REVIEW OPEN ACCESS

Decoding TREM2 Signaling Pathways

Linking Macrophage Glycolysis to Inflammatory Diseases in the CNS

Yanfei Che,[1] Ziman Yu,[1] Songjie Ji,[2,3,*] and Dan Yang[1,*]

Neurol Neuroimmunol Neuroinflamm 2026;13:e200527. doi:10.1212/NXI.0000000000200527

Correspondence
Prof. Yang
Jsj000jsj@163.com
or Dr. Ji
jisongjie@gmail.com

MORE ONLINE
Supplementary Material

Abstract

Triggering receptor expressed on myeloid cells 2 (TREM2) is a key immunomodulatory receptor broadly expressed on myeloid cells such as macrophages and microglia. It plays versatile roles in neurodegenerative diseases, tissue repair, and tumor immunity by orchestrating glucose metabolism and inflammatory responses. This review systematically summarizes the structural characteristics of TREM2, its ligand-binding mechanisms, and downstream signaling pathways—including the phosphoinositide 3-kinase/protein kinase B(PI3K/Akt), mitogen-activated protein kinase (MAPK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and signal transducer and activator of transcription 3 (STAT3) cascades—with a particular focus on its central role in macrophage metabolic reprogramming. In neurodegenerative diseases such as Alzheimer disease, TREM2 contributes to the attenuation of neuroinflammation and slows disease progression by promoting β-amyloid (Aβ) clearance, inhibiting tau hyperphosphorylation, and modulating microglial polarization. Loss-of-function sequence variants, such as R47H, disrupt lipid metabolism, impair phagocytic activity, and destabilize immune homeostasis, thereby significantly increasing disease susceptibility. Furthermore, by enhancing glycolysis and suppressing fatty acid oxidation, TREM2 facilitates macrophage polarization toward a reparative M2 phenotype, promoting neuroregeneration and remyelination in conditions such as spinal cord injury and multiple sclerosis.

Within the tumor microenvironment, TREM2 influences tumor progression and therapeutic resistance by modulating the metabolic reprogramming of tumor-associated macrophages (TAMs)—notably through activation of pyruvate kinase muscle isozyme M2 (PKM2)–dependent glycolysis—and promoting an immunosuppressive phenotype. In metabolic disorders such as diabetes and obesity, TREM2 exerts protective effects by inhibiting NLRP3 inflammasome activation and maintaining lipid homeostasis, highlighting its therapeutic potential.

This review also outlines the translational prospects of TREM2 as a therapeutic target, including the development of agonists, gene regulatory strategies, and its potential use as a biomarker. Future studies should aim to elucidate the ligand-specific biased signaling and dynamic regulatory networks of TREM2 within tissue microenvironments to advance precision interventions in neuroimmunometabolic diseases.

Introduction

Overview of TREM2

Structure and Function of TREM2

Triggering receptor expressed on myeloid cells 2 (TREM2) is a cell surface receptor that belongs to the immunoglobulin (Ig) superfamily. It is predominantly expressed on cells of the myeloid lineage, including macrophages, dendritic cells, and, most notably, microglia—the

---

*These authors contributed equally to this work as co-corresponding authors.

[1]Department of Traditional Chinese Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [2]Department of Orthopaedic Surgery, Beijing Jishuitan Hospital, Capital Medical University, China; and [3]Department of Joint Surgery, Beijing Jishuitan Guizhou Hospital, Guiyang, China.

The Article Processing Charge was funded by Peking Union Medical College Hospital, Chinese Academy of Medical Sciences.

