REVIEW ARTICLE

TREM2 in Health and Disease: A Comprehensive Review of Its Roles in Neurodegeneration and Metabolic Disorders

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Abstract

The transmembrane glycoprotein triggering receptor expressed on myeloid cells-2 (TREM2) is prominently found in peripheral tissue macrophages and brain microglia. It plays several critical roles, particularly in lipid metabolism, microglial function, immune response, and Alzheimer's disease. Polymorphisms of TREM2 are associated with a higher prevalence of neurodegenerative presentations such as Alzheimer's disease (AD), Parkinson's disease, and frontotemporal dementia. TREM2 is important for the energy metabolism of microglia; a lack of it impairs lipid and glycolysis metabolism, which compromises microglial function in AD. Furthermore, soluble TREM2 concentrations in cerebrospinal fluid are utilized as biomarkers for the early detection and monitoring of neurodegenerative conditions. TREM2 influences systemic lipid metabolism. It regulates the uptake, efflux, and intracellular processing of lipids in macrophages, affecting conditions such as atherosclerosis, non-alcoholic fatty liver disease, and obesity. TREM2 is vital for microglial function and central nervous system homeostasis, and its modulation offers therapeutic potential for neurodegenerative diseases. Continued research on TREM2's mechanisms is essential for progressing targeted interventions. This paper investigates the diverse roles of TREM2 in various physiological and pathological contexts, specifically focusing on metabolic syndromes, neurodegeneration (AD), and atherosclerosis. Despite significant advancements in our understanding of TREM2, the review addresses several critical gaps concerning its functions and potential for therapeutic applications.

Key words: Alzheimer's disease, lipid metabolism, microglia, neurodegeneration, phagocytosis, Triggering receptor expressed on myeloid cells-2

INTRODUCTION

The receptor family is characterized by a single immunoglobulin variable domain, to which the transmembrane glycoprotein triggering receptor expressed on myeloid cells (TREM)-2 is present. The *TREM* gene cluster in both humans and mice includes genes encoding *TREM-1, TREM-2, TREM-4, TREM-5,* and *TREM-like* genes.[1] The TREM2 gene, located on chromosome 6q21.1, consists of five exons and spans 41,126,246–41,130,922 base pairs, encoding a 230-amino-acid polypeptide. TREM2 is translated from 693bp complementary DNA, which codes for the cytoplasmic tail, transmembrane domain, and extracellular immunoglobulin-like domain of this transmembrane glycoprotein that interacts with the tyrosine kinase-binding protein DAP12 to perform its signaling actions.[2] TREM2 contributes to inflammation and phagocytosis and exhibits microglia-based expression.[3] The myeloid cells in the brain express TREM2, which regulates immune cell function. TREM2, in association with its intracellular adaptor DAP12, has been identified as a hub

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gene, emphasizing its crucial role in neurodegeneration.[4] TREM2 requires the adaptor protein TYROBP, which has immunoreceptor tyrosine-based activation motif (ITAMs) (functional docking sites), for transmitting intracellular signals (Figure 1).[5] TREM2-deficient macrophages' RNA sequencing has revealed deficiencies in energy pathways, ATP levels, and biosynthetic activities in addition to impairment in mTOR activation. This indicates that TREM2 is required for sustaining biosynthetic metabolism and cellular energy through mTOR signaling.[6] The *TREM2* gene's R47H mutation, the apolipoprotein E (APOE) 4 variant, Increases Alzheimer's disease (AD) risk approximately threefold. The two main characteristics of AD are hyperphosphorylated tau clumps and amyloid-β (Aβ) plaques. TREM2 is bound by phospholipids and lipoproteins such as APOE and CLU. Because of the R47H variation, TREM2's ligand-binding capacity is compromised, which results in decreased transcriptional reactions and microglial phagocytosis.[7] TREM2 can also improve the phagocytic function of microglia; the clearance of apoptotic neurons is due to upregulation of TREM2, whereas its deletion reduces microglial phagocytosis and ingestion of Aβ plaques.[8] Overall survival in skin cutaneous melanoma, adenocarcinoma, and cervical squamous cell carcinoma is correlated with higher expression of TREM2. However, it is linked to a reduced chance of survival in cases of renal clear cell carcinoma, liver hepatocellular carcinoma, and lower-grade gliomas. Acute myeloid leukemia exhibits low levels of TREM2 expression, while glioblastoma multiforme exhibits high levels. Variations in TREM2 expression have been observed among cancer types.[9] This review explores the multifaceted roles of TREM2 in modulating immune responses and maintaining homeostasis in both the central nervous system (CNS) and peripheral tissues. In the CNS, TREM2 is primarily expressed in microglia, where it regulates lipid metabolism, including cholesterol and phospholipids. It also facilitates the shift of microglia toward a disease-associated phenotype, which is essential for clearing pathological aggregates such as Aβ. This clearance process significantly impacts the progression of neurodegenerative disorders.

