on sTREM2 regarding its origin, genetic variation, and possible functions as a biomarker in neurological disorders and as a potential active player in CNS diseases and target for therapies.

1. Introduction

TREM2 (Triggering receptor expressed on myeloid cells 2) is an innate immune receptor expressed by myeloid cells including macrophages, dendritic cells, osteoclasts and, in the central nervous system (CNS), by microglia (Bouchon et al., 2001; Cella et al., 2003; Piccio et al., 2007; Schmid et al., 2002; Turnbull et al., 2006; Wu et al., 2015). TREM2 is a type I trans-membrane glycoprotein with an extracellular V-type immunoglobulin (Ig) ectodomain, a connecting stalk followed by a transmembrane region and a C-terminal tail (Klesney-Tait et al., 2006). Secretase shedding of the receptor ectodomain gives rise to soluble TREM2 (sTREM2), which can be detected in the peripheral blood and cerebrospinal fluid (CSF) (Piccio et al., 2008). sTREM2 may also be derived by translation of an alternative transcript that is lacking the transmembrane domain (Del-Aguila et al., 2019).

At the plasma membrane, TREM2 receptor signalling occurs through association with DAP12 and DAP10 adaptor proteins, which interact with the intracellular C-terminus of TREM2. Intracellular signalling is mediated through recruitment of the tyrosine-protein kinase SYK (for DAP12) or the phosphatidylinositol 3-kinase (PI3K; for DAP10). Upon ligand binding, the TREM2/DAP12 or DAP10 complex mediates protein phosphorylation and activates multiple downstream signalling events resulting in Ca^{2+} mobilization and activation of mitogen-activated protein kinase (MAPK)-mediated cascades among other pathways (Peng et al., 2010; Ulland et al., 2017; Xing et al., 2015). These intracellular signals promote myeloid cell survival (Otero et al., 2012; Wang et al., 2015), proliferation (Otero et al., 2012), phagocytosis (Takahashi et al., 2005), actin cytoskeleton remodelling (N'Diaye et al., 2009), and

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cell metabolism (Wang et al., 2015). TREM2 is also required for transcriptional changes that shift microglia from homeostatic to disease-associated microglia (DAM) in mouse models of neurodegenerative disease (Keren-Shaul et al., 2017).

TREM2 receptor signalling is initiated by ligand binding to its ectodomain. Several classes of polyanionic molecules have been proposed to bind TREM2 ectodomain, such as bacterial components (Daws et al., 2003), anionic and zwitterionic lipids (Wang et al., 2015); myelin (Cignarella et al., 2020; Poliani et al., 2015); nucleic acids (Kawabori et al., 2015); apolipoprotein E (ApoE) (Atagi et al., 2015; Bailey et al., 2015; Kober et al., 2020); lipoprotein particles (Yeh et al., 2016); and β-Amyloid (Aβ) peptide (Zhao et al., 2018). Therefore, TREM2 appears to be a promiscuous receptor whose activation can occur under diverse contextual conditions. However, so far, a specific physiologic TREM2 ligand remains uncertain. Cells proposed to express a ligand for TREM2 include astrocytes (Daws et al., 2003; Piccio et al., 2007); dendritic cells (Ito and Hamerman, 2012); bone marrow derived macrophages (BMDM) (Hamerman et al., 2006); neurons (Hsieh et al., 2009); and apoptotic cells (Hsieh et al., 2009).

Rare bi-allelic loss of function mutations in *TREM2* or *DAP12* are sufficient to cause autosomal recessive Nasu–Hakola disease (NHD), which is characterized by early-onset dementia and bone cysts (Klunemann et al., 2005; Paloneva et al., 2001; Paloneva et al., 2000; Paloneva et al., 2002). Rare genetic variants in *TREM2* in heterozygosis are associated with increased risk for Alzheimer's disease (AD) (Guerreiro et al., 2013b; Jonsson et al., 2013); frontotemporal dementia (FTD) (Borroni et al., 2014); Parkinson's disease (PD) (Rayaprolu et al., 2013); and amyotrophic lateral sclerosis (ALS) (Cady et al., 2014), even though the data in support of the association of TREM2 variants with neurological diseases other than AD is still limited. These genetic findings suggest compromised neuroprotective functions of TREM2 on microglia during neurodegeneration. Given the centrality of TREM2 to several neurodegenerative diseases, much research has focused on TREM2 as a biomarker for microglia activation and a potential therapeutic target.