Glossary

AD = Alzheimer disease; **ADAM10/17** = a disintegrin and metalloproteinase 10/17; **Aβ** = amyloid-beta; **AKT** = protein kinase B; **ALI** = acute lung injury; **AMD** = age-related macular degeneration; **ApoE** = apolipoprotein E; **Arg** = arginase 1; **CD86** = cluster of differentiation 86; **CDR** = complementarity-determining region; **Cryo-EM** = cryogenic electron microscopy; **CXCL3** = C-X-C motif chemokine ligand 3; **DAMPs** = damage-associated molecular patterns; **DAP12** = DNAX-activation protein 12; **EAE** = experimental autoimmune encephalomyelitis; **EMT** = epithelial-mesenchymal transition; **ER** = endoplasmic reticulum; **ERK** = extracellular signal-regulated kinase; **FAO** = fatty acid oxidation; **GBM** = glioblastoma; **GWAS** = genome-wide association study; **HIF-1α** = hypoxia-inducible factor 1-alpha; **ICH** = intracerebral hemorrhage; **Ig** = immunoglobulin; **IgV** = Ig-like variable; **IRG1** = immune-responsive gene 1; **IL-1β** = interleukin-1 beta; **ITAM** = immunoreceptor tyrosine-based activation motif; **JAK** = Janus kinase; **LAMs** = lipid-associated macrophages; **LCN2** = lipocalin-2; **LOF** = loss-of-function; **LPS** = lipopolysaccharide; **MAPK** = mitogen-activated protein kinase; **MASLD** = metabolic dysfunction–associated steatotic liver disease; **mTOR** = mammalian target of rapamycin; **MS** = multiple sclerosis; **NF-κB** = nuclear factor kappa-light-chain-enhancer of activated B cells; **NHD** = Nasu-Hakola disease; **NLRP3** = nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing protein 3; **NMOSD** = neuromyelitis optica spectrum disorder; **NETs** = neutrophil extracellular traps; **OXPHOS** = oxidative phosphorylation; **PD** = Parkinson disease; **PI3K** = phosphoinositide 3-kinase; **PKM2** = pyruvate kinase muscle isozyme M2; **RIP** = regulated intramembrane proteolysis; **ROS** = reactive oxygen species; **SAH** = subarachnoid hemorrhage; **SCs** = schwann cells; **SCAMs** = synthetic constitutively active mutants; **SCI** = spinal cord injury; **SDH** = succinate dehydrogenase; **SHP1-BTK** = Src homology region 2 domain-containing phosphatase-1-Bruton tyrosine kinase; **SPR** = surface plasmon resonance; **STAT3** = signal transducer and activator of transcription 3; **sTREM2** = soluble TREM2; **SYK** = spleen tyrosine kinase; **TAMs** = tumor-associated macrophages; **TBI** = traumatic brain injury; **TCA** = tricarboxylic acid; **TREM2** = triggering receptor expressed on myeloid cells 2; **TYROBP** = TYRO protein tyrosine kinase binding protein; **Ym1** = chitinase 3-like protein 3.

resident immune cells of the CNS.[1] TREM2 has emerged as a critical regulator in a range of biological processes, such as innate immune surveillance, inflammatory modulation, phagocytosis, tissue remodeling, and the metabolic reprogramming of immune cells in response to environmental cues.

The biological function of TREM2 is tightly linked to its molecular architecture, which comprises 4 key domains (eFigure 1): (1) an extracellular N-terminal Ig-like variable (IgV) domain responsible for ligand recognition, (2) a stalk region enriched with O-linked glycosylation sites, (3) a single-pass transmembrane helix, and (4) a cytoplasmic tail that lacks intrinsic signaling motifs. Structural analyses have shown that the IgV domain adopts a β-sandwich fold stabilized by 2 conserved disulfide bonds (Cys34–Cys113 and Cys48–Cys63). This configuration creates a ligand-binding pocket with electropositive surface patches critical for interacting with anionic ligands such as phospholipids and sulfatides.[2]

TREM2 lacks intrinsic cytoplasmic motifs and relies on the adaptor DAP12 TYRO protein tyrosine kinase binding protein (TYROBP) for signal transduction. Ligand engagement induces conformational changes in the TREM2-DAP12 complex, exposing DAP12's ITAM motif, which recruits spleen tyrosine kinase (SYK) to trigger downstream pathways that regulate microglial survival, proliferation, phagocytosis, and inflammation. Signaling is ligand-specific: phosphatidylserine preferentially activates AKT-driven phagocytosis, whereas apolipoprotein E (ApoE) promotes STAT3-mediated anti-inflammatory responses. The IgV domain is critical for function, with the R47H variant disrupting a conserved salt bridge, reducing ligand binding, and impairing microglial clustering around Aβ plaques and clearance of apoptotic neurons, thereby increasing Alzheimer disease (AD) susceptibility.[2]

Beyond lipid and protein ligands, the stalk region contributes to glycan recognition, with Thr79 and Ser81 identified as critical residues. TREM2 is also regulated by intramembrane proteolysis mediated by ADAM10/17, releasing soluble TREM2 (sTREM2), which modulates inflammatory tone. Structural studies further show that transmembrane residues stabilize TREM2-DAP12 assembly, whereas mutations such as T66M disrupt this process, leading to defective surface expression as seen in Nasu-Hakola disease.

Functionally, TREM2 acts as a broad-spectrum pattern recognition receptor, binding ligands such as phospholipids, apoptotic debris, bacterial components, and Aβ aggregates. Dysregulation or genetic variants impair these interactions, reducing microglial phagocytosis and immune regulation, thereby exacerbating AD progression. In addition, TREM2 signaling reprograms microglial metabolism toward glycolysis and mitochondrial activation, ensuring sufficient energy to sustain phagocytosis, cytokine release, and tissue repair.