Structure reference

- Protein name: TREM2
- UniPort accession number: Q9NZC2
- Organism: *Homo sapiens* (Human)
- Structural data (PDB ID): pdb_00006z0h.

Soluble TREM2 (STREM2) structure and signaling

TREM2 soluble form is also known as sTREM2, originating in plasma and cerebrospinal fluid (CSF), and is created through receptor shedding or alternative splicing. Alternatively, spliced variants and an isoform produced by Proteolytic cleavage at the transmembrane region by ADAM10 or ADAM17 generate the soluble fragment of TREM2 (sTREM2). Numerous human biofluids, organs, and cell types contain these isoforms, including brain tissue, monocytes, microglia, CSF, and plasma.[10] TREM2 undergoes regulated intramembrane proteolysis, which starts on the surface of the cell and is caused by the enzyme ADAM10, shedding full-length TREM2. As a result of the shedding process, STREM2 is released into the CSF. The following process includes the intramembranous proteolytic processing of the membrane-bound C-terminal fragment by γ-secretase.[11] CSF levels of STREM2 vary in response to disease progression, physiological circumstances, and genetic variations. Modulating and tracking STREM2 levels may have clinical significance and therapeutic efficacy, according to pre-clinical and clinical research.[12] Elevated levels of total and phosphorylated tau in the CSF have been positively correlated with sTREM2 concentrations across multiple studies.[13] sTREM2 CSF levels grow throughout moderate cognitive impairment and AD stages when tau aggregation takes place, but they sharply decrease during the early pre-dementia interval before Alzheimer's diagnosis, corresponding with amyloid aggregation. These levels then decline further when AD progresses to the dementia phase (Figure 2).[14] The presence of sTREM2 on the surface of neurons suggests that it may help to promote communication between microglia and neurons.[15] Research has elucidated that STREM2 engages APOE, a principal hereditary susceptibility locus associated with AD, as a ligand. The complement system, which identifies synapses for microglia to remove during inflammatory responses, may also be impacted by sTREM2. This mechanism is essential for controlling synaptic pruning, which may become dysregulated in AD, leading to synaptic degeneration and cognitive impairments.[11]

TREM2 GENETIC VARIANTS AND FUNCTIONAL IMPACT

Key TREM2 variants implicated in disease susceptibility

R47H (rs75932628): This missense mutation leads to a substitution of arginine with histidine at position 47. The R47H point mutation is predominantly found in individuals of European descent and is rare in Asian and African populations.[16]

R62H (rs143332484): Another missense mutation correlated with increased AD susceptibility. Like R47H, it affects the extracellular domain of TREM2, potentially altering ligand binding and receptor function.[17,18]

D87N (rs142232675), T96K (rs2234353), L211P (rs2234256), and R136Q (rs149622783): These rare variants have been linked in numerous studies to the incidence of AD.[19]

H157Y (rs2234255): This variant has been linked to AD risk in some populations, though findings are less consistent across studies (Table 1).

TREM2 variants in other neurodegenerative diseases

Variants in TREM2 have been associated with neurodegenerative conditions apart from AD:

Frontotemporal dementia (FTD): Variants such as R47H and T66M have been associated with FTD in certain familial cases.[20]

Parkinson's disease (PD): The R47H variant has been implicated in increased PD risk, particularly in North American populations.[20]

Nasu–Hakola disease (PLOSL): This rare autosomal recessive condition manifests with the development of bone cysts and premature cognitive decline. Moreover, triggered by homozygous loss-of-function mutations in TREM2.[18]

PHYSIOLOGICAL SIGNIFICANCE OF TREM2

During instances of physiological stress, TREM2 expression in microglia is critical for maintaining metabolic homeostasis. It accomplishes this by identifying a variety of ligands that help regulate the neuropathology implicated in AD pathology, including lipids, lipoproteins, and oligomeric forms of Aβ. TREM2 is conveyed by tissue-resident macrophages, comprising those in bone (osteoclasts), adipose tissues, and the stem cell microenvironment of the hair follicle, in addition to microglia.[21]