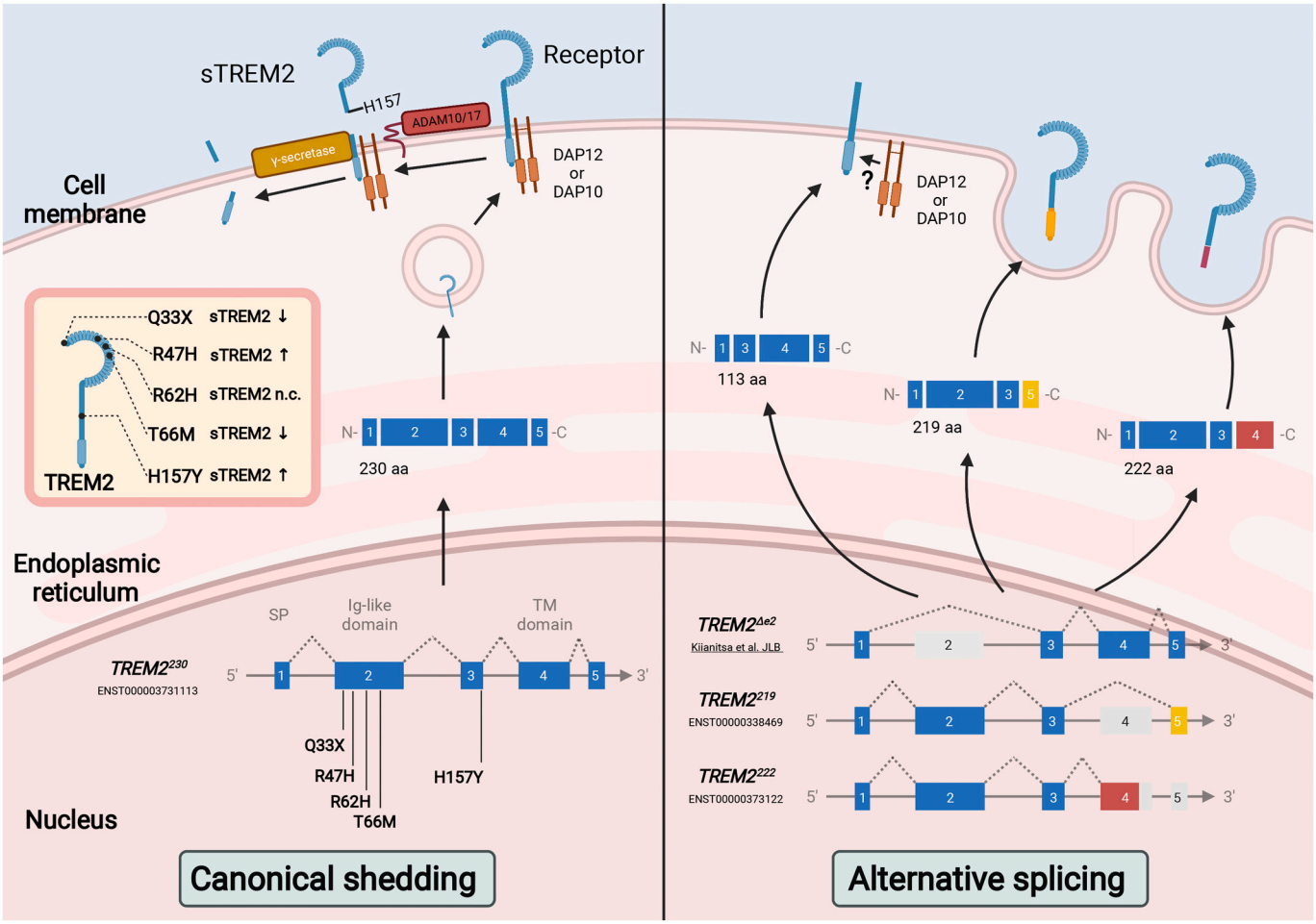

Fig. 1. Shedding and alternative splicing are responsible for soluble TREM2 (sTREM2) production. *Canonical shedding* (left): *ENST00000373113* is the canonical transcript and consists of five exons: exon 1 encodes for a signalling peptide (SP), exon 2 encodes for an immunogloblin-like (Ig-like) domain, and a transmembrane (TM) domain is present within exon 4. *ENST00000373113* mRNA, after being translated into the full-length receptor (230 amino acids-aa), is transported to the membrane. Here, ADAM10/ADAM17 sheddase initiate the proteolytic processing by cleaving TREM2 receptor on residue H157 and by liberating its ectodomain, sTREM2. Subsequent processing of the membrane retained C-terminal fragment (CTF) by γ-secretase within the transmembrane domain (TM) releases the intracellular domain (ICD) into the cytosol. A short peptide may be secreted. The box on the left indicates just some of the *TREM2* genetic variants (p.Q33X, p.R47H, p.R62H, p.T66M, p.H157Y), their location in the TREM2 ectrodomain and if they are associated with increased, decreased or unchanged sTREM2 levels. *Alternative splicing* (right): *ENST00000373122* transcript (222 aa) lacks exon 5 and results to a different amino acid sequence in exon 4. Since exon 4 contains the TM domain and this sequence is disrupted, this protein is likely secreted to the extracellular milieu. ENST00000338469 transcript (219 aa) derives from the skipping of exon 4, leading to a frameshift and a different amino acid sequence in exon 5. This protein is likely secreted due to skipping of exon 4 which contains the TM domain. $TREM2^{\Delta e2}$ transcript (113 aa) lacks exon 2 and retains all other exons in-frame. This protein has been described to be located at the cytosol and cell membrane. Due to conserved C-terminal sequence, this transcript may compete with the full-length receptor for its adaptors, such as DAP12/DAP10, and consequently inhibit TREM2 signalling.

Here, we review the genetic and functional characteristics of sTREM2, and the implications for sTREM2 in aging and neurological disease.

2. Origin, function and genetic modulators of soluble TREM2

TREM2 was initially studied as a trans-membrane receptor expressed on myeloid cells (e.g. dendritic cells, macrophages, osteoclasts), even though several putative murine and human *TREM2* transcripts lacking the transmembrane domain were described as encoding a soluble form (Begum et al., 2004; Melchior et al., 2006; Schmid et al., 2002). In 2008, a sTREM2 protein was identified in human cerebrospinal fluid (CSF) and serum, ranging between about 24 and 40 kDa due to a high degree of glycosylation (Piccio et al., 2008). Subsequent studies have investigated the cellular origins of sTREM2, how it is generated and its possible functions.

2.1. sTREM2 origin: shedding versus alternative splicing

Two processes, independently or in cooperation, are responsible for sTREM2 protein generation: (i) proteolytic cleavage and shedding of the TREM2 ectodomain and/or (ii) translation of an alternative spliced TREM2 transcript lacking the transmembrane domain (Schmid et al., 2002; Wunderlich et al., 2013) (Fig. 1).

2.1.1. TREM2 shedding

Proteolytic ectodomain shedding is a mechanism to fine tune levels and function of a membrane receptor and its soluble form. Ectodomain shedding consists of an irreversible post-translational proteolytic modification whereby the sheddase cleaves a membrane protein substrate just outside its transmembrane domain, resulting in the release of a soluble N-terminal extracellular ectodomain and leaving behind a C-terminal fragment (CTF) that remains bound to the membrane (Black, 1980; Ehlers and Riordan, 1991; Kapeller et al., 1973; Lichtenthaler et al., 2018). Through this process, cleavage of TREM2 on myeloid cells leads to the release of sTREM2 (Kleinberger et al., 2014; Piccio et al., 2008) (Fig. 1).

Members of the disintegrin and metalloproteinase domain-containing protein (ADAM) family catalyse TREM2 ectodomain shedding (Kleinberger et al., 2014; Wunderlich et al., 2013), specifically ADAM10 and ADAM17. Mass spectrometry determined that TREM2 is cleaved between histidine 157 and serine 158 (H157-S158) to generate sTREM2 (Feuerbach et al., 2017; Schlepckow et al., 2017; Thornton et al., 2017). Feuerbach and colleagues showed that ADAM17 plays a major role in sTREM2 generation in THP1 and CHO cell lines, while other groups found that ADAM10 is implicated in sTREM2 shedding in human macrophages, HEK293 cells, and murine microglia (Schlepckow et al., 2017; Thornton et al., 2017). Therefore, it remains uncertain whether there is a single ADAM protein that explains the majority of sTREM2 cleavage.

TREM2 proteolytic processing occurs sequentially. ADAM-mediated sheddase activity first liberates sTREM2 from the plasma membrane and then the CTF is cut by γ-secretase, clearing the remaining protein from the membrane (Wunderlich et al., 2013) (Fig. 1). Inhibition of γ-secretase results in TREM2-CTF accumulation at the membrane, which sequesters the TREM2/ adaptor protein DAP12 complex, impairs its phosphorylation leading to reduced TREM2 signalling (Wunderlich et al., 2013). In general, shedding can be regulated by a myriad of mechanisms ranging from modulation of protein trafficking and protein cleavage to regulation of the receptor localisation at the membrane by lipids (Lichtenthaler et al., 2018). Therefore, there may be several mechanisms involved in activating sheddase and γ-secretase activity with the potential to regulate shedding of sTREM2 and sTREM2/ TREM2-mediated cellular functions.

2.1.2. TREM2 alternative splicing

Murine *Trem2* transcripts lacking the transmembrane domain were first described in 2002, suggesting that sTREM2 could be generated through alternative splicing (Schmid et al., 2002). Subsequently, four major *TREM2* transcripts have been reported in human brains: ENST00000373113, ENST00000373122, ENST00000338469, and *TREM2*$^{\Delta e2}$ (Jin et al., 2014; Kiianitsa et al., 2021) (Fig. 1). ENST00000373113, the canonical and the longest *TREM2* transcript, contains 5 exons and encodes the full-length, 230 amino acid (aa) transmembrane receptor protein and is the most highly expressed (Del-Aguila et al., 2019). ENST00000373122 lacks exon 5 and is the second longest transcript (222 aa); in this transcript exon 4 contains an alternative start that changes its coding sequence. ENST00000338469 (219 aa) excludes exon 4, which encodes the transmembrane domain. ENST00000338469 transcript is estimated to represent about 25% of the total *TREM2* mRNA in the brain, suggesting that around 20–25% of total sTREM2 protein might be derived from translation of this transcript and not through the cleavage of the full-length transmembrane TREM2 via sheddase activity (Del-Aguila et al., 2019). ENST00000338469 likely encodes a form of TREM2 that is secreted due to the complete lack of the transmembrane domain. *TREM2*$^{\Delta e2}$ lacks exon 2 (encoding the Ig-like ectodomain) but retains the other exons in-frame. Therefore, it is possible that *TREM2*$^{\Delta e2}$ eventually produces a non-functional receptor on the membrane with no ligand binding capacity (Kiianitsa et al., 2021).

In conclusion, alternative splicing of *TREM2* mRNA can impact TREM2 biology in multiple ways: by giving rise to (i) full length TREM2 transcripts; (ii) TREM2 isoforms lacking the transmembrane domain that are therefore secreted; and (iii) *TREM2* transcripts encoding predicted dysfunctional ligand binding. However, it remains unclear if ENST00000373122, ENST00000338469 and TREM2$^{\Delta e2}$ transcripts are translated, whether the transcripts produce predicted functional effects, and their ultimate role in microglia function and disease.

Using a splicing-guided aggregation approach, a recent study predicted 10 low-frequency variants, two of which are located in the exon 2 (rs143332484 and rs201258314) and the other eight in the flanking introns of the *TREM2* gene in AD patients. These variants impact splicing regulatory elements (SREs) and could potentially affect the splicing level of *TREM2* exon 2, resulting in an increased tendency towards exon 2 skipping (Han et al., 2021). Thus, multiple genetic variants that modify not only sTREM2 shedding but also *TREM2* gene splicing, eventually affecting the overall sTREM2 levels, may exist in the population. Future studies aimed at understanding the relative contributions of proteolytic shedding versus alternative splicing as the source of sTREM2 production will be needed. This will aid to fully clarify the overall function of TREM2 in physiological and pathological conditions.

2.2. Impact of genetic variants on sTREM2 levels in body fluids

Recessive *TREM2* pathogenic mutations cause NHD, a progressive and severe pre-senile dementia associated with bone cysts (Paloneva et al., 2002). Additionally, a single copy of rare variants in *TREM2* increase susceptibility to a number of neurodegenerative diseases including AD, FTD, FTD-like syndrome and PD (Borroni et al., 2014; Guerreiro et al., 2013a; Guerreiro et al., 2013b; Guerreiro et al., 2013c; Jonsson et al., 2013; Kleinberger et al., 2014; Rayaprolu et al., 2013). The impact of these genetic variants on sTREM2 and their role on TREM2 and microglia function in physiology and disease is an area of active investigation.

