

TREM2: At the Crossroads of CNS Immunity and Lipid Metabolism

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Received: 21 July 2025; Accepted: 15 August 2025; Published: 2 September 2025

Abstract:

Triggering receptor expressed on myeloid cells 2 (TREM2) is a transmembrane receptor that plays a crucial role in immune regulation and metabolic homeostasis. It is mainly expressed on microglia in the central nervous system (CNS) and is involved in various biological functions such as immune regulation, cell proliferation and survival, neuronal phagocytosis, calcium mobilization, autophagy, and synaptic pruning. In recent years, studies have found that TREM2 not only participates in neuroimmunity by regulating microglia but also is closely related to lipid metabolism and lipid droplet formation. The role of their interaction in the CNS has attracted increasing attention, indicating that TREM2 may be at the crossroads of immune regulation and lipid metabolism in the CNS. Therefore, this article elaborates on the core role of TREM2 in regulating immunity and lipid metabolism in the CNS from the aspects of TREM2's research status in CNS immunity, lipid metabolism, interaction, and related diseases.

Keywords:

Triggering Receptor Expressed on Myeloid Cells 2, Neuroinflammation, Lipid Metabolism, Lipid Droplets

1. Introduction

As the intrinsic immune cells of the central nervous system (CNS), microglia (MG) are the first line of defense against disease damage and play important roles in synaptic pruning, damage repair, homeostasis maintenance, cell debris phagocytosis, and communication with other neurons [1]. Previous studies have shown that MG activation is associated with neuroinflammation, and the discovery of triggering receptor expressed on myeloid cells 2 (TREM2) has become a key breakthrough in MG research [1]. TREM2 is an immune receptor mainly expressed on the surface of MG, which can activate downstream signaling pathways (such as PI3K/Akt) by recognizing lipid ligands (such as apolipoproteins). Lipid droplets (LDs) are highly dynamic inflammatory organelles that play roles in lipid storage, metabolism, and signal transduction. They increase significantly when MG respond to lipid overload and are also important factors leading to MG dysfunction [2]. The interaction between

TREM2-mediated immunity and lipid metabolism in the CNS has attracted increasing attention, suggesting that TREM2 may be an important hub for MG immune regulation and lipid metabolism. This article systematically elaborates on the research progress of TREM2-mediated “immune-lipid metabolism” interaction in the CNS from the perspective of TREM2 regulating CNS immunity and lipid metabolism.

2. Structure and Function of TREM2

2.1. Basic Biological Characteristics of TREM2

TREM2 is a transmembrane protein of the immunoglobulin receptor family, consisting of an extracellular domain, a transmembrane domain, and a short cytoplasmic tail region. The extracellular domain of TREM2 binds to DNA, lipopolysaccharides (LPS), amyloid- β (A β), lipoproteins, apolipoprotein E (APOE), and phospholipids to coordinate the brain's immune surveillance and defense mechanisms [3]; its cytoplasmic tail region lacks signal motifs and needs to rely on the immunoreceptor tyrosine-based activation motif (ITAM) of the intracellular adaptor protein DNAX-activating protein of 12 kDa (DAP12) to exert its function. After TREM2 binds to DAP12 to form a dimer (TREM2/DAP12), ITAM is phosphorylated by SRC family tyrosine kinases, followed by activation of the downstream tyrosine motif SYK, initiating downstream signal cascades and immune responses[4]. Most current studies believe that TREM2 in the CNS is mainly expressed in MG and is involved in immune regulation and lipid metabolism.

2.2. TREM2 and CNS Immunity

Among the TREM family, TREM1 promotes inflammatory responses, while TREM2 inhibits them. TREM2 mutation was first identified as a genetic factor for Nasu-Hakola disease, a rare neurodegenerative disease characterized by bone cysts and pathological fractures in early adulthood, and its pathological mechanism is related to MG activation. Subsequent studies have shown that upregulated TREM2 activity inhibits neuroinflammatory responses in animal models of Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), and other CNS diseases [6].