PATHOLOGICAL SIGNIFICANCE OF TREM2

Role in CNS disorders

Neurodegeneration

Various investigations have studied the interrelation between TREM2 and the risk of several neurodegenerative diseases, such as AD, PD, ischemic stroke, FTD, amyotrophic lateral sclerosis, Lewy body dementia, posterior cortical atrophy, Creutzfeldt–Jakob disease, progressive supranuclear palsy, and PD.[22] The most prevalent TREM2 mutation that causes Alzheimer's is rs75932628, a single-nucleotide polymorphism leading to an arginine-to-histidine substitution at position 47 (R47H).[23] TREM2 is crucial for preserving microglial metabolic fitness under stressful conditions. Higher amounts of phosphorylated tau (p-tau), total tau, and Aβ have been linked with increased levels of sTREM2 in CSF, according to recent studies, particularly in individuals with both tau and Aβ pathologies. Evidence from the 5×FAD transgenic (TG) model indicates that sTREM2 improves behavioral outcomes and decreases Aβ buildup. In addition, APP mice with overexpressed sTREM2 have reduced plaque load and reversed memory problems.[24] Findings from cuprizone (CPZ)-mediated demyelination and 5×FAD models overexpressing Aβ indicate that microglial activation states extend well beyond the conventional M1/M2 paradigm. The introduction of single-cell RNA sequencing (scRNA-seq) has established a unique transcriptional landscape of microglia obtained from Aβ-overexpressing 5×FAD mice. Because of this approach, disease-associated microglia (DAM) were established. These microglia are recognized by the overexpression of genes linked to lysosomal performance (Cst7, Cd68, Cstb/d, and Lyz2), phagocytosis (TREM2, Tyrobp, and Axl), inflammation (interleukin [IL]-1β, Ccl6), lipid metabolism (APOE, Lpl, and Ch25h), and cell survival (Csf1 and insulin-like growth factor-1 [IGF1]).[25] The buildup of Aβ plaques and a weakened immune response are caused by impaired TREM2 binding to Aβ fibrils. Furthermore, research on immunofluorescence in the brains of R47H carriers indicates microglia are less triggered, which impairs their ability to operate as barriers.[26] We investigated whether elevated *TREM2* gene dosage would change the function of DAM and additional AD-relevant traits by crossing BAC-TREM2 with 5×FAD mice, an aggressive animal model that carries five familial APP and PSEN1 mutations linked to amyloid deposition in AD. Thioflavin S (ThioS) staining of amyloid plaques in cortical slices obtained from 7-month-old 5×FAD and 5×FAD/BAC-TREM2 mice showed that the 5×FAD/TREM2 mice had considerably less amyloid plaque load. After that, we used ELISA to quantify the Measurement of cortical lysate concentrations of both soluble and aggregated Aβ40/Aβ42. We discovered that 4-month-old 5×FAD/TREM2 mice have low levels of soluble and insoluble Aβ42. After 7 months, the alterations in Aβ levels were attenuated and did not achieve statistical significance. In the present AD mouse model, Aβ40 is a minor Aβ species, and there was no evidence of notable differences in its levels with age. In the RNA sequencing, we investigated human-specific APP transcript reads to see if the decrease in amyloid load was due to alterations in APP expression. We discovered that transgene expression was observed at similar levels in the 5×FAD and 5×FAD/TREM2 cortices. TREM2-intervented modifications in microglia-plaque interactions are therefore most likely responsible for the reduced plaque burden.[27]

Role in metabolic syndromes

Obesity

TREM2 is a key mediator of managing osteoclastogenesis and responses of microglia. TREM2 overexpression is shown to elevate fat deposition, negatively impacting overall health. Microglia that lack TREM2 demonstrate defects in lipid metabolism. In experiments with mice that