Bi-allelic mutations in *TREM2* that are associated with NHD and FTD lacking bone manifestations (Guerreiro et al., 2013c; Le Ber et al., 2014; Paloneva et al., 2002) (i) act as loss of function missense mutations leading to early-stop codons (e.g. p.Q33X) (Paloneva et al., 2003; Soragna et al., 2003); (ii) cause amino acid substitutions in the stalk region (e.g. p.D134G and p.K186N) (Paloneva et al., 2002), or (iii) in the ectodomain (e.g. p.Y38C, p.T66M, and p.V126G) (Guerreiro et al., 2013a; Guerreiro et al., 2013b; Guerreiro et al., 2013c; Le Ber et al., 2014). Among rare *TREM2* risk variants, p.R47H and p.R62H are the

most frequent and have the biggest effect size on modifying AD risk (Jin et al., 2014; Ridge et al., 2016). Other rare *TREM2* variants linked to AD risk include p.N68K, p.D87N, p.T96K, p.R98W, and p.H157Y, among others (Cuyvers et al., 2014; Guerreiro et al., 2013b; Song et al., 2017) (location at transcript and protein levels of some of these TREM2 genetic variants is presented in Fig. 1).

NHD-causing mutations likely impact TREM2 protein folding and stability, whereas AD risk variants likely decrease binding to the putative cellular TREM2 ligand/s (Kober et al., 2016). In terms of protein maturation, mutations within the Ig-like domain of TREM2 receptor, such as p.T66M and p.Y38C, result in misfolding of TREM2 and/or retention of the immature protein within the endoplasmic reticulum (Kleinberger et al., 2014; Park et al., 2015; Song et al., 2017). Impaired protein trafficking and maturation, leads to lower cell surface levels of TREM2, reduced shedding with reduced sTREM2 and TREM2 CTF levels detected in vitro in HEK293 cell line (Kleinberger et al., 2014). Consistent with these findings, quantification of sTREM2 levels in the CSF and plasma of patients carrying the two copies of the *TREM2* p.T66M or p.Q33X NHD mutations were extremely low or undetectable (Kleinberger et al., 2014). A decrease in sTREM2 levels in patients carrying one copy of *TREM2* p.T66M, and p.Q33X was confirmed in an independent study, which also demonstrated a similar dramatic reduction in CSF sTREM2 levels in *TREM2* p.R136Q and p.D87N mutation carriers (Piccio et al., 2016). By contrast, intracellular trafficking is unaffected for risk variants such as p.R47H (Kleinberger et al., 2014; Wang et al., 2015). CSF sTREM2 levels detected in carriers of one copy of the p.R47H variant were significantly higher compared to non-carriers and cognitively normal individuals (Piccio et al., 2016; Suarez-Calvet et al., 2019). Notably, only CSF, but not plasma sTREM2 levels, changed in individuals carrying heterozygous *TREM2* variants linked to AD risk compared to non-mutation carriers (Ashton et al., 2019; Kleinberger et al., 2014). Overall, these findings indicate that NHD and AD-associated TREM2 genetic variants can predispose to CNS pathology by different functional mechanisms. Low sTREM2 levels in NHD-associated variants suggest that the pathology is due to loss of function caused by impaired maturation and cell surface expression of the protein, while more complex mechanisms could be implicated for variants associated with AD risk (e.g. p.R47H).

Although the majority of the *TREM2* variants were found within the Ig-like domain, genetic studies also identified sequence variants within the stalk region of the TREM2 receptor. These latter variants may not be involved in ligand binding and may also not be as sensitive to subtle structural changes as the highly-folded Ig-like domain (Paradowska-Gorycka and Jurkowska, 2013). The stalk region contains the cleavage site recognized by the TREM2 sheddase acting at the histidine 157 and serine 158. Strikingly, a mutation, which increases the risk for AD, (p.H157Y) is located in the stalk region (Guerreiro et al., 2013b; Jiang et al., 2016; Song et al., 2017) (Fig. 1). By analysing the proteolytic processing of this variant, two groups revealed that the p.H157Y variant enhances shedding (Schlepckow et al., 2017; Thornton et al., 2017). Interestingly, enhanced shedding reduces the amount of full-length TREM2 receptor on the cell surface. Thus, like the NHD mutations, the consequence of variants located within the Ig-like domain or the stalk region is also reduced cell surface expression of TREM2, albeit through distinct cellular mechanisms (enhanced shedding versus impaired trafficking to the membrane). The overall effect in both cases, is likely reduced receptor signalling activity.

2.3. Potential functions of sTREM2

The influence of sTREM2 shedding on downstream TREM2 receptor signalling, and the endogenous function, if any, of sTREM2 itself, are not fully understood. Maintaining TREM2 on the cell surface with antibodies that stabilize TREM2 on the membrane and prevent sTREM2 proteolytic shedding, have been shown to enhance downstream TREM2 receptor signalling and readouts of receptor function such as microglial cell phagocytic activity (Schlepckow et al., 2020; Szykowska et al., 2021). This suggests that TREM2 removal from the cell membrane by ADAM metalloprotease activity and the generation of sTREM2 could negatively regulate TREM2 receptor activity. It is unclear, but we might speculate that sTREM2 shedding occurs normally after ligand binding, to modulate receptor activity, by blocking downstream intracellular signalling (Fig. 2). Constant maturation and trafficking to the cell surface of newly synthesised TREM2 protein would be required under these conditions in the cell for ongoing receptor activity. Based on this view, levels of sTREM2 (measured in CSF or plasma) might reflect the degree of TREM2 receptor engagement with its ligand (potentially the ligand being a soluble molecule or cell-bound ligand), its shedding, and the flux of new TREM2 protein through the trafficking pathway. Supporting this idea is evidence for both upregulation of TREM2 protein expression and sTREM2 levels in CSF under conditions of increased microglial activation (and presumably elevated downstream TREM2 receptor signalling) such as in inflammatory neurologic diseases (Diaz-Lucena et al., 2021; Piccio et al., 2008). However, the relationship between endogenous ligand binding and the shedding mechanism remains to be elucidated.

The question remains whether sTREM2, once released from the membrane, exerts a specific function. This issue has been difficult to resolve. After shedding, sTREM2 could conceivably have an agonistic effect by binding a specific TREM2 ligand on other cells, or alternatively, function as a decoy by competing with the transmembrane full length TREM2 receptor for ligand binding (Fig. 2). The nature of TREM2 ligands and the context of their engagement with the receptor complicates the understanding of sTREM2 function. TREM2 appears to be a promiscuous receptor that can bind diverse molecules that have general polyanionic properties - bacterial membrane components, lipids including myelin, ApoE and lipoproteins, Aβ, DNA and others (Cignarella et al., 2020; Poliani et al., 2015; Wang et al., 2015; Yeh et al., 2016). Therefore, TREM2 activation and the ligand/s involved appears to depend on context. Another open question is to what extent sTREM2 or TREM2 can bind in-trans ligands on the surface of other cells. Interestingly, in macrophages, TREM2 receptor was shown to bind membrane-associated ligands in-trans on other macrophages (Hamerman et al., 2006) and on astrocytes (Piccio et al., 2007). Moreover, more recent work has reported evidence for sTREM2 binding on neurons (Song et al., 2018; Zhong et al., 2019) (Fig. 2).