Collectively, these findings highlight TREM2 as an integrative regulator of immune surveillance, inflammation, and metabolic adaptation. Its structural variants underscore the tight link between architecture and function, positioning

TREM2 as both a molecular hub of microglial responses and a promising therapeutic target in neurodegenerative disease.[3]

Methods

We performed a structured literature search in PubMed, Web of Science, and Scopus up to August 2025 using the terms "TREM2," "macrophage," "microglia," "glycolysis," "immunometabolism," and "neuroinflammation." Reference lists of included articles were also screened to capture additional studies.

Eligible publications were original research (cell, animal, or clinical studies), systematic reviews, and meta-analyses published in English that investigated TREM2-related signaling, metabolic regulation, or neuroinflammatory mechanisms. Studies were excluded if they lacked full text, were conference abstracts or editorials, or did not directly address TREM2 function.

Two authors independently assessed titles, abstracts, and full texts. Extracted data included experimental models, signaling pathways, metabolic outcomes (e.g., glycolytic activity and mitochondrial function), and neuroinflammatory phenotypes. Disagreements were resolved by consensus. Data were synthesized narratively and organized according to signaling cascades and their impact on macrophage/microglial metabolism and neuroinflammation.

Data Availability

All data supporting this review are available in the cited references.

Context-Dependent Roles of TREM2 in Myeloid Immunity and Lipid Metabolic Regulation

TREM2 plays a critical regulatory role in myeloid-lineage immune cells, most notably in macrophages and microglia. While these 2 cell types share common innate immune functions, their tissue context and disease-specific responses reveal distinct, yet complementary, roles for TREM2 signaling (Table 1, eTable 1).

In peripheral macrophages, TREM2 supports survival, proliferation, and phagocytosis. A key function is the clearance of myelin debris, essential for regeneration after tissue injury. In demyelinating diseases such as multiple sclerosis (MS), TREM2-expressing macrophages facilitate debris removal, promote repair, and limit chronic inflammation.[6] Beyond its role in neuroinflammation, TREM2 also influences tumor immunology: in glioblastoma (GBM), higher TREM2 expression correlates with improved outcomes, and experimental overexpression reprograms tumor-associated macrophages toward antitumor phenotypes.[e1] These findings suggest that TREM2 may serve as a context-sensitive immune modulator, with relevance extending beyond classical neurodegenerative frameworks.

In microglia, the resident immune cells of the CNS, TREM2 expression is highly dynamic and context-specific. During acute CNS disorders such as spinal cord injury and MS, TREM2 can drive either protective or detrimental phenotypes depending on the inflammatory milieu, reflecting its signaling plasticity.[11]

TREM2 also regulates lipid metabolism and cholesterol handling in microglia. Loss-of-function mutations impair lipid processing, leading to metabolic stress and compromised myelin repair. In Alzheimer disease, TREM2 deficiency reduces lipid droplet formation and increases ER stress, while genetic variants affecting lipid binding impair clearance of amyloid-β and myelin debris, accelerating disease progression.[7,e2] In age-related macular degeneration (AMD), TREM2 defines a neuroprotective microglial subset marked by galectin-3 expression, further underscoring its role in tissue-specific immune defense.[12]

In summary, TREM2 acts as a versatile molecular hub in myeloid cells. A central theme is its mechanistic duality—promoting repair in some contexts while contributing to pathology in others. Understanding this divergence across peripheral and central environments will be critical for developing targeted therapies, positioning TREM2 as a promising therapeutic target in neurodegenerative, inflammatory, and neoplastic disorders.

Basic Mechanism of TREM2 Signaling Pathway

Ligand Recognition and Functional Activation

Lipid-Based Ligands

The function of TREM2 is mediated by its extracellular immunoglobulin-like domain, which allows it to recognize

Table 1 Glycolysis and Immune Cell Function

Cell function	Axis or target	Related diseases	References
Metabolic reprogramming in immune cells	Glycolysis, TCA cycle, lipid metabolism	Inflammatory diseases, metabolic disorders (e.g., diabetes and atherosclerosis)	4
Glycolytic regulation of macrophage polarization	HIF-1α, succinate	Chronic inflammation, neurodegeneration	5
TREM2 as a modulator of macrophage immunometabolism	TREM2, SHP1-BTK	Neurodegenerative diseases (e.g., Alzheimer disease and multiple sclerosis), sepsis, atherosclerosis	6–10

Abbreviations: HIF-1α = hypoxia-inducible factor 1-α; SHP1-BTK = Src homology region 2 domain-containing phosphatase-1-Bruton tyrosine kinase; TCA = tricarboxylic acid; TREM2 = triggering receptor expressed on myeloid cells 2.

a broad spectrum of ligands, Aβ, and pathogen-associated molecular patterns (PAMPs). Among these, lipid ligands are critical for modulating microglial phagocytosis and immune metabolism (Figure 1). Charge-dependent interactions between TREM2 and anionic lipids regulate microglial activity, while mutations such as R47H impair this process, leading to dysfunction associated with neurodegenerative disease.[2,13]