globally overexpress TREM2, there is a noted decline in insulin sensitivity following excess caloric intake, which is linked to increased body fat. This suggests that TREM2 may have harmful effects on metabolic health.[28] In the CNS, TREM2 is identified as a lipid receptor that is required for regulating the metabolism of phospholipids and cholesterol. In current research, TREM2 interacts with APOE, a crucial lipid transporter in the CNS.[29] APOE is essential for receptor-mediated lipid uptake and cholesterol efflux. The TREM2-DAP12 signaling pathway may increase microglia's export of cholesterol and decrease intracellular cholesterol accumulation as cholesteryl esters (CE), maybe through the activation of phospholipase C gamma 2. It is possible that lipoproteins carrying APOE transport effluxed cholesterol. The microglial activity to myelin injury is also mediated by TREM2, which increases the phagocytic activity of myelin remnants and can advance remyelination.[30] Microglia's metabolism of cholesterol is controlled by the TREM2 signaling pathway. Nugent *et al*. found that microglia from TREM2-deficient (TREM2-/-) mice contained >10 times as many Esterified cholesterol species and CE oxidation products of microglia from TREM2-sufficient (TREM2+/+) mice in a model treated with CPZ, which mimics demyelination and the lipid overload that can result from it. The scientists inhibited acetyl-CoA acetyltransferase 1, an enzyme found in the endoplasmic reticulum (ER), which oversees turning free cholesterol into CEs, to investigate the mechanisms underlying this CE buildup. In addition, they enhanced the expression of ABCA1 and ABCG1, two cholesterol transporters. The TREM2−/− mice models showed less CE deposition as a result of both of these treatments. Accordingly, a TREM2 deficiency may be associated with issues with microglial cholesterol efflux, which could result in intracellular cholesterol being stored as CEs.[31] When a high-fat diet (HFD) is given, TREM2−/− mice showed higher levels of obesity and insulin resistance than their wild-type (WT) counterparts. TREM2−/− mice exhibited a decrease in adipose tissue mass, but the adipocytes were larger because of hypertrophy, and the rate of cell death was increased. Furthermore, adipocyte-derived MCP-1 expression is downregulated in TREM2−/− mice, reducing the amount of MCP-1 in the bloodstream in comparison to WT mice. Furthermore, TREM2−/− mice showed less F4/80+CD11c+ macrophage infiltration into their adipose tissue. These macrophages were incapable of producing crown-like structures, which are essential for removing cellular debris and dead adipocytes. Mice fed an HFD also showed an elevated inflammatory response from adipose tissue macrophages (ATMs) when TREM2 was absent. Furthermore, TREM2−/− animals fed an HFD showed more serious hepatic steatosis than WT mice.[32] Both in WT and TG mice, TREM2-Ig therapy reduced the body weight increase brought on by an HFD. Visceral fat depots, including epididymal and retroperitoneal white adipose tissue, decreased in size and weight as a result of this treatment. However, only TG mice treated with TREM2-Ig showed a decrease in liver weight. When compared to controls, TREM2-Ig-treated animals showed a marked suppression of the upregulation of adipogenic genes triggered by HFD, including peroxisome proliferator-activated receptor gamma (PPARγ2), C/EBPα, fatty acid synthase (FAS), and CD36. Conversely, it was shown that Wnt10b and adiponectin levels had increased. TREM2-Ig-treated WT mice also showed increased expression of genes linked to insulin resistance in their liver and EWAT, indicating improved insulin sensitivity. While TREM2-Ig treatment enhanced GSK3β phosphorylation, hIg-treated HFD-fed TG mice showed a decrease in this phosphorylation. Furthermore, the elevated β-catenin phosphorylation seen in control animals was suppressed by TREM2-Ig. TREM2-Ig treatment of 3T3-L1 cells led to enhanced expression of Wnt10b and decreased accumulation of lipids and adipogenic genes such as PPARγ2, C/EBPα, CD36, and FAS. PPARγ, C/EBPα, and FAS expression were all decreased by TREM2-Ig treatment in primary mouse embryonic fibroblasts, but Wnt10b levels were elevated.[33]

Non-alcoholic fatty liver disease

Worldwide, about 30% of adults are affected by non-alcoholic fatty liver disease (NAFLD), a prevalent chronic liver impairment. The main features of non-alcoholic steatohepatitis include fibrosis, ER stress, mitochondrial dysfunction, and significant hepatic inflammation.[34] The two primary phenotypes that they display are alternative (anti-inflammatory, M2) and classical (pro-inflammatory, M1). Increased inflammation and tissue damage are associated with pro-inflammatory microglia, which release pro-inflammatory cytokines (e.g., IL-1β, IL-18, IL-6, and tumor necrosis factor-alpha [TNF-α]) and free radicals. Conversely, anti-inflammatory microglia aid in the healing of the CNS by generating anti-inflammatory facilitators such as growth factors and IL-10, as well as by improving the deletion of debris by phagocytosis.[35] The three primary phenotypes of microglial activation are M0, M1, and M2. Pro-inflammatory responses, anti-inflammatory responses, and surveillance are all influenced by these characteristics, respectively.