Despite ongoing questions around the specific contexts of TREM2 and sTREM2 ligand binding, there is evidence for functional effects of sTREM2 in vivo and in vitro (Wu et al., 2015; Zhong et al., 2017; Zhong et al., 2019). In transfected HEK293 cells, Aβ binds to the TREM2 ectodomain and triggers sTREM2 shedding, but this effect is reduced for the AD associated *TREM2* p.R47H variant which is impaired in its Aβ binding capability. The binding of sTREM2 to Aβ also inhibits Aβ aggregation pathways (Vilalta et al., 2021; Zhao et al., 2018). Stemming from these studies is the argument for exploring mechanisms of increasing sTREM2 (or sTREM2 shedding) for potential AD therapy. In primary cultured murine microglial cells, sTREM2 promotes cell survival and stimulates the production of inflammatory cytokines depending on NF-κB (Zhong et al., 2017). sTREM2 carrying AD risk variants was less potent in mediating these effects. In the same study, stereotaxic injection of sTREM2 delivered to the hippocampi of either wild-type or *Trem2*-knockout mice elevated the expression of inflammatory cytokines and induced morphological changes in microglia. These data indicate that sTREM2 triggers microglial activation inducing inflammatory responses and promoting survival (Zhong et al., 2017). A follow up paper demonstrated that injection of sTREM2 into the hippocampus (direct or adenovirus mediated) of 5XFAD transgenic mice (an AD mouse model with amyloid plaque accumulation), reduced amyloid plaque load and enhanced microglial proliferation, migration and clustering around plaques. These effects correlated with amelioration of synaptic impairment and memory deficits in this model and were abolished by the depletion of microglia, indicating that sTREM2 exerts neuroprotection through microglia direct or indirect activity (Zhong

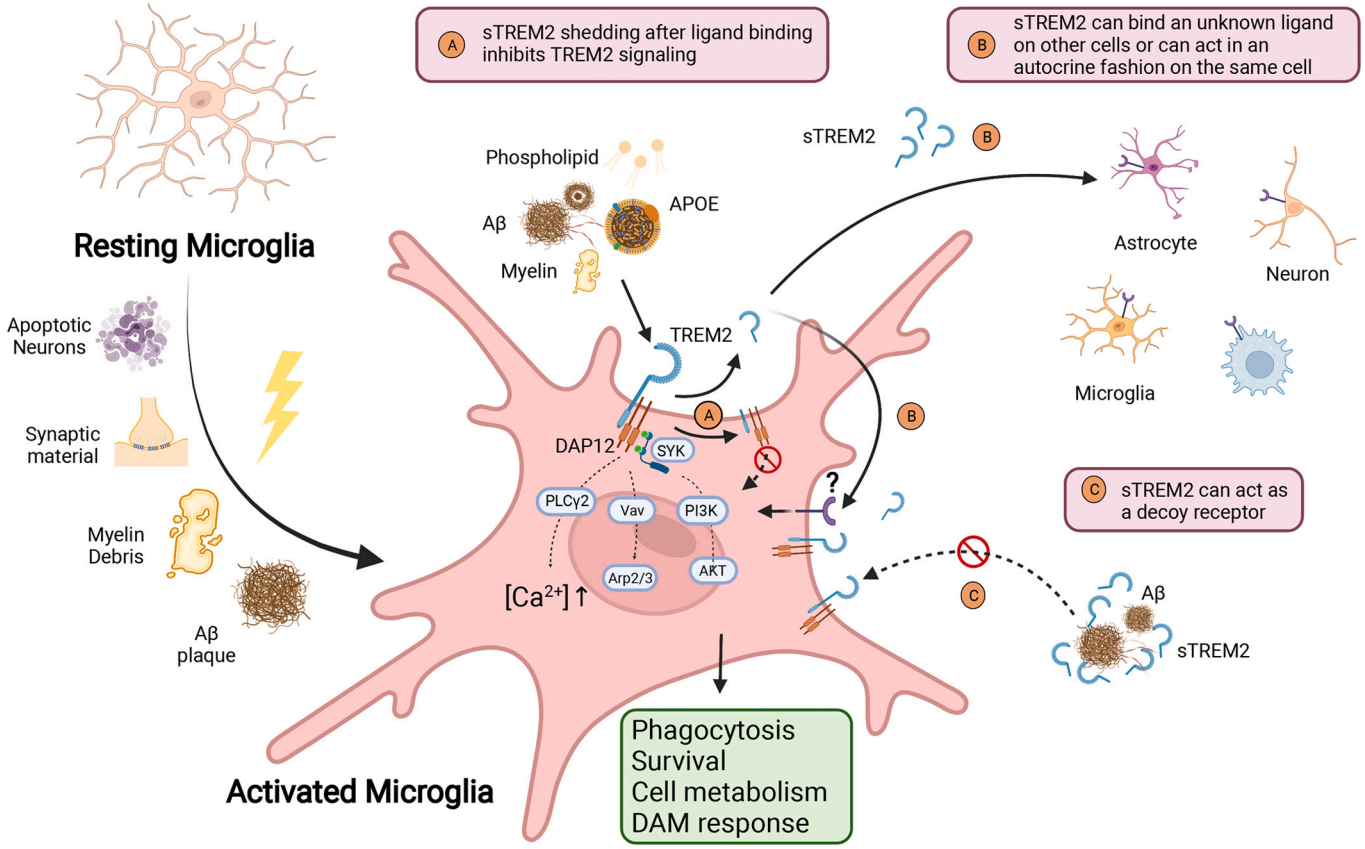

Fig. 2. Potential functions and possible ligands of sTREM2. Resting microglia become activated by specific signals (i.e. apoptotic neurons, synaptic material, myelin debris and Amyloid-β plaques), which can be sensed both in pathological and physiological conditions. Membrane-bound TREM2 receptor can bind, among other molecules, phospholipids, myelin, ApoE, and Amyloid-β. Ligand binding to TREM2 results in phosphorylation of tyrosine residues within an ITAM motif of the DAP12 cytoplasmic domain, as well as recruitment of Syk kinase to activate downstream signalling pathways which regulate Ca2+ mobilization, cell cytoskeletal remodelling, and gene transcription. After being released in the extracellular milieu, sTREM2 could act by (A) inhibiting TREM2 receptor signalling pathway due to ectodomain shedding and lack of its ligand binding capacity; (B) binding an unknown receptor on other cells (i.e. astrocytes, neurons, macrophages) or on microglia itself thus acting in an autocrine fashion; (C) acting as a decoy receptor thus preventing further binding of the specific ligand to membrane TREM2 receptor and eventually inhibiting TREM2 signalling.

et al., 2019). However, further research is needed to validate some of these studies and to better determine the full spectrum of proposed sTREM2 roles in cell survival and neuroprotection.

2.4. Genetic modifiers of sTREM2

The genetic architecture regulating CSF sTREM2 levels so far, appears to be restricted to a single genomic locus. Two independent studies have illustrated that variants in chromosome 11, near the *MS4A* gene locus are significantly associated with CSF sTREM2 levels (Deming et al., 2019; Piccio et al., 2016). The importance of this genomic region in regulating CSF sTREM2 levels is highlighted by the finding of two independent signals, one of which is associated with reduced CSF sTREM2 levels (rs6591561) and the other associated with elevated CSF sTREM2 levels (rs1582763) (Deming et al., 2019). The variant associated with reduced CSF sTREM2 levels (rs6591561) is located in an exonic region of *MS4A4A* and results in a missense change (p.M159V). In an AD case-control dataset, this variant is also associated with increased risk for AD (Deming et al., 2019) and this was confirmed in a recent study in a large cohort of Icelanders (Ferkingstad et al., 2021). Alternatively, the variant associated with elevated CSF sTREM2 levels (rs1582763) occurs in an intergenic region near *MS4A4A* and *MS4A6A* and is associated with reduced AD risk. While the exact mechanism by which genes in the *MS4A* genomic loci impact AD are not fully understood, there is evidence that MS4A4A and MS4A6A are enriched in microglia in the brain and expressed at the cell surface with TREM2. Additionally, modifying expression of *MS4A4A* is sufficient to alter sTREM2 levels in human macrophages (Deming et al., 2019). Beyond the *MS4A* gene locus, variants that pass genome wide significance have not been identified. Additionally, despite the reported roles of APOE and CD33 (Griciuc and Tanzi, 2021; Kamboh et al., 2012) in genetic risk for AD and the functional relationship between APOE, CD33 and TREM2 in microglia, there is no evidence of an association between *APOE* or *CD33* SNPs and CSF sTREM2 levels (Deming et al., 2019).

3. Factors influencing sTREM2 in physiological conditions

Key demographic variables, including age, sex and ethnicity may impact CSF and blood sTREM2 levels. Independent studies have shown that CSF sTREM2 levels positively correlate with age (Gisslen et al., 2019; Henjum et al., 2016; Knapskog et al., 2020; Moore et al., 2021; Piccio et al., 2016; Suarez-Calvet et al., 2016a; Suarez-Calvet et al., 2016b; Suarez-Calvet et al., 2019) (Table 1). Changes in the brain microenvironment are known to affect microglia gene expression and phenotype during aging (Pan et al., 2020). Therefore, elevation of CSF sTREM2 levels with aging could be a biomarker of these changes under physiological or pathological conditions. Along with increased CSF biomarkers of astrocyte activation (e.g. chitinase 3-like 1) and synaptic injury (e.g. neurogranin), elevated sTREM2 may reflect microglial activation related to microcirculatory damage during aging with associated vascular remodelling (Moore et al., 2021). Sleep disturbances associated with age and/or prodromal neurodegenerative disease may

Table 1
Summary of the main studies describing changes in soluble TREM2 in neurological disorders and TREM2 variant carriers.