Phosphatidylserine (PS) and cardiolipin (CLP) are among the most studied lipid ligands of TREM2. PS is typically exposed on the surface of apoptotic cells, and binding to TREM2 promotes phosphorylation of SYK, initiating downstream signaling cascades.[2,13] The R47H mutation substantially reduces TREM2's affinity for PS.[13,e3] Molecular dynamics simulations show that TREM2 forms highly stable complexes with cardiolipin (CLP), exhibiting the strongest binding among all lipid ligands with an affinity of −80.87 kcal/mol.[13]

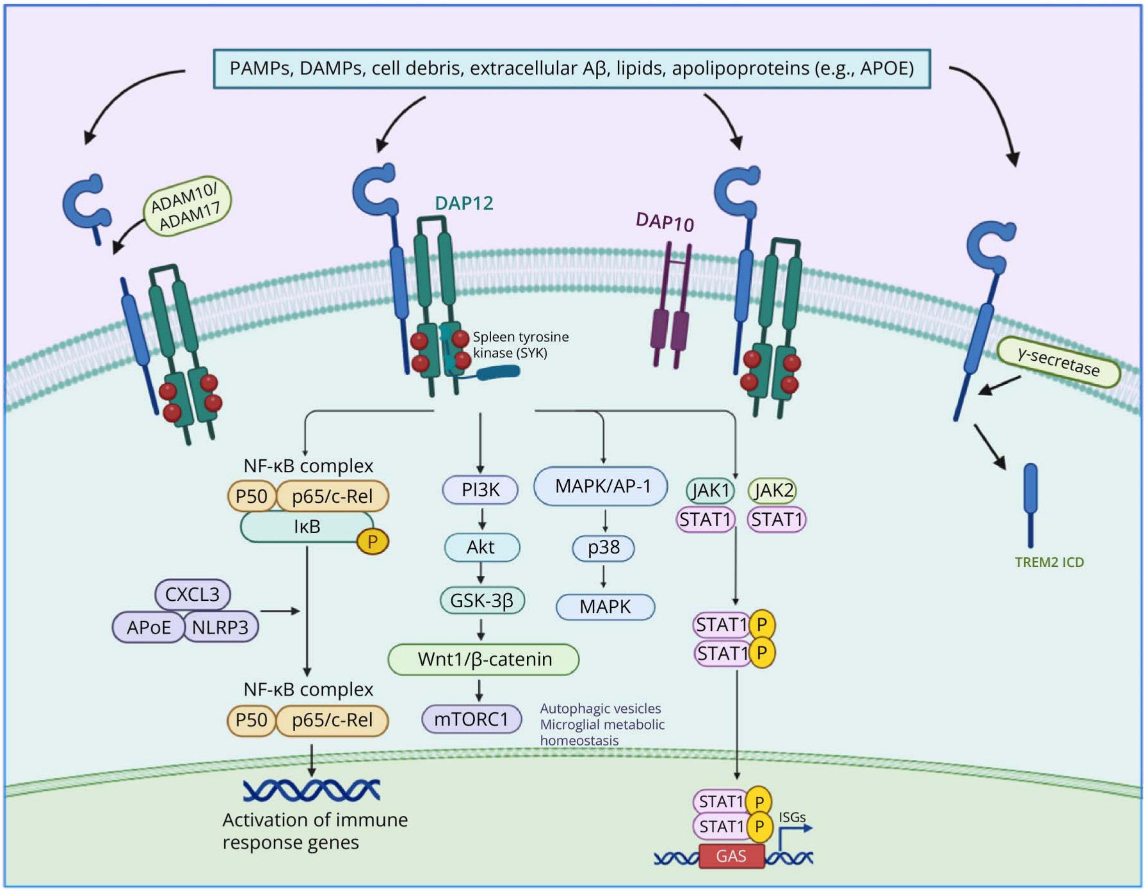
In addition, TREM2 shows preferential binding to negatively charged lipid head groups, such as phosphatidylserine analogs (PSF) and damage-associated lipids released from degenerating neurons.[13,e3] This lipid-sensing capability is central to the immune function of microglia in disease conditions such as Alzheimer.

β-Amyloid Binding and Neuroimmune Activation

In AD, Aβ oligomers serve as direct ligands of TREM2, activating the immune response in microglia and macrophages.[14,e4] Structural studies reveal that TREM2 binds Aβ oligomers with nanomolar affinity through its immunoglobulin domain, establishing a crucial receptor-ligand interaction that is significantly compromised by disease-associated mutations such as R47H.[14,e4] This binding event modulates downstream signaling—including SYK and GSK3β phosphorylation—thus shaping the microglial response. TREM2 deficiency reduces microglial phagocytosis of Aβ and worsens plaque accumulation and neurotoxicity,[e5] while TREM2 overexpression enhances Aβ clearance and attenuates AD pathology.[15] In addition, sTREM2 can bind Aβ42 and inhibit its fibril formation, exerting potential neuroprotective effects.[15,e6]

These findings support the development of TREM2-targeted therapies, including agonist antibodies and gene therapies, to enhance Aβ clearance and mitigate disease progression.