M0 phenotype

In a healthy state, microglial cells undergo a "resting" condition, characterized by an immobile, branching shape, limited expression of activation markers, and functional dormancy. Microglia that are at rest in a healthy CNS exhibit little to no antigen-presenting cell activity.[36] The precise role of resting microglia is still unknown, but even in a healthy CNS, these cells are very dynamic and actively move in their delicate ramified processes.[37]

M1 phenotype

The M1 phenotype is pro-inflammatory and contributes to neuroinflammatory processes.[38] Through the stimulation of decreased nicotinamide adenine dinucleotide phosphate oxidase (respiratory burst), activated M1 microglia generate reactive oxygen species, which improves the formation of

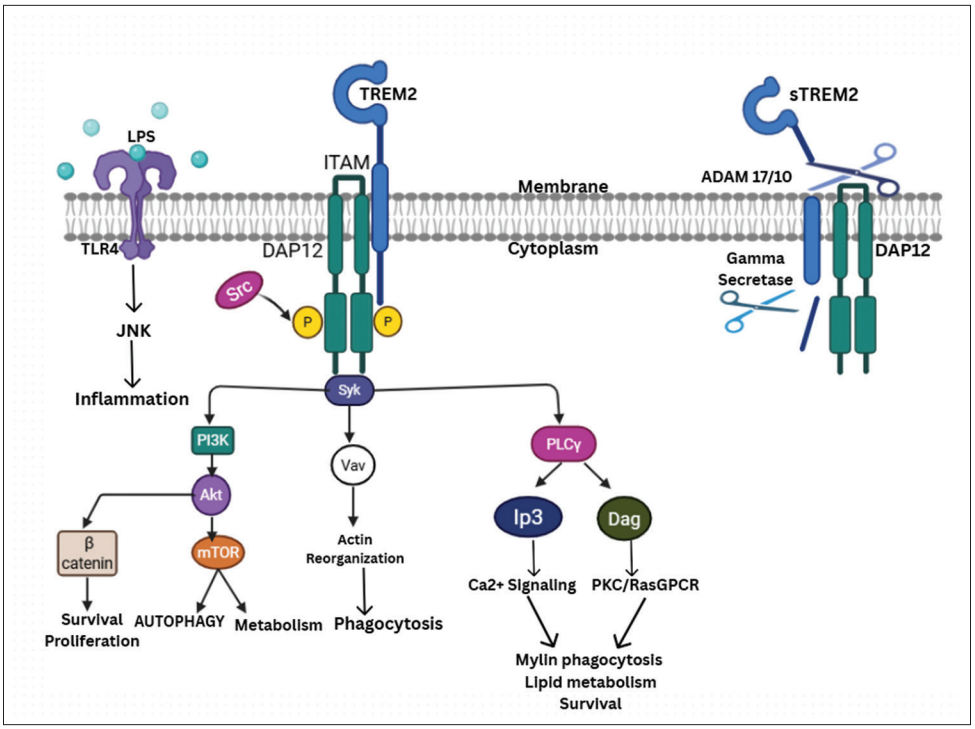

Figure 1: The TREM2 signaling pathway: TREM2 consists of an extracellular domain that contains a V-type immunoglobulin-like domain, a transmembrane region, and a short cytoplasmic domain that lacks intrinsic signaling motifs. TREM2 functions by forming a heterodimeric complex with adaptor proteins DAP10 or DAP12. When a ligand binds to TREM2, the ITAM within DAP12 becomes phosphorylated on tyrosine residues. This phosphorylation event recruits and activates the tyrosine kinase Syk, which triggers a cascade of downstream signaling events. These events include the activation of the PI3K/AKT-mTOR pathway, actin remodeling, Ca2+ mobilization, and the activation of both the nuclear factor kappa B and MAPK signaling pathways. In addition, TREM2 signaling is regulated by proteolytic processing. The extracellular domain of TREM2 can be cleaved by ADAM10 or ADAM17, leading to the release of soluble TREM2. Meanwhile, the intracellular domain (ICD) of TREM2 is cleaved by γ-secretase, producing TREM2 ICD. Both of these processes contribute to the downregulation of TREM2 signaling activity. TREM2: Triggering receptor expressed on myeloid cells-2