Disease	Groups	Change in CSF sTREM2 (*serum/plasma if reported*)	Correlations with CSF sTREM2 (*across all groups unless otherwise stated*)
Multiple sclerosis (MS); other inflammatory neurological diseases (OIND)			
(Piccio et al., 2008)	MS, OIND, non-inflammatory neurological diseases (NIND).**	↑ in MS and OIND compared to NIND. n.c. in serum levels.	+ with CSF Ig and proteins. not with MS clinical measures, age at lumbar puncture, serum sTREM2.
(Ohrfelt et al., 2016)	MS, SPMS, PPMS, healthy controls; before and after treatment (Natalizumab, Mitoxantrone).	↑ in MS, SPMS and PPMS vs. controls. ↓ after treatment in MS to the levels in controls.	+ with disease duration and IgG index in whole MS group. not with MS clinical measures and albumin ratio.
(Oldoni et al., 2020)	MS only.	Not reported.	+ with CHI3L1. not with age, disease duration, clinical measures, CHIT1 or NfL.
(Ioannides et al., 2021)	MS, other neurological diseases (OND)[#], healthy controls.	↑ in MS vs. OND. n.c. in serum levels among groups.	+ with sCD27, NfL, pNfH, clinical measures.
Alzheimer's Disease (AD)			
(Kleinberger et al., 2014)	AD, FTD, healthy controls.	↓ in AD and FTD vs. controls. n.c. in plasma levels.	sTREM2 levels undetectable or very low in p.T66M and p.Q33X mutation carriers (see also below).
(Gispert et al., 2016)	AD, preAD, MCI due to AD, healthy controls.	↑ in MCI and AD vs controls.	+ with age, CSF t-tau and p-tau. not with Aβ42. + with grey matter volume in MCI group.
(Henjum et al., 2016)	AD, MCI, healthy controls.	n.c.	+ with age, Aβ42 (in controls), CSF t-tau, p-tau (in whole cohort).
(Heslegrave et al., 2016)	AD, healthy controls.	↑ in AD vs controls.	+ with CSF t-tau, p-tau and CHI3L1. not with Aβ42.
(Piccio et al., 2016)	AD, healthy controls.	↑ in AD vs. controls. ↑ in males vs females. n.c. in plasma levels.	+ with age, CSF t-tau and p-tau. not with Aβ42, plasma sTREM2.
(Suarez-Calvet et al., 2016a)	Autosomal dominant AD: AD mutation carriers, non-carrier siblings (DIAN cohort).	↑ in mutation carriers relative to non-carriers (5 years before expected symptom onset). ↑ in males vs females.	+ with age, CSF t-tau, p-tau. not with Aβ42 or ApoE status
(Suarez-Calvet et al., 2016b)	AD continuum (preclinical AD, MCI due to AD, AD), healthy controls, suspected non-AD tauopathy (SNAP; amyloid negative, tauopathy).	↑ MCI-AD vs. controls and AD. ↑ SNAP vs. controls and preclinical AD. ↑ MCI-AD vs. MCI-non-AD and controls.	+ with age, CSF t-tau, p-tau not with sex. -with CSF Aβ42 (in whole cohort)
(Suarez-Calvet et al., 2018)	ADAD (mutation carriers and non-carriers) from the DIAN cohort; ADNI participants (healthy controls, AD continuum, SNAP)	n.c. with ApoE status. Not reported.	+ with CSF levels of proganulin in mutation carriers (DIAN cohort), AD continuum and SNAP group (ADNI cohort). not with CSF progranulin in non-carriers (DIAN) and healthy controls (ADNI)
(Ewers et al., 2019)	ADNI cohort; AD, MCI, healthy controls.	↑ in AD vs. controls.	+ of high CSF sTREM2 levels at baseline with slower cognitive decline and hippocampal atrophy.
(Suarez-Calvet et al., 2019)	ADNI cohort: classified based on biomarker profiles (A/T/N) and clinical stages; TREM2 variant carriers.	↑ Tau/Neurodegeneration (T/N) + (both Aβ + and Aβ-) ↓ in Aβ + and T/N-	+ with age, CSF t-tau, p-tau. not with sex, ApoE status and Aβ42.
(Knapskog et al., 2020)	AD, MCI due to AD, healthy controls.	n.c. between AD, MCI and controls. ↑ in Tau (T) + vs T- using the A/T/N classification.	+ with age, CSF p-tau (in AD/MCI and controls). not with Aβ42, ApoE status and sex.
(Park et al., 2021)	Participant from the memory clinic (Asan, South Korea) divided in amyloid + and – based on PET imaging.	Not reported.	+ with CSF t-tau, p-tau -with plasma sTREM2 not with NfL
(Pascoal et al., 2021)	People across aging and AD spectrum.	Not reported.	+ with in vivo microglial activation (human PET imaging [^{11}C] PBR28 ligand). + with tau, CNS pathology, cognitive impairment. -with $A\beta_{42/40}$.

(*continued on next page*)

Table 1 (*continued*)

Disease	Groups	Change in CSF sTREM2 (*serum/plasma if reported*)	Correlations with CSF sTREM2 (*across all groups unless otherwise stated*)
(Rauchmann et al., 2020)	Healthy controls, MCI and AD classified based on the A/T/N framework.	↑ T/N + and SNAP groups	+ with pro-inflammatory molecules (TNF-α, TNFR1, TNFR2, ICAM1, VCAM1, and IP-10) + with anti-inflammatory molecules (TGFβ1, IL-10, and IL-9) -IL-21
Parkinson's disease			
(Peng et al., 2020)	PD, healthy controls.	↑ in PD. n.c. in plasma.	+ with CSF α-synuclein. + with age in PD but not healthy controls.
(Wilson et al., 2020)	PD-cognitively normal, PD-MCI, PD-dementia, healthy controls.	↑ in PD-cognitively normal. n.c. in other PD clinical sub-groups vs healthy controls. ↑ in PD with abnormal CSF tau vs pure Lewy Body PD or healthy controls. n.c. in plasma.	+ with age + with CSF tau. not with CSF Aβ. + in PD (tau-positive) with better Montreal Cognitive Assessment scores.
Frontotemporal dementia			
(Woollacott et al., 2018)	FTD with different clinical phenotypes and genetic subtypes, healthy controls.	n.c. overall between FTD and healthy controls. ↑ in FTD GRN mutation carriers (*n* = 3) vs. controls and *C9orf72* (n = 3) and *MAPT* (*n* = 4) mutation carriers. n.c. between *C9orf72* and *MAPT* mutation carriers vs. controls. ↑ in AD biomarker positive FTD vs AD biomarker negative.	+ with age. + with CSF tau and Aβ42
(van der Ende et al., 2021)	FTD- *GRN,* FTD- *C9orf72,* healthy controls.	n.c. (but very high levels in subset of *GRN* mutation carriers, not *C9orf72*). n.c. between pre-symptomatic and symptomatic mutation carriers. n.c. with sex.	+ with age.
(Roos et al., 2018)	*CHMP2B* FTD-3, healthy controls.	n.c.	+ with age.
(Kleinberger et al., 2014)	FTD, healthy controls.	↓ (slightly) in FTD. n.c. in plasma.	Not reported.
(Piccio et al., 2016)	FTD, healthy controls.	↑ in FTD vs. controls. n.c. in plasma.	Not reported.
Prion diseases			
(Diaz-Lucena et al., 2021)	Sporadic Creutzfeldt-Jakob disease sCJD, genetic gCJD (mutations in the prion protein gene *PRNP*), iatrogenic iCJD, fatal familial insomnia (FFI), AD, MS, non-primarily neurodegenerative neurological disease controls (ND), healthy controls.	↑↑ in sCJD, gCJD and iCJD vs. healthy controls and ND. n.c. in FFI, AD or MS cohorts vs. healthy controls or ND. ↑ in sCJD and gCJD vs. AD. n.c. with sex. ↑ (plasma) sCJD vs healthy controls.	+ with CSF t-tau, 14.3.3 and YKL-40. + with CJD disease stage/ progression. Not with disease duration. Not with age.
Chronic traumatic encephalopathy			
(Alosco et al., 2018)	Former NFL players, healthy controls.	n.c.	+ with CSF t-tau CSF t-tau ↑ with cumulative head impact index.
CNS infection			
(Gisslen et al., 2019)	Untreated HIV+ infection, anti retroviral treated (ART)- HIV+, HIV+ associated dementia (HAD), HIV negative healthy controls.	↑↑ in HAD. ↑ in untreated HIV+. n.c. in ART-HIV+.	+ with CSF t-tau and NfL. + with age. + with decreasing CD4+ T-cell counts.
(Li et al., 2020)	Neurosyphilis (NS) infection, syphilis/ non-NS infection.	↑ in NS vs syphilis/ non-NS.	+ with age + with CSF NfL. + with NS disease progression.
TREM2 variant carriers (linked with AD, FTD or NHD)			
(Kleinberger et al., 2014) (Piccio et al., 2016) (Ashton et al., 2019) (Suarez-Calvet et al., 2019) Reviewed in (Yang et al., 2020)	TREM2 mutation carriers (various), controls/non-carriers.	In CSF: ↑ in p.R47H carriers ↑ in p.H157Y tested in only one carrier. n.c. in p.R62H carriers ↓↓ (or undetectable) in all the other AD, NHD, FTD risk variants carriers In plasma: ↓ in homozygous *TREM2* mutation carriers with NHD or FTD n.c. in heterozygous *TREM2* variants linked to AD	In most studies, including TREM2 variant carriers did not change the correlations of sTREM2 observed in CSF. + with CSF t-tau and P-tau_{181P} in AD *continuum,* SNAP and healthy controls not with CSF Aβ. Plasma sTREM2 did not correlate with age, sex and cognitive decline.