In pathological conditions, TREM2 serves as a signal center for tissue damage, regulating MG phagocytosis and inflammatory responses to maintain tissue homeostasis. Chen et al. [6] found in a mouse model of intracerebral hemorrhage (ICH) that activation of TREM2 could activate the PI3K/Akt signaling pathway, reduce neuroinflammation and neuronal apoptosis, and improve neurological function after ICH. Zhang et al. [9] and Zhao et al. [8] demonstrated in MG and astrocytes, respectively, that overexpression of TREM2 inhibits the activation of the NF- κ B inflammatory pathway, thereby reducing the release of pro-inflammatory factors. This suggests that TREM2 is not limited to regulating MG function, and its wide expression may play a role in various biological processes. Similarly, Li et al. [10] proved through the TREM2-targeted agonist Hecubine that TREM2 downregulates the TLR4/MyD88/NF- κ B signaling pathway and inhibits neuroinflammation. This is also the first time that a targeted agonist (Hecubine) has been used to prove that TREM2 reduces neuroinflammation both in vitro and in vivo, indicating that TREM2 agonists are expected to become potential therapeutic targets for neuroinflammation-related diseases. Conversely, TREM2 deficiency or mutation leads to the transformation of MG to a pro-inflammatory state. For example, Wei et al. [11]

showed that TREM2-deficient MG have increased lipid synthesis and decreased lipolysis, resulting in LDs accumulation, which in turn leads to downregulation of the TGF- β 1/Smad 2/3 signaling pathway, transforming MG to a pro-inflammatory phenotype and exacerbating neuroinflammation. Fu et al. [12] confirmed in in vitro experiments that after TREM2 mutation, MG phagocytosis decreases and pro-inflammatory factors are released. This indicates that TREM2, as an upstream signaling molecule, plays an important role in maintaining the dynamic balance of inflammation in response to CNS disease damage. This role enables MG to exert anti-inflammatory effects in a timely manner, while TREM2 can be regulated to prevent excessive anti-inflammatory responses. In addition, in mouse MG, anti-inflammatory molecules such as galectin 1/3, interleukin-1 receptor antagonist, and progranulin are expressed in a TREM2-dependent manner [7]. This indicates that TREM2 not only exerts anti-inflammatory effects through signaling pathways but also induces a variety of anti-inflammatory molecules to play a synergistic role, further confirming the core position of TREM2 in CNS immunity.

2.3. TREM2 and CNS Lipid Metabolism

The mammalian CNS is highly enriched in lipids, which play important roles in cell membrane structure and signal transduction. The white matter of the CNS is mainly composed of myelin, which is mainly composed of cholesterol. Therefore, cholesterol metabolism plays a key role in CNS myelin regeneration and is core-regulated by TREM2 [13]. Due to the existence of the blood-brain barrier, the CNS has a unique cholesterol metabolism microenvironment. The synthesis of cholesterol in the brain is regulated by cholesterol regulatory element-binding proteins and their cleavage-activating proteins, and can be oxidatively modified to 24(S)-hydroxycholesterol, which can then pass through the blood-brain barrier, representing the main pathway for cholesterol efflux from the brain. In addition, cholesterol is esterified to form cholesterol ester (CE), which accumulates continuously with triglyceride (TG) to form LDs, which then enter the cytoplasm in a “budding” manner, bind to other neutral lipids, or fuse with other LDs. LDs are cellular storage compartments containing neutral lipids surrounded by a single layer of phospholipids and are considered markers of inflammation [16]. In the case of energy deficiency, LDs can be decomposed through two pathways, lipolysis and lipophagy, to provide energy for maintaining the basic functions of MG. LDs can establish functional contact sites with mitochondria and endoplasmic reticulum, reduce intracellular lipotoxicity and endoplasmic reticulum stress, and play important roles in intracellular signal transduction and metabolism.