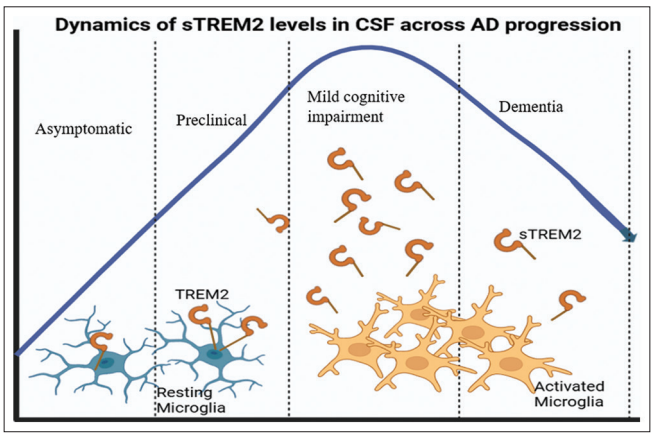

Figure 2: This infographic illustrates the association between CSF sTREM2 levels and cognitive function across AD stages. It suggests that higher sTREM2 concentrations are associated with better mental performance in early stages but decline as the disease progresses. AD: Alzheimer's disease, sTREM2: Soluble triggering receptor expressed on myeloid cells-2, CSF: Cerebrospinal fluid

pro-inflammatory cytokines like IL-1β and TNF-α. This begins a chain reaction of inflammation.[39]

M2 phenotype

M2 polarization, commonly referred to as alternative macrophage activation, is characterized by the production of neurotrophins and anti-inflammatory cytokines. M2 microglia generate growth factors such as IGF-1 and anti-inflammatory cytokines such as IL-10, induced by IL-4 or IL-13, which also increases phagocytosis.[39] The release of neurotrophic and anti-inflammatory molecules, the M2a (alternative activation) state, facilitates tissue repair and regenerative processes; however, pro-inflammatory and anti-inflammatory mediators are expressed by the M2b transitional state (type II alternative activation), which is essential for the regulation of immune function. Conversely, the M2c state (acquired deactivation) releases anti-inflammatory cytokines, provides neuroprotection, and then facilitates the removal of myelin debris.[40] We investigated the consequences of TREM2 deficiency on the advancement of NAFLD in this work. Using WT (WT; TREM2+/+) and TREM2-deficient (TREM2−/−) mice, we first examined the amounts of apoptotic-cell-associated proteins in their livers under steady-state settings. Compared to control animals, we observed increased levels of Bax, a pro-apoptotic protein,

Table 1: TREM2 variants and associated diseases

Variant (protein change)	SNP ID/ mutation	Associated diseases	Inheritance	Functional impact	Notes
R47H	rs75932628	AD, PD, FTD, ALS	Heterozygous	Loss-of-function; impairs microglial phagocytosis	Significantly increases AD risk (OR~4.5); also linked to FTD and PD
Q33X	rs104894002	NHD, FTD-like syndromes	Homozygous	Early stop codon; complete loss of TREM2 function	Causes Premature dementia, presenting with or without skeletal cystic lesions
Y38C	-	NHD, AD, FTD-like syndromes	Homozygous	Missense mutation; disrupts protein structure	Associated with both NHD and FTD phenotypes
T66M	rs201258663	NHD, FTD-like syndromes	Homozygous	Missense mutation impairs protein folding	Observed in both NHD and FTD cases
D87N	rs142232675	AD	Heterozygous	Missense mutation; reduces TREM2 function	Significantly associated with AD
H157Y	rs2234255	AD	Heterozygous	Missense mutation; increases sTREM2 shedding	Potential risk modifier for AD
R62H	rs143332484	AD	Heterozygous	Missense mutation; modest effect	Associated with increased AD risk
L211P	rs2234256	Not associated with disease	Heterozygous	Missense mutation; benign	No significant association with AD
c. 482+1G>A/c. 482+2T>C	-	NHD, FTD	Homozygous	Splice-site mutations result in truncated proteins	Lead to exon skipping and loss of function