Studies are listed in chronological and alphabetic order.
↑ = increase; ↓ = decrease; n.c. = no change;
+ = positive correlations; − = negative correlation; or not = no correlation.
* viral meningitis, encephalitis, optic neuritis, neuromyelitis optica and acute disseminated encephalomyelitis;** headache, degenerative disk disease, normal

pressure hydrocephalus, seizure disorder and stroke or small vessel disease # central or peripheral nervous system diseases; some inflammatory and non-inflammatory. SPMS = secondary progressive MS; PPMS = primary progressive MS; CHIT1 = chitinase 1; CHI3L1 (or YKL-40) = chitinase-3–like protein 1; NfL = neurofilament light chain; pNfH = phosphorylated neurofilament heavy chain; t-tau = total tau; p-tau = phosphorylated tau; MCI = mild cognitive impairment; ADNI: Alzheimer's Disease Neuroimaging Initiative; DIAN = Dominantly Inherited Alzheimer Network; SNAP=Suspected Non-Alzheimer's Pathophysiology. A/T/N (Amyloid/Tau/Neurodegeneration) = to stratify AD categories based on CSF biomarker profiles proposed in the National Institute on Aging-Alzheimer's Association research framework (Jack et al., 2018).

also impact microglial cell activity and sTREM2 levels (Hu, 2021; Stokholm, 2017). Age has further been reported as a correlate of elevated TREM2 mRNA in the brain in one study (Forabosco, 2013).

Higher sTREM2 levels have been described in males compared to females (Piccio et al., 2016; Suarez-Calvet et al., 2016a, 2016b; Wilson et al., 2020), but this was not consistently observed in independent cohorts (Knapskog et al., 2020). Furthermore, levels of sTREM2 were found to be lower in two independent cohorts of African American (AA) compared to Non-Hispanic White (NHW) older adults with or without cognitive impairment (Schindler et al., 2021). Interestingly, significantly lower levels of AD biomarkers (total tau and phosphorylated tau) and neurofilament light chain (NfL) were also observed in the AA group compared to NHW, after adjusting for other sociodemographic factors (age, sex, education). The AA group was more likely to have *TREM2* risk variants associated with lower sTREM2 levels (Schindler et al., 2021), which could, in part, contribute to what was observed.

In addition to genetic and demographic factors, modifiable elements such as physical exercise could impact microglial activation and ensuing dynamics of CSF sTREM2, but this is an area in need of further investigation (Jensen et al., 2019). These data provide potential clues regarding the significance and physiological influences that impact on CSF sTREM2.

Levels of sTREM2 in the CSF fail to show any correlation with sTREM2 levels in peripheral blood or with measures of blood brain barrier integrity (e.g. albumin ratio) (Piccio et al., 2008; Piccio et al., 2016) suggesting its intrathecal production. However, one study reported that CSF sTREM2 levels were negatively correlated with plasma sTREM2 levels (Park et al., 2021), with higher sTREM2 plasma levels associated with age.

Collectively, these studies highlight the contribution of demographic, genetic and environmental factors to sTREM2 levels and should be considered in analyses and study design when evaluating sTREM2 in different neurological disease.

4. sTREM2 in the context of different neurological diseases

CSF sTREM2 is emerging as a biomarker of microglia activation in the brain. Levels of sTREM2 have been extensively investigated in the CSF and blood in the context of several neurological disorders (Table 1). However, because sTREM2 is released in CSF under healthy physiological conditions, measuring subtle changes during disease initiation and progression has been challenging. Although sTREM2 is reliably elevated under many different CNS disease conditions, the spatiotemporal nature of microglia/macrophage activation and the variable, dynamic release of sTREM2 along disease trajectories, limits its sensitivity as a standalone biomarker of microglial activation. Nevertheless, measures of sTREM2 are emerging as informative of disease pathogenesis.

4.1. Multiple Sclerosis and other inflammatory neurological conditions

Multiple sclerosis (MS) is the most common inflammatory demyelinating disease of the CNS, triggered by autoimmune mechanisms and characterized by inflammation, demyelination and axonal loss. The most common form is relapsing-remitting MS (RRMS), defined by episodes of neurological dysfunctions that can resolve completely or leave certain degrees of disability. Over time, in most cases, the disease becomes progressive with accumulating disability. A small proportion of people with MS manifest a disease that is progressive from the beginning - primary progressive MS (PPMS). A combination of neuroinflammatory and neurodegenerative pathogenic mechanisms underlie the complex and heterogeneous clinical course (Reich et al., 2018). The identification of non-invasive biomarkers that correlate with disease activity and progression, would facilitate the design of personalized therapeutic strategies.

The earliest report of sTREM2 in human CSF and serum, involved the investigation of people with MS (RRMS and PPMS) compared to a diverse range of other inflammatory neurological diseases (OIND: viral meningitis, encephalitis, optic neuritis, neuromyelitis optica and acute disseminated encephalomyelitis) and cases of non-inflammatory neurologic conditions (NIND: headache, degenerative disk disease, normal pressure hydrocephalus, seizure disorder, stroke and small vessel disease) (Piccio et al., 2008). Levels of sTREM2 were significantly elevated in CSF of subjects with MS as well as OIND compared to NIND, thus suggesting that CSF sTREM2 potentially reflects macrophage/microglia activation during neuroinflammation in general, without being a MS-specific marker. No differences were observed in serum sTREM2 levels. The lack of correlation between sTREM2 levels in CSF and in serum or relative to albumin ratio (as a marker of blood brain barrier integrity) suggests intrathecal origin of CSF sTREM2 and a marker of CNS inflammation (Piccio et al., 2008). Interestingly, in this study, expression of TREM2 receptor was detected only on $CD14^{+}$ monocytes in the CSF, and these $TREM2^{+}$ cells were enriched in NIND compared to MS and OIND, suggesting an inverse relationship between TREM2 receptor at the cell surface and CSF sTREM2. Elevation of CSF TREM2 in MS compared to controls was also shown in another study (Ohrfelt et al., 2016). Notably, CSF sTREM2 levels were normalized to the control levels, in subjects treated with natalizumab or mitoxantrone. This study also reported significant correlations between CSF sTREM2 levels and disease duration in MS but an absence of correlation between sTREM2 and clinical disease severity (measured by expanded disability status scale or MS severity score) (Kurtzke, 1983; Roxburgh et al., 2005) in either the whole MS group or the RR-MS group (Ohrfelt et al., 2016). A recent study backs up these findings and further describes evidence for a positive correlation between CSF sTREM2 levels and T-cell activation and axonal injury in MS (Ioannides et al., 2021). However, another study found no correlation of CSF sTREM2 levels, measured at diagnosis in untreated MS patients, with disease duration, measures of disease activity, levels of chitotriosidase/chitinase 1 (CHIT1) and NfL; whereas, a modest correlation with levels of chitinase-3–like protein 1 (CHI3L1 or YKL-40), another microglial marker, was found (Oldoni et al., 2020). This study did show however, that *TREM2* mRNA was modestly upregulated in the rim of chronic active MS lesions. By contrast, mRNA of macrophage/microglia-associated CHIT1 was robustly upregulated in MS lesions and CSF CHIT1 protein levels were significantly elevated in MS patients at diagnosis. Overall, this indicates that microglial activation occurs early in MS and could influence the progression of the disease in ways that remain to be determined. In animal models of MS, TREM2 receptor on myeloid cells (microglia or macrophages) is essential for neuroprotective activities involving phagocytosis and clearance of myelin debris and promotion of remyelination (Cantoni et al., 2015; Cignarella et al., 2020; Takahashi et al., 2007). CSF sTREM2 may be a surrogate marker of these microglia activities during CNS inflammation and its resolution in MS (Dong et al., 2021).