Figure 1 Cooperation and Crosstalk of TREM2-Associated Signaling Networks: NF-κB JAK-STAT and PI3K/Akt Pathways



PI3K/Akt = phosphoinositide 3-kinase/protein kinase B; TREM2 = triggering receptor expressed on myeloid cells 2.

Core Signaling Mechanisms

TREM2-DAP12 Complex and SYK Activation

TREM2 lacks intrinsic kinase activity and thus requires interaction with the adaptor protein DAP12 to initiate signal transduction. DAP12 contains an immunoreceptor tyrosine-based activation motif (ITAM) and is predominantly expressed in myeloid and lymphoid cells.[16]

On ligand binding, TREM2 associates with DAP12, triggering recruitment and phosphorylation, which activates downstream pathways including PI3K/Akt, NF-κB, and nuclear factor of activated T cells (NFAT).[17,e7,e8] This signaling axis controls cell survival, inflammation, and phagocytosis (Figure 1). Notably, the TREM2-CTF (C-terminal fragment)-DAP12 complex inhibits NF-κB activation while sTREM2 activates Akt and NFAT1 signaling to promote cytokine production.[17,e9] A negative feedback mechanism also exists: inhibitory receptors such as LILRB2 downregulate TREM2 signaling via immunoreceptor tyrosine-based inhibitory motifs (ITIMs), maintaining immune balance.[18]

Role of Src Family Kinases

TREM2 signaling is further amplified through interactions with Src family kinases (SFKs), such as Lyn, Fyn, and c-Src. These kinases are involved in early phosphorylation events of immune receptors and can modulate downstream cascades such as NLRP3 inflammasome activation.[19]

In the tumor microenvironment,TREM2 exerts complex and multifaceted effects. On one hand, it may collaborate with Src family kinases (SFKs) to facilitate immune evasion by tumor-associated macrophages (TAMs), thereby contributing to tumor progression and therapeutic resistance.[20,e10] SFKs influence macrophage migration, integrin signaling, and expression of immune checkpoint molecules such as PD-L1.[21,e11]

At the molecular level, SFK domains (SH2, SH3, kinase) phosphorylate TREM2-interacting molecules and modulate pathways such as ERK1/2, contributing to immune modulation and tumor progression.[22,e12]

Integration of Downstream Signaling Pathways

PI3K/Akt Pathway

The PI3K/Akt pathway serves as a central node downstream of TREM2 across diverse cellular contexts. To elucidate its multifaceted contribution to neuroinflammation, it is instructive to examine its regulation in other disease models, which reveal conserved mechanistic principles directly applicable to CNS pathology. In neurodegenerative conditions such as AD, TREM2 activation of PI3K/Akt signaling inhibits glycogen synthase kinase-3β (GSK-3β), thereby reducing tau hyperphosphorylation and ameliorating cognitive deficits.[23] By contrast, in autism models, TREM2 knockout upregulates the PI3K/Akt/mTOR axis, enhancing autophagy and behavior.[23] A particularly significant finding involves intracerebral hemorrhage (ICH), where ApoE has been identified as a novel high-affinity TREM2 ligand. Mechanistically, ApoE-mediated TREM2 activation increases endogenous TREM2 expression in ICH models, which in turn modulates the PI3K/Akt pathway to exert neuroprotection by attenuating both neuroinflammation and neuronal apoptosis[24] (Figure 1, Table 2).

In lipopolysaccharide (LPS)-induced models of acute lung injury, upregulation of TREM2 expression was shown to enhance activation of the PI3K/Akt signaling pathway. This activation facilitates macrophage polarization from the proinflammatory M1 phenotype to the anti-inflammatory M2 phenotype, thereby suppressing inflammatory responses. Consequently, this regulatory cascade attenuates pathologic features such as pulmonary interstitial edema, hemorrhage, and inflammatory cell infiltration, while preserving the integrity of the alveolar-capillary barrier.[25]

In cancer, TREM2 expression correlates with PI3K inhibitor resistance, suggesting its involvement in tumor metabolism.[23] In renal carcinoma and metabolic disease, TREM2 activation leads to M2 polarization and macrophage pyroptosis.[e13-e15]