AD: Alzheimer's disease, PD: Parkinson's disease, FTD: Frontotemporal dementia, ALS: Amyotrophic lateral sclerosis, NHD: Nasu–Hakola disease, TREM2: Triggering receptor expressed on myeloid cells-2, SNP: Single-nucleotide polymorphism

and higher levels of cleaved caspase-3 levels were observed under TREM2-deficient conditions, consistent with impaired phagocytic function of TREM2−/− Kupffer cells. Next, we gave both WT and TREM2−/− mice an HFD for 2 weeks to evaluate the accumulation of apoptotic cells within hepatic tissue throughout the evolution of NAFLD. Annexin V staining (AV+ cells), a marker of various apoptotic cells, was comparable in TREM2−/− and WT mice. This indicates that during brief HFD exposure, compensatory mechanisms are triggered to promote the absorption of dead cells even in a TREM2-deficient state. Furthermore, liver samples from HFD-fed WT and TREM2−/− mice showed a decrease in the proportion of "metabolically active" CD206+ macrophages, even though macrophages from NAFLD rats showed impaired lipid metabolism and enhanced TREM2 expression. Expressing the pro-inflammatory marker iNOS or the anti-inflammatory marker ARG1. In addition, we observed that TREM2−/− mice macrophages expressed an elevated level of YM1, a protein with anti-inflammatory yet pro-fibrotic properties, and less of the costimulatory molecule CD80 than controls.[41]

Role in atherosclerosis

Atherosclerosis is the world's leading cause of death from complications, including heart attacks and stroke.[42] TREM2hi macrophages that are resident-like, pro-inflammatory, and anti-inflammatory are the three main subpopulations of macrophages found in animal models of atherosclerosis. In the artery, a specific population of $TREM2^{+}CD9^{+}$ macrophages is identified by gene ontology analysis.[43] Using single-cell RNA sequencing (scRNA-seq) data from aortic cells in atherosclerotic Ldlr−/−mice, *TREM2* gene expression dynamics were evaluated. We found that macrophages under atherosclerotic conditions exhibited high levels of TREM2, whereas only a small percentage of other immune cell types exhibited detectable TREM2 expression: Neutrophils (5.1%) and T cells (1.2%). TREM2 expression was determined in various macrophage subpopulations by further study of mononuclear phagocytes (MPCs). The greatest levels were found in lipid-laden or foamy macrophages, which correlate with the prior findings of populations TREM2^hiGpnmb^hi and TREM2^hiSlamf9^hi, which accumulate during the disease. Conversely, dendritic cells showed less TREM2 expression. In addition, while at lower levels than the macrophages, a subgroup of smooth muscle cells (referred to as VSMC_2) that proliferate in the advanced stages of the disorder also expressed TREM2. Foamy cell-associated genes such as Lgals3, Spp1, and APOE were also present in these cells. Higher amounts of soluble and total TREM2 (sTREM2) were found in atherosclerotic aortas, as well as higher levels of sTREM2 in the blood, which is consistent with

the buildup of TREM2-expressing cells. Foamy macrophages exhibited a significant degree of TREM2 expression, while it was also observed in some fibroblasts and fibromyocytes, and MPCs in human atherosclerotic coronary arteries.[44] A genome-wide CRISPR screen and a trajectory inference were performed using merged scRNA-seq profiles obtained from atherosclerotic tissue samples to establish TREM2 as a key modulator of foamy macrophage expansion. When TREM2 was precisely deleted from macrophages, the amount of atherosclerotic plaque decreased, foamy macrophage death increased, and macrophage proliferation decreased. TREM2-deficient foamy macrophages showed reduced cell proliferation pathways and were unable to downregulate cholesterol production pathways after lipid loading. This was followed by increased macrophage cytotoxicity following cholesterol loading, decreased cholesterol efflux, and induction of the ER stress response. TREM2 is a viable treatment target for atherosclerosis since this study identifies a regulatory network operative in foamy macrophages that is critical in maintaining the buildup of cholesterol and its influence on cellular viability.[45] TREM2 represents a potential target for therapeutic intervention of cardiovascular disorders since it is a key factor in abnormal immunological signaling.[46]