4.2. Alzheimer's disease

AD is the leading cause of dementia worldwide with currently no adequate treatment options available. It is characterized by progressive memory loss and cognitive decline (Holtzman et al., 2011). Sporadic AD is the most common form, occurring late in life (>65 years of age), while

early onset (<65 years of age) familial AD (FAD) is rare and is caused by genetic mutations in the β-Amyloid Precursor Protein (*APP*), and Presenilin (*PSEN1* or *PSEN2)* genes. The two hallmarks of AD pathology in the CNS are extracellular amyloid plaques composed of fibrils of Aβ peptides and neurofibrillary tangles within neurons, derived from abnormally aggregated, hyperphosphorylated tau protein. These abnormal protein aggregates are accompanied by synaptic and neuronal loss. Increasing evidence suggests a critical role of neuroinflammation and microglia activation in the pathogenic mechanisms leading to AD (Hansen et al., 2018; Wang and Colonna, 2019). The current framework for AD biomarker characterization in the CSF include the measurements of Aβ peptides, tau and phosphorylated tau, with the two most studied species being p-tau181 and p-tau217 (Barthelemy et al., 2020; Olsson et al., 2016).

Levels of sTREM2 in blood and CSF of subjects with AD or mild cognitive impairment (MCI) have been investigated in cross-sectional studies with variable results. Whilst most studies report slightly higher levels of sTREM2 in the CSF of subjects with AD diagnosis compared to cognitively normal controls (Ewers et al., 2019; Heslegrave et al., 2016; Piccio et al., 2016), one study reported lower levels in AD (Kleinberger et al., 2014), and others reported no differences in subjects with AD or MCI compared to normal controls (Henjum et al., 2016; Knapskog et al., 2020). These contrasting results could be due to differences in the clinical phase of disease in cognitively affected individuals and the presence of preclinical AD participants among the control groups across the different cohorts.

There is evidence that supports the hypothesis that CSF sTREM2 increases in a disease stage-dependent fashion in AD, with the highest levels in early symptomatic stages reflecting changes in microglia activation status in response to neuronal degeneration (Suarez-Calvet et al., 2016a; Suarez-Calvet et al., 2016b). According to this, temporal changes of CSF sTREM2 during AD natural history were measured in a cohort of autosomal dominant AD mutation carriers and their non-carrier siblings enrolled in the Dominantly Inherited Alzheimer Network (DIAN). This showed that CSF sTREM2 was increased in FAD mutation carriers compared to non-carriers, and the increase was measured 5 years before the expected symptom onset, with a difference that remained significant 5 years after expected symptom onset, but not later (Suarez-Calvet et al., 2016a). Changes in sTREM2 followed initial changes in Aβ and tau biomarkers, suggesting that microglia activation is secondary to these pathological events (Suarez-Calvet et al., 2016a). Increased sTREM2 was selectively seen in those with mild clinical symptoms compared to noncarriers and cognitively normal FAD mutation carriers (Suarez-Calvet et al., 2016a). Levels of sTREM2 were also shown to be increased early during the disease in subjects with MCI due to AD (CSF AD $A\beta_{1-42}$ and biomarker positive) compared to controls (AD biomarker negative) and to preclinical and clinical AD (AD biomarker positive). Interestingly, in this study sTREM2 levels were also higher in a group of cognitively normal subjects with suspected non-AD pathology (tau positive and amyloid negative) compared to controls and preclinical AD, suggesting that sTREM2 elevation could be a correlate of neuronal injury relating to the CSF tau biomarker more than amyloid pathology (Suarez-Calvet et al., 2016b). Notably, in a study in subjects with MCI and CSF biomarker evidence of AD, higher CSF sTREM2 levels were associated with higher grey matter volume after controlling for CSF Aβ and tau, suggesting protective effects of elevated sTREM2 in the brain (Gispert et al., 2016). In a longitudinal study of subjects with AD and CSF biomarker evidence of AD pathology ($A\beta_{1-42}$ and p-tau181 positive), higher CSF sTREM2 levels at baseline were associated with attenuated decline in memory and cognition in the subsequent 11 years, while a higher ratio of CSF sTREM2 to p-tau181 predicted slower progression to symptomatic stages or from MCI to AD dementia (Ewers et al., 2019). This study supports the premise that microglia activation, reflected by elevated CSF sTREM2, could be neuroprotective in the early stages of AD.

Overall, most of the AD studies report that levels of sTREM2 in CSF correlate with total and/or phosphorylated tau, but not with Aβ (Henjum et al., 2016; Heslegrave et al., 2016; Knapskog et al., 2020; Park et al., 2021; Piccio et al., 2016; Suarez-Calvet et al., 2016a; Suarez-Calvet et al., 2019), even after adjustment for potential confounding variables such as age, sex and ApoE4 status (Suarez-Calvet et al., 2016a). The correlation of CSF total/p-tau with sTREM2 could reflect pathological events in the cascade leading to neurodegeneration, but not pure Aβ deposition. Accordingly, several reports demonstrated increased levels of CSF sTREM2 concomitantly with biomarker evidence of tau pathology and neurodegeneration, and not of Aβ pathology, which instead was associated with a decrease in sTREM2 (Rauchmann et al., 2020; Suarez-Calvet et al., 2019). These results were based on subject classification according to the National Institute on Aging-Alzheimer's Association research framework, which groups markers of amyloid deposition (A), tau pathology (T), and neurodegeneration (N). (Jack et al., 2018). A recent study suggests that microglia activation correlates with tau pathology progression according to the Braak stages in AD (Pascoal et al., 2021). In this study, a cohort of subjects across the aging and AD spectrum was studied by PET imaging for microglia activation and tau pathology. CSF sTREM2, correlated with [^{11}C]PBR28 PET imaging, suggesting that sTREM2 could be a proxy for in vivo microglia activation. Microglial activation was in turn highly associated with tau pathology, atrophy, vascular white matter pathology and cognitive impairment, supporting the link between sTREM2 and AD pathophysiology (Pascoal et al., 2021). Interestingly, CSF sTREM2 was correlated also with the CSF $A\beta_{42/40}$ ratio, in contrast to what was previously reported by other groups.

sTREM2 levels have also been studied in relation to other soluble proteins in the CSF correlated to neuroinflammation or neurodegeneration. Notably, one recent study reported an association of sTREM2 in plasma with levels of NfL in CSF and plasma in a cohort of subjects with or without AD as well as a negative correlation between plasma and CSF sTREM2 considering the whole cohort (Park et al., 2021). Higher CSF sTREM2 levels were concomitant with higher levels of progranulin in CSF, another protein reflecting microglia activation which progressively increases during the AD continuum (Suarez-Calvet et al., 2018). Furthermore, sTREM2 was positively associated with levels of pro-inflammatory (e.g. TNFα, TNFR1, TNFR2), anti-inflammatory (e.g. TGFβ1, IL-10) protein and adhesion molecules (e.g. ICAM1, VCAM1) in participants from the ADNI cohort, implicating TREM2 in the neuroinflammatory responses in CNS during AD (Rauchmann et al., 2020).

4.3. Other neurodegenerative diseases

Measures of CSF sTREM2 have been evaluated in PD (Peng et al., 2020; Wilson et al., 2020), FTD (Roos et al., 2018; van der Ende et al., 2021; Woollacott et al., 2020; Woollacott et al., 2018), Creutzfeldt-Jacob disease (CJD) (Diaz-Lucena et al., 2021), chronic traumatic encephalopathy (Alosco et al., 2018) and CNS infection (Gisslen et al., 2019; Li et al., 2020). Correlations with specific clinical disease diagnoses relative to healthy controls are variable, but in these studies, CSF sTREM2 was shown to correlate with neuronal injury markers (CSF total-tau/p-tau, NfL or others), and with increasing age of the subjects. This is consistent with the studies of AD where CSF sTREM2 was variably associated with clinical disease diagnosis but was consistently positively correlated with CSF tau and p-tau in pre-symptomatic cases. On the other hand, plasma sTREM2 rarely associated with neurodegenerative disease – the exception being prion diseases where both CSF and plasma sTREM2 were significantly elevated (Diaz-Lucena et al., 2021).

