



TREM2 IS AN IMPORTANT MARKER AND MEDIATOR OF MICROGLIA

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ABSTRACT

Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) is a receptor expressed primarily by microglia and is an important marker of their functional activation. Through interaction with the DAP12/TYROBP adaptor, TREM2 regulates numerous intracellular signaling pathways involved in cell survival and immune response. This receptor promotes the phagocytosis of apoptotic cells, cellular debris, lipids, and protein aggregates, contributing to the maintenance of central nervous system (CNS) homeostasis. TREM2 also plays a key role in microglia lipid metabolism, enabling proper management of lipids derived from tissue damage and neurodegeneration. TREM2 activation promotes metabolic adaptations that support mitochondrial function and the energy production required for phagocytic activity. Genetic alterations in TREM2 are associated with an increased risk of neurodegenerative diseases, particularly Alzheimer's disease. In these contexts, loss of receptor function compromises microglia's ability to effectively clear debris and pathological proteins, promoting the progression of neuronal damage. For these reasons, TREM2 is considered not only a marker of microglial activation but also a central mediator of microglial neuroprotective functions.

KEYWORDS: *TREM2, receptor, microglia, phagocytosis, CNS*

INTRODUCTION

Microglia are specialized macrophage-like cells residing in the brain and spinal cord and represent the main active immune defence of the central nervous system (CNS) (1). Microglia act as sentinels, constantly monitoring their surroundings to remove pathogens and cellular debris and remodel synaptic connections. Microglia exhibit a distinct receptor profile that reflects their role in neuronal homeostasis (2).

Microglial receptors are proteins that can be present either on the surface or within macrophages. These receptors allow microglia to detect damage, infections, cellular debris, and changes in the brain environment (3). Microglia express some markers and receptors that are relatively specific or much more abundant than those of peripheral macrophages (4). The main receptors are Toll-like receptors (TLRs), which recognize components of bacteria, viruses, and molecules released by damaged cells; scavenger receptors, which bind cellular debris, oxidized lipoproteins, and aggregated proteins; cytokine receptors, which enable the response to immune signals; complement receptors, which recognize complement proteins; and receptors that regulate microglial activation (5). Among these receptors is triggering receptor expressed on myeloid cells 2 (TREM2), which promotes phagocytosis, survival, and the response to damage (6).

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TREM2 is a major molecule present on most myeloid cells, including microglia, where it acts in response to neurodegenerative injury and mediates phagocytosis (7). It is also expressed by macrophages and osteoclasts. TREM2 belongs to the mononuclear phagocyte system and is involved in pathogen recognition (8). Microglia cells act as sentinels of the nervous system by binding their receptors, eliminating dead cells and debris, modulating inflammation, participating in responses against infections and injuries, and contributing to the remodelling of synaptic connections (9) (Table I).

Table I. Proper TREM2 signalling is essential for microglial metabolism, phagocytosis, central nervous system (CNS) homeostasis, and protection against neurodegeneration.

<i>Characteristics of TREM2:</i>	
-	Expressed primarily by microglia
-	Important marker of neuroprotection and microglial function
-	Interacts with the DAP12/TYROBP adaptor to activate various intracellular signalling pathways
-	Promotes the removal of apoptotic cells, cellular debris, lipids, and protein aggregates
-	Helps maintain CNS homeostasis
-	Regulates processes involved in cell survival and the immune response
-	Allows for proper lipid management
-	Induces metabolic adaptations and promotes phagocytosis
-	Genetic variants of TREM2 increase the risk of neurodegenerative diseases

THE EFFECTS OF TREM2 IN THE CENTRAL NERVOUS SYSTEM

Clinical studies have shown that alterations in receptors such as TREM2 and TLR4, amongst others, have been associated with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis (10). TREM2 is a transmembrane receptor expressed by immune cells in the brain, particularly microglia (11). TREM2 transduces signals only when associated with the adaptor DAP12 (TYROBP), as it cannot perform signalling alone (12). When TREM2 binds its ligands (APOE, lipoproteins, phospholipids, etc.) exposed by apoptotic cells and β -amyloid, DAP12 is phosphorylated and recruits the tyrosine kinase SYK, activating various intracellular pathways such as MAPK/ERK, PLC γ 2, PI3K–Akt–mTOR, and others (13). TREM2 controls how microglia perceive and respond to neuronal damage.