Therapeutic targeting of TREM2

TREM2 is critically involved in mediating neuroinflammation and CNS immune monitoring. It has become a viable target for therapeutic development in the treatment of neurodegenerative diseases such as Alzheimer's.[47] TREM2 activation may enhance neuronal function and postpone neurodegenerative alterations, according to certain research. AL002 is one TREM2 pathway activator that has demonstrated potential as a treatment option. A Phase I trial assessed how the humanized monoclonal IgG1 antibody AL002, which targets TREM2, affected biomarkers in CSF. Two days after a single dose of AL002, researchers observed a rise in soluble CSF-1 receptor (sCSF-1R) levels, and sTREM2 concentrations decreased progressively with increasing dose. The rise in sCSF-1R signifies increased microglial proliferation, while the reduction in sTREM2 implies that the treatment may disrupt proteolytic shedding or cause TREM2 internalization. The preliminary trial outcomes demonstrated that AL002 exhibits a favorable safety and tolerability profile and efficiently targets its intended targets. According to these findings, AL002 may serve as a viable treatment strategy for AD, with the possibility of having neuroprotective effects that go beyond AD pathology. Additional evidence of AL002's pharmacodynamic effects is provided by outcomes from the Phase I INVOKE trial conducted in healthy individuals, which show that therapy activates the TREM2 pathway and increases microglial activity.[48] AL002 intravenous injections administered once a week for 4 weeks were well tolerated by cynomolgus monkeys. This treatment led to a decline in TREM2 abundance within the frontal cortex and hippocampal regions, as did sTREM2 levels in CSF exhibited a dose-dependent elevation. Moreover, the brain and CSF both showed elevations in biomarkers linked to TREM2 signaling. A separate intravenous infusion of AL002 elicited a dose-dependent response. A reduction in CSF sTREM2 levels was associated with increased expression of biomarkers reflective of TREM2-dependent signaling and microglial activation, indicating effective engagement with brain targets in a Phase I research with 64 healthy participants. During a 12-week period, no significant side effects were detected, and the single dosage of AL002 demonstrated efficient CNS penetration and favorable tolerability.[49] INVOKE-2 is a randomized, double-blind, placebo-controlled, dose-ranging Phase II clinical trial designed to assess the safety and efficacy of AL002 in individuals with early-stage AD. Three different intravenous dosage schedules of AL002 (15 mg/kg, 40 mg/kg, or 60 mg/kg, given every 4 weeks) or a placebo were randomly allocated to the participants.[50] The trial was carried out in 11 different nations at various centers using a common closed design, which meant that participants continued on their prescribed course of therapy until the final patient was enrolled after 48 weeks of treatment, for a total study period of 96 weeks. Although AL002 indicated target engagement, it failed to accomplish its primary goals since there was no discernible decrease in amyloid positron emission tomography imaging or slowing of cognitive degradation. The medication did not yield quantifiable clinical or biomarker benefits, despite the fact that higher sTREM2 levels indicated pharmacodynamic engagement. Furthermore, amyloid-related imaging abnormalities were among the adverse events, which highlighted safety issues, particularly for APOE ε4 carriers. In addition to posing additional difficulties for TREM2-targeted treatments, these findings offer insightful information that forces an examination of the benefits and drawbacks of TREM2 for therapeutic intervention in AD.[51]

CONCLUSION AND FUTURE DIRECTIONS

This review highlights the numerous physiological and pathological situations in which TREM2 functions, with a focus on obesity and AD. We now know a lot more about TREM2; there are still many crucial questions about its roles and potential applications in therapy. Obesity and ATMs: ATMs are diverse in both their origin and their purpose. The majority of $TIM4^{+}$ $MHCII^{-}$ macrophages, which have an embryonic origin, are seen in lean environments. Obesity, however, causes bone marrow-derived $TIM4^{-}$ $MHCII^{+}$ macrophages to be recruited. The exact processes behind this metamorphosis are still unknown, but these alterations contribute to metabolic dysregulation. TREM2 in the molecular pathology of AD: TREM2 is essential for helping to activate microglia, encourage Aβ phagocytosis, and lessen neuroinflammation. Its relationship with APOE is essential for lipid metabolism and the microglia's general operation. In pre-clinical models, therapeutic approaches that improve

Aβ clearance and cognitive outcomes, including TREM2-activating antibodies, have shown promise. Therapeutic targeting: Although there is therapeutic promise for TREM2 activation in AD, the timing, dose, and long-term implications of such therapies must be carefully considered. We also need to investigate how TREM2 regulation affects other diseases, including neurodegeneration and obesity. Differences between human data, animal models, and *in vitro* research show that more representative models are required to predict therapy results with accuracy. Finally, TREM2 is shown to be an important regulator of immunological responses and a defender of tissue homeostasis. Targeting TREM2 has potential for precision immunotherapy and customized medicine. Treatment results may be enhanced by customizing medications to efficiently alter the immunological milieu by evaluating each patient's TREM2 expression and function. To fully utilize TREM2's therapeutic potential across a range of disorders, thorough research filling up the gaps mentioned above will be necessary.

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