4.3.1. Parkinson's disease

PD involves accumulation of α-synuclein in Lewy bodies, but also very often implicates co-pathologies of Aβ deposits and tau neurofibrillary tangles. Two studies have reported elevated CSF sTREM2 in PD compared to healthy controls (Peng et al., 2020; Wilson et al., 2020). In the latter study, the elevation in sTREM2 was found in "cognitively

normal" PD cases compared to healthy control subjects, but not in PD cases with MCI or dementia relative to healthy controls (Wilson et al., 2020). Nevertheless, considerable in-group variation in sTREM2 occurred in the PD cohorts compared to the healthy controls. Further stratification of the PD groups based on co-neuropathologies showed that CSF sTREM2 positively correlated with CSF α-synuclein (Peng et al., 2020) and CSF tau, but not Aβ (Wilson et al., 2020). There were no changes in plasma sTREM2 in these PD cohorts. Although high CSF tau correlated with high sTREM2 in PD, higher sTREM2 levels also reflected better cognitive scores (Wilson et al., 2020). This observation is in line with the report from the ADNI that showed that higher CSF sTREM2 was associated with slower rates of cognitive decline in AD (Ewers et al., 2019).

4.3.2. Frontotemporal dementias

FTD represents a heterogenous group of clinical syndromes with different histopathological features and genetic causations (including mutations in chromosome 9 open reading frame 72 (*C9orf72*), microtubule associated protein Tau (*MAPT*), granulin (*GRN*), charged multivesicular body protein 2b (*CHMP2B*), fused in sarcoma (*FUS*) or TAR DNA-binding protein 43 (*TDP-43*). Whilst CSF sTREM2 measured in FTD-*CHMP2B* or in FTD-*GRN* was overall not significantly increased, large in-group variability was noted for the mutation carriers relative to the healthy controls (Kleinberger et al., 2014; Piccio et al., 2016; Roos et al., 2018; van der Ende et al., 2021; Woollacott et al., 2018). FTD-*C9orf72* or FTD-*MAPT* mutation carriers did not show elevated CSF sTREM2. Other studies have reported elevated sTREM2 coinciding with "suspected non-AD pathology" (tau-positive, Aβ-negative neurodegenerative disease), which may reflect unspecified tauopathy, potentially FTDs (Rauchmann et al., 2020; Rauchmann et al., 2019). FTD syndrome linked to homozygous p.T66M or p.Y38C mutations in *TREM2* show drastic reduction in CSF sTREM2, but this reflects a severe loss of function in these proteins (Kleinberger et al., 2014) (see above). Recent evidence, in a small group of pre-symptomatic FTD-*GRN* patients, has linked high CSF sTREM2 levels with a better disease prognosis (van der Ende et al., 2021). So sTREM2 may reflect an early protective response to neuronal injury. The high variability and small sample sizes of these rare FTD cohorts indicate that further studies of sTREM2 in FTD are warranted to get a clearer mechanistic picture.

Mouse models show that knockout of *Grn* causes abnormal microglial activation, which might explain the elevated sTREM2 in some FTD-*GRN* cases (van der Ende et al., 2021). However, there is also histopathological evidence for extensive microglia and astrocyte activation in other forms of FTD, so the reason for such variability in CSF sTREM2 across the different FTD subtypes is unclear (Roos et al., 2018). What the studies do all consistently show is a correlation between increasing CSF sTREM2 and p-tau/total tau in both control and FTD cases of various forms. Diverse spatiotemporal aspects of microglial activation and neuronal injury in different heterogenous FTD types, and variable interaction with other demographic factors such as age, might explain why elevated sTREM2 was not measured in all FTD cases. Further studies are needed to understand how dynamic fluctuations in sTREM2 over time in any one individual could relate to disease prognosis and progression.

4.3.3. Prion diseases

Prion diseases are a family of rare, rapidly progressing, and fatal neurodegenerative diseases caused by the mis-folded disease-causing prion protein (PrPsc), that initiates a cascade of extensive degeneration resulting in severe dementia, ataxia and other motor symptoms (Colby and Prusiner, 2011). Subclasses include sporadic and inherited Creutzfeldt-Jakob disease – sCJD and gCJD respectively. Fatal familial insomnia (FFI) is another subclass, involving PrPsc protein pathogenesis in thalamic nuclei. Very rare variant forms of prion disease (vCJD), are transmissible through ingestion of material contaminated with mis-folded PrPsc protein. A comprehensive study of TREM2 in prion diseases, showed that *TREM2* mRNA and total TREM2 protein in autopsy frontal cortex and cerebellum were significantly elevated in sCJD relative to controls (Diaz-Lucena et al., 2021). This was accompanied by significant elevation of sTREM2 in both CSF and plasma in sCJD. A positive correlation between *TREM2* and *CD68* mRNA suggested that microglia were the main contributor to the upregulation of TREM2. The same study also evaluated sTREM2 in groups of cases with FFI, AD, MS or non-neurodegenerative neurologic conditions and found no changes relative to controls. Thus, the global neurodegenerative events and severe, short disease duration in sCJD could explain why sTREM2 levels in CSF were so much higher in this disease. No correlation between sTREM2 and disease duration was observed. The elevated brain *TREM2* mRNA, total protein as well as plasma sTREM2 levels appear unique to sCJD and not observed in AD or other neurodegenerative diseases. However, the common correlate of CSF sTREM2 with neuronal damage markers (total tau, 14.3.3, NfL, etc) was again observed in sCJD and is consistent with microglial activation in response to neuronal injury. The spatially restricted degenerative events in most neurodegenerative diseases may mean that CSF sTREM2, a global measure of CNS microglia/macrophage activity, may not always be sensitive enough to detect dynamic regionalised changes in microglia.

5. Future perspective and clinical implications

TREM2 has emerged undoubtably as a key molecule in microglia biology with implications spanning across different neurological diseases. Preclinical studies have been instrumental to underpin TREM2 functions in modulating microglia metabolism, survival, proliferation, and phagocytic activities. Mechanistic studies in humans are limited, but we have learned a great deal from genetic studies and clinical phenotypes associated with *TREM2* mutations. The existence of a soluble form of TREM2 in body fluids was reported more than 10 years ago (Piccio et al., 2008). Since then, a thorough characterization of sTREM2 levels in physiological and pathological conditions has been done as outlined in this review. However, whether sTREM2 is just an innocent bystander and proxy of microglia activation or an active player in CNS pathology is still a matter of debate. Despite this uncertainty,it is becoming clear that these studies have a high potential to be translated into the clinic. CSF sTREM2 has been evaluated as a biomarker of microglia activation in the context of neuroinflammatory and neurodegenerative diseases. A considerable amount of research was done in AD where CSF sTREM2 has also given important insights into disease pathogenesis by informing on the sequence of microglia activation in relation to Aβ deposition, tau aggregation, neurodegeneration and onset of clinical symptoms (reviewed above). Additionally, the TREM2 receptor is an attractive target in the CNS with respect to therapeutics research focusing on enhancing TREM2-mediated protective functions on microglia. Systemic administration of agonist antibodies specific for TREM2 was able to ameliorate the phenotype of transgenic mouse AD models by enhancing microglia responses to Aβ plaques and improving cognitive function with (Price et al., 2020; Schlepckow et al., 2020) or without also impacting plaque load (Wang et al., 2020). Moreover, treatment with an anti-TREM2 antibody promotes myelin debris clearance in the cuprizone model of CNS demyelination (Cignarella et al., 2020), suggesting a broad beneficial effect of TREM2 activation in neurodegenerative and neuroinflammatory diseases. The use of anti-TREM2 antibodies to modulate microglia functions has reached the clinic. Results on safety, tolerability, pharmacokinetics and pharmacodynamic effects of an anti-TREM2 agonistic antibody (named AL002) have been reported in a phase I trial in humans (NCT03635047) (Wang et al., 2020). This treatment (intravenous administration) was generally safe and well tolerated, with no drug-related serious adverse events (Wang et al., 2020). As part of this study, the effect of AL002 on CSF sTREM2 was assessed. Systemic administration of a single dose of AL002 caused a dose-dependent decrease in sTREM2 which may indicate that AL002 interferes with proteolytic shedding, by blocking the cleavage site; but it

could also induce the internalization of TREM2, thereby reducing surface TREM2 available for cleavage (Wang et al., 2020). Whether a reduction of sTREM2 in the brain contributes to the effect of the antibody remains to be determined in humans. Preclinical studies suggest that treatment with sTREM2 ameliorates the pathology and clinical course of mouse AD models, possibly by engaging TREM2 ligand on other cells or in the extracellular space (e.g. Aβ as previously suggested) (Zhong et al., 2017; Zhong et al., 2019). Despite much progress in the past few years, there are still many outstanding questions that require further investigation, including: (i) whether we want to activate or block TREM2; (ii) how disease stage impacts activation or blocking approaches; (iii) effect of sTREM2 as agonist on TREM2 ligand or as a decoy.

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