TREM2 is an important regulator of lipid metabolism, inflammation, and phagocytosis (14). It can bind to various lipid molecules, including lipoproteins (such as ApoE), anionic phospholipids, lipids derived from apoptotic cells, and oxidized lipids. This ability allows myeloid cells to sense lipid-rich environments and adapt their metabolic response.

Additionally, TREM2 primarily recognizes signals associated with tissue damage, such as apoptotic cells, damaged myelin, and pathological protein aggregates (15). Microglia use TREM2 as a sensor of toxic protein accumulations, dying neurons, and cellular debris (16). Activated TREM2 promotes lipid uptake by microglia and induces transcriptional programs that increase their ability to store and metabolize fatty acids (13). TREM2 reduces the toxicity of free lipid accumulation and contributes to the formation of foam cells in macrophages (17).

The TREM2-DAP12-SYK signalling pathway regulates metabolic pathways by enhancing fatty acid oxidation, maintaining ATP production, and supporting cell survival under conditions of lipid stress (18). TREM2 deficiency can lead to energy dysfunction and impaired ability to utilize lipids as an energy source (19). TREM2 is now considered an important molecule linking lipid metabolism, innate immunity, and metabolic and neurodegenerative diseases.

TREM2 is involved in both cell survival and phagocytosis, two key functions of microglia, macrophages, and osteoclasts (20). When TREM2 binds its ligands, it transduces signals through the DAP12/TYROBP adaptor, which contains ITAM motifs (21). The DAP12-SYK pathway activates numerous proteins involved in cytoskeletal dynamics, including Rho family GTPases (Rac1 and Cdc42) (22). TREM2 activates the SYK, PI3K-AKT, ERK/MAPK, and mTOR signalling pathways in a cascade (23). This activation promotes increased protein synthesis, inhibition of apoptosis, ATP production, maintenance of mitochondrial function, and resistance to metabolic stress.

TREM2 is considered a phagocytic receptor. Cells expressing TREM2 can clear cellular debris, myelin fragments, apoptotic cells, lipid particles, indirectly opsonised microorganisms, and protein aggregates. Activation of TREM2 induces the formation of the phagocytic cup; extension of cellular pseudopodia, target internalization, and reorganization of the actin cytoskeleton (24).

In the absence of TREM2, myeloid cells exhibit impaired energy metabolism, reduced ability to adapt to lipid-rich environments, reduced viability, and increased susceptibility to cell death. In the CNS, TREM2 supports the survival of

microglia during pathological conditions, including neuronal damage, demyelination, and the accumulation of β -amyloid in Alzheimer's disease. TREM2 mutations reduce the ability of microglia to effectively respond to injury (25).

The TREM2 receptor is an important biological factor involved in Alzheimer's disease and is a key regulator of the microglial response to amyloid plaques (26). TREM2 is expressed primarily by microglial cells in the CNS and is capable of recognizing lipids, apolipoproteins such as APOE, or material from damaged cells. Alzheimer's disease results in the accumulation of the peptide amyloid- β , neurons, lipids, and damaged cell membranes. These act as ligands for TREM2 and activate microglia. Activated microglia migrate toward amyloid plaques, form a compact barrier, limit the spread of toxic fibrils, and remove debris and lipid material. TREM2 dysfunction fails in the protective microglial response. TREM2 can undergo genetic variants, as occurs with the TREM2 R47H variant, carriers of which have a 2–4-fold increased risk of developing Alzheimer's disease compared to non-carriers; while carriers of the APOE $\epsilon 4$ allele have a sporadic risk (27).

Research studies targeting TREM2 may help to clarify the dynamics of neurodegenerative diseases and the role of TREM2 and could possibly allow for new therapeutic options.

CONCLUSIONS

TREM2 is a receptor that links damage recognition, phagocytosis, and metabolic adaptation, allowing myeloid cells to eliminate debris and dead cells while maintaining their functional integrity and survival. TREM2 is a key regulator of microglial function, integrating immune, metabolic, and phagocytic signals. By controlling cell survival, debris clearance, and lipid homeostasis, it contributes to maintaining CNS homeostasis. Alterations in its function are associated with reduced neuroprotective capacity of microglia and an increased risk of neurodegeneration, such as in Alzheimer's disease. For this reason, TREM2 is now considered both an important biomarker and a promising therapeutic target in neurodegenerative diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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