These divergent effects are influenced by cell type, disease context, and experimental manipulation, highlighting the plasticity of TREM2 signaling.[22,23,e16] TREM2 has been shown to inhibit tumor progression both in vivo and in vitro by modulating the Wnt1/β-catenin and ERK signaling pathways, suggesting its potential as a therapeutic target in colorectal cancer.[e17] By contrast, in hepatocellular carcinoma, TREM2 contributes to tumorigenesis through activation of the PI3K/AKT/β-catenin signaling axis.[e18] In glioma cell lines, silencing TREM2 markedly suppresses cell proliferation, invasion, and migration, while significantly enhancing apoptosis. Moreover, in gastric cancer models, the TREM2/DAP12/Syk signaling complex activates the PI3K/AKT pathway, which subsequently promotes epithelial-mesenchymal transition (EMT), as supported by multiple experimental studies.[26]

MAPK Pathway

The mitogen-activated protein kinase (MAPK) pathway—comprising ERK, c-Jun N-terminal kinase (JNK), and p38 subfamilies—serves as a critical downstream effector of TREM2 signaling, mediating its diverse roles in inflammation resolution, immune modulation, and tissue repair across various pathologic contexts.

In cutaneous wound healing, TREM2 inhibits the MAPK/AP-1 signaling cascade through IL-4–mediated binding, thereby reducing local inflammation and accelerating tissue regeneration.[e19] In models of acute lung injury (ALI), overexpression of TREM2 downregulates MAPK-related proteins, leading to attenuation of pulmonary inflammation.[27]

In a myocardial ischemia-reperfusion injury model, TREM2 expression promotes the acquisition of lipid-associated

Table 2 Integration of Downstream Signaling Pathways

Pathway	Disease(s)	Axis or target	References
PI3K/Akt pathway	AD	TREM2 → PI3K/Akt → GSK-3β inhibition	23
	Autism	TREM2 knockout → PI3K/Akt/mTOR activation	23
	ICH	ApoE → TREM2 → PI3K/Akt activation	24
	ALI	TREM2 → PI3K/Akt activation → M2 macrophage polarization	25
	Cancer	TREM2 correlates with PI3K inhibitor resistance	23
	Renal carcinoma	TREM2 activation → M2 polarization	
	Metabolic disease	TREM2 activation → macrophage pyroptosis	
	Colorectal cancer	TREM2 inhibits tumor progression via Wnt1/β-catenin and Erk	
	Hepatocellular carcinoma	TREM2 → PI3K/Akt/β-catenin pathway	
	Glioma	TREM2 silencing inhibits PI3K/Akt pathway	26
	Gastric cancer	TREM2/DAP12/Syk → PI3K/Akt → EMT	26
MAPK pathway	Skin wound healing	TREM2 → IL-4 binding → MAPK/AP-1 suppression	
	ALI	TREM2 overexpression → MAPK downregulation	27
	Myocardial ischemia-reperfusion injury	TREM2 drives LAM features → MAPK inhibition	28
	AD	TREM2 → MAPK modulation → tau phosphorylation reduction	29
	Autism	TREM2 knockout → p38 MAPK activation	30
	Tumors	TREM2 supports TAM polarization via MAPK	23–30
	General repair	TREM2 deficiency enhances SYK–MAPK synergy	
NF-κB pathway	AD Osteoarthritis	TREM2 → NF-κB/CXCL3 axis → M2 polarization	31
	Spinal cord injury	TREM2 → APOE/NF-κB pathway → M2 polarization	32
	Glioma	TREM2 knockout → NF-κB p50 inhibition → NO and pro-inflammatory cytokines up	33
	General inflammation	TREM2 knockdown → NF-κB activation → NLRP3 inflammasome	34
STAT3 pathway	Sepsis-induced ALI	TREM2 deficiency → STAT3 hyperactivation → ferroptosis	
	EAE	TREM2-ZAP70-STAT3 signaling → Th17 differentiation	
	General macrophage inflammation	TREM2 knockdown → STAT3-mediated IL-6/TNF-α production	27
	Basal cell carcinoma	TREM2$^+$ SCAMs → TNF-M/JAK-STAT3 pathway activation	35
	NHD	TREM2/DAP12 deficiency → STAT3 pathway activation	36

Abbreviations: AD = Alzheimer disease; AKT = protein kinase B; ALI = acute lung injury; ApoE = apolipoprotein E; CXCL3 = C-X-C motif chemokine ligand 3; DAP12 = DNAX-activation protein 12; EAE = experimental autoimmune encephalomyelitis; EMT = epithelial-mesenchymal transition; ICH = intracerebral hemorrhage; JAK = Janus kinase; LAM = lipid-associated macrophage; MAPK = mitogen-activated protein kinase; mTOR = mammalian target of rapamycin; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; NHD = Nasu-Hakola disease; NLRP3 = nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing protein 3;NO = nitric oxide; PI3K = phosphoinositide 3-kinase; SCAMs = synthetic constitutively active mutants; STAT3 = signal transducer and activator of transcription 3; SYK = spleen tyrosine kinase; TREM2 = triggering receptor expressed on myeloid cells 2.