TREM2 can bind to a variety of lipids, such as phospholipids, high-density lipoprotein, low-density lipoprotein, and APOE. The current mechanisms by which TREM2 regulates cholesterol metabolism are as follows: ① TREM2 promotes MG cholesterol efflux and reduces CE accumulation through the phospholipase $\text{C}\gamma 2$ (PLC $\gamma 2$) signaling pathway [18]. ② TREM2-APOE interaction: Cholesterol binds to APOE, and APOE is esterified under the mediation of ATP-binding cassette transporter A1 (ABCA1) to form high-density lipoprotein, which then interacts with TREM2 to complete the transport of cholesterol between neurons and glial cells and maintain CNS lipid homeostasis [15]. Studies have shown [19] that after cuprizone (CPZ) treatment, the levels of CE in the brain, microglia, and astrocytes of APOE $^{-/-}$ mice are significantly increased, and CE also accumulates abnormally in the cerebrospinal fluid. This indicates that APOE, as a cholesterol transporter, cooperates

with TREM2 to maintain cholesterol homeostasis, and its deficiency leads to more extensive lipid metabolism disorders.

3. Research Status of TREM2 in CNS-Related Diseases

3.1. TREM2-Mediated Interaction Between Immunity and Lipid Metabolism

As a key marker of lipid metabolism, the dynamic changes of LDs are closely related to MG function. Myeloid cells form LDs in response to inflammation and stress, and LDs can reprogram MG to induce their transformation to a lipid droplet-associated phenotype (LDAM) [20]. In the hippocampus, LDAM accounts for more than 50% of all MG, showing a state of severely impaired phagocytic function and release of high levels of pro-inflammatory factors [21]. This indicates that TREM2 participates in the functional remodeling of MG by regulating LDs metabolism.

Inflammatory signals and LDs formation regulate each other: LPS, as an inflammation inducer, is widely used in in vitro and in vivo experimental studies. LPS can increase the expression of the lipid droplet-associated protein PLIN2 by activating the p38 α / β and PI3K/Akt pathways, promoting LDs formation. At the same time, fatty acids from LDs degradation can be used as substrates to participate in the synthesis of inflammatory mediators. In CNS diseases, Hugo Oyamada et al. [2] found that the pro-inflammatory factor IL-21 induces LDs accumulation and increases the expression of CD36 and APOE, impairing MG function and inducing MG to secrete high levels of pro-inflammatory factors, forming a “inflammation-LDs-inflammation” vicious cycle.

In addition, PLC γ 2, as a downstream molecule of the TREM2/DAP12 signaling axis, is considered a key signal node connecting immune activation and lipid metabolism: On the one hand, after being activated by TREM2/DAP12, it interacts with SYK to promote cholesterol efflux, reduce LDs accumulation, and exert anti-inflammatory effects; on the other hand, after A β binds to TLR4, it activates downstream PLC γ 2 signal transduction, inducing pro-inflammatory responses. It is worth noting that in the case of TREM2 deficiency, the TLR4/PLC γ 2 signaling pathway may abnormally enhance lipid metabolism, leading to a hyperinflammatory state [23]. This may be because the TLR4/PLC γ 2 signaling pathway is abnormally enhanced due to imbalance in the state of TREM2 deficiency, resulting in lipid metabolism disorders, which further confirms the core role of TREM2 in coordinating immune homeostasis and lipid balance.

3.2. TREM2 and AD

AD is a neurodegenerative disease characterized by neuroinflammation and abnormal lipid metabolism, caused by the deposition of A β plaques and the formation of neurofibrillary tangles. A β -driven LDs accumulation and impaired phagocytic function are related to the increase of reactive oxygen species, which exacerbate the occurrence of neuroinflammation in AD [24]. Current studies on the role of TREM2 in AD pathology mainly focus on the following mechanisms: ① Phagocytosis of A β plaques: TREM2 can bind to a variety of lipids, among which phosphatidylserine (PtSer) can trigger TREM2-dependent synaptic pruning and cell clearance [25]. In AD, dystrophic neurons produce many externalized phosphatidylserine (ePtdSer) aggregates, which bind to A β plaques to form ePtdSer + A β complexes. TREM2 can recognize this complex and trigger MG to phagocytose A β . However, when TREM2