macrophage (LAM) characteristics by cardiac macrophages and microglia, which is associated with suppression of MAPK signaling. Notably, the p38 MAPK axis is critically implicated in adverse cardiac remodeling; inhibition of this pathway mitigates both inflammation and structural damage in post-infarction myocardium.[e19,e20] These findings suggest that $SPP1^+$ LAMs may modulate cardiac remodeling via TREM2-dependent regulation of MAPK signaling.[28]

In the CNS, TREM2 indirectly modulates MAPK signaling in AD, reducing tau phosphorylation and alleviating neuroinflammation. Specifically, TREM2 upregulation suppresses the TLR4/MAPK pathway, which contributes to the attenuation of inflammatory cascades.[29] In autism spectrum disorder (ASD) models, TREM2 deficiency leads to hyperactivation of the p38 MAPK pathway, indicating that upregulation of TREM2 may confer neuroprotective effects in ASD.[30]

In the tumor microenvironment, TREM2 supports tumor-associated macrophage (TAM) polarization toward an immunosuppressive M2-like phenotype and contributes to immune evasion.[23,e21] Mechanistically, TREM2 deficiency enhances spleen tyrosine kinase–mitogen-activated protein kinase (SYK-MAPK) signaling synergy and promotes inflammasome activation, whereas intact TREM2 signaling facilitates M2 polarization and tissue repair.[e12,e22]

NF-κB Pathway

TREM2 interacts with the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway primarily through its adaptor protein DAP12. On ligand binding, the TREM2-DAP12 complex facilitates the recruitment and activation of downstream signaling molecules that lead to NF-κB activation, thereby initiating the transcription of inflammation-related genes. TREM2-DAP12 signaling influences NF-κB transcriptional activity, thereby regulating inflammation. Knockdown of TREM2 enhances NF-κB–mediated NLRP3 activation and pyroptosis, increasing IL-1β and IL-18 production.[34,e23]

In diseases such as AD and osteoarthritis, TREM2 promotes M2 macrophage polarization via the NF-κB/CXCL3 axis, improving inflammatory resolution.[31,e24] Studies have shown that curcumin-treated olfactory ensheathing cells (OECs), referred to as aOECs, can significantly upregulate the expression of APOE. As a high-affinity ligand of TREM2, APOE binds to TREM2 on the surface of microglia, activating the TREM2 signaling pathway. This activation inhibits NF-κB activity, thereby promoting the polarization of microglia from the proinflammatory M1 phenotype to the anti-inflammatory M2 phenotype. Specifically, the expression of M1 markers such as iNOS and CD86 is reduced, while the expression of M2 markers such as Arg-1 and CD206 is increased, thereby alleviating inflammation after SCI.[32] In tumor-associated microglia, the NF-κB p50 subunit promotes anti-inflammatory gene expression and drives polarization toward an immunosuppressive phenotype. TREM2 deficiency disrupts this pathway, suppressing the anti-inflammatory profile and potentially enhancing antitumor immunity. By modulating TREM2–NF-κB p50 signaling, it is possible to reduce glioma progression and tumor-associated angiogenesis, highlighting this axis as a promising therapeutic target.[33]

STAT3 Pathway

TREM2 also regulates immune homeostasis through the STAT3 (signal transducer and activator of transcription 3) signaling axis.

In sepsis-induced acute lung injury (ALI) models, TREM2 deficiency leads to STAT3 hyperactivation, oxidative stress, and ferroptosis, while SHP1 agonist reverses this process.[e25]

In EAE models, TREM2-ZAP70-STAT3 signaling promotes Th17 differentiation and autoimmune pathology.[e26] In macrophages, TREM2 knockdown exacerbates LPS-induced IL-6 and TNF-α production via STAT3, indicating its role in restraining excessive inflammatory responses.[27,e27]

In a murine model of basal cell carcinoma (BCC), researchers identified a subset of TREM2$^+$ skin cancer–associated macrophages (SCAMs) that promote the expansion of distinct tumor epithelial cell populations. This proliferative support is mediated through TNF-M/JAK-STAT3 (janus kinase–signal transducer and activator of transcription) signaling and occurs independently of immune suppression mechanisms.[35] Notably, basal cell carcinomas appear to establish a protumorigenic, spatially organized, and self-sustaining TREM2$^+$ myeloid niche. By contrast, in Nasu-Hakola disease (NHD), a rare neurodegenerative disorder caused by TREM2-DAP12 deficiency, aberrant activation of the STAT3 signaling pathway has been observed. Patients with NHD may benefit from therapeutic interventions targeting the JAK-STAT pathway, which help restore microglial signaling balance and attenuate disease progression.[36]

These findings underscore TREM2's central role as a molecular link between immune signaling and metabolic adaptation, offering novel therapeutic targets for immune-mediated and neurodegenerative diseases (eFigure 2).