is deficient or mutated, this recognition function is lost. This is also the first time to clearly define the core role of the ePtdSer-TREM2 axis in MG-targeted clearance of A β , revealing the driving force behind TREM2-mediated MG phagocytosis of A β . Unfortunately, the specific binding site of TREM2-ePtdSer-A β has not been clarified. ② “TREM2-APOE” interaction. The description of “lipid particles” in the AD brain 100 years ago attracted the attention of early researchers to the potential role of lipid metabolism disorders. Recent studies have shown that TREM2 is responsible for phagocytosis, while APOE promotes lipid processing. The two are related in lipid metabolism, MG activation, and A β clearance to maintain MG function [24]. It is worth noting that studies have shown that apolipoprotein E4 (APOE4) and the rare arginine-47-histidine (R47H) mutation of TREM2 are high-risk factors for AD [27]. This may be because, on the one hand, TREM2 preferentially binds to APOE4 with low esterification, and the strong affinity between the two weakens the binding of TREM2 to A β , leading to A β accumulation and promoting the development of inflammation [24]; on the other hand, APOE4 and R47H hinder the effective processing of cholesterol, resulting in excessive accumulation of LDs and thus accelerating disease progression.

In addition, the extracellular domain of TREM2 can bind to APOE and A β respectively, and the domains of APOE and A β can also interact with each other, which complicates the interaction between TREM2-APOE/A β . However, it is currently clear that TREM2 is a key regulator of cholesterol metabolism and LDs formation. Deficiency or mutation will lead to abnormal lipid metabolism of MG, forming a “LDs-inflammation” vicious cycle.

3.3. *TREM2 and MS*

MS is a chronic, inflammatory demyelinating and remyelinating disease of the CNS [28]. In the early stage of MS, approximately 40% of phagocytes are composed of MG, and their pro-inflammatory phenotype is related to active demyelination, while the anti-inflammatory phenotype is related to remyelination [29]. In demyelinating diseases, TREM2 is considered a key transcription factor for cholesterol metabolism during chronic myelin phagocytosis, driving the transformation of MG to disease-associated microglia (DAM), phagocytosing myelin debris, and repairing neuroinflammation. In a cuprizone (CPZ)-induced chronic demyelination model, the expression of DAM-related genes (such as APOE) in the brain of TREM2^{+/+} MG mice is significantly upregulated, while MG in the brain of TREM2^{-/-} MG mice cannot be reprogrammed, still maintaining a homeostatic phenotype, and CE accumulates significantly in the brain, with exacerbated neuronal damage [19]. This phenomenon indicates the role of TREM2 in breaking the “demyelination-lipid accumulation-neurotoxicity” vicious cycle.

Another more in-depth study showed that the activation state of TREM2 is directly related to remyelination. Treatment of CPZ mouse models with TREM2 agonists can increase the clearance rate of myelin debris by MG, proving that TREM2 activation can promote remyelination [30]. Similarly, a study by Yu et al. [13] showed that the drug FTY720 (a sphingosine-1-phosphate (S1P) analog, currently mainly used in the clinical treatment of relapsing-remitting MS) regulates the subcellular distribution of ABCA1 in a TREM2-dependent manner, promotes cholesterol excretion, reduces LDs accumulation, and thus enhances remyelination after ischemic white matter injury. This finding not only confirms the core position of TREM2 in cholesterol metabolism but also suggests that the “TREM2-ABCA1-cholesterol metabolism” axis can be used

as a potential therapeutic target for demyelinating diseases, providing a new perspective for the clinical intervention of MS.

4. Conclusions

As a receptor on the surface of MG, the extracellular domain of TREM2 can bind to lipids, LPS, ApoE, A β , etc., participating in the phagocytosis of lipids by MG. In the cell, it binds to DAP12 to initiate downstream signaling pathways, which are crucial for MG phagocytosis, inflammation, lipid metabolism, and its own proliferation and survival. At the same time, TREM2 may also exert anti-inflammatory effects by enhancing the lipid phagocytosis of MG, reducing LDs accumulation and neuroinflammatory responses. In conclusion, TREM2, as a hub for CNS immune regulation and lipid metabolism, affects CNS-related diseases.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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