Glycolysis and Immune Cell Function in Neuroinflammation

Metabolic Reprogramming as a Determinant of Immune Cell Function

Immune cells dynamically reprogram core metabolic pathways—glycolysis, the tricarboxylic acid (TCA) cycle, and lipid metabolism—to orchestrate their functional and inflammatory responses. Among these, glycolysis is particularly indispensable for immune cell activation and effector function, especially during the rapid expansion and activity of T cells.[4] In response to pathogens, injury, or inflammatory stimuli, immune cells—including macrophages and T cells—undergo extensive metabolic reprogramming to meet increased energy and biosynthetic demands. Unlike resting cells that depend mainly on oxidative phosphorylation (OXPHOS), activated immune cells preferentially use aerobic glycolysis—the so-called "Warburg effect"[37] (Figure 2).

On stimulation with Toll-like receptor 4 (TLR4) agonists such as LPS, they show increased glucose uptake, enhanced glycolytic flux, and activation of the pentose phosphate pathway (PPP), while TCA cycle activity decreases. This metabolic reprogramming meets the heightened energetic and anabolic demands of immune activation, supporting protein, lipid, and nucleic acid synthesis[e28,e29] (Figure 2).

Glycolytic Control of Macrophage Polarization and Immune Signaling

Glycolytic Pathways as Drivers of Macrophage Functional Differentiation

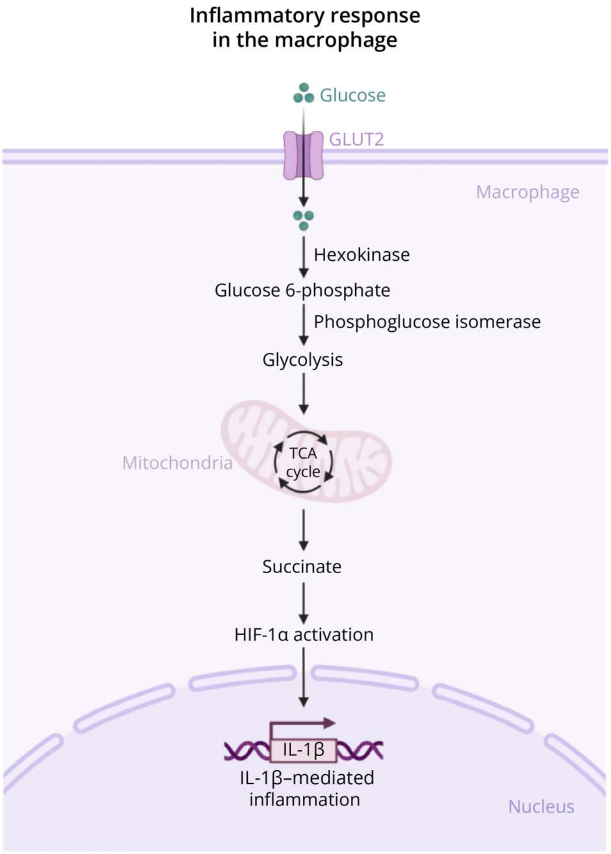
Glycolysis, as a core metabolic pathway, not only supplies adenosine triphosphate (ATP) but also regulates signaling cascades and cellular phenotypes within the immune system, particularly in macrophages. Its importance is amplified under inflammatory conditions, where oxygen availability is limited. Recent studies underscore the dual role of glycolytic intermediates as metabolic substrates and signaling molecules, directly shaping macrophage function.

Macrophages demonstrate extraordinary metabolic plasticity, dynamically polarizing between M1 and M2 phenotypes in response to microenvironmental cues. M1 macrophages rely on glycolysis and accumulate metabolites, which enhance proinflammatory gene expression by stabilizing hypoxia-inducible factor 1-alpha (HIF-1α) and supporting cytokine production. By contrast, M2 macrophages preferentially use oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO), driving anti-inflammatory functions and facilitating tissue regeneration.[5,38]

This interplay between metabolism and immune signaling provides a mechanistic framework for macrophage involvement in diverse pathologies, from chronic inflammation to neurodegeneration.

Studies have demonstrated that external stimuli—particularly toll-like receptor (TLR) signals—reshape cellular metabolism to enable specific immune functions.[e30] It has been demonstrated that TLR-induced histone acetylation is mediated by ATP-citrate lyase, linking metabolic reprogramming to epigenetic regulation. Other studies have[e31] emphasized the interplay between glycolysis and fatty acid metabolism in macrophage polarization. Further investigations have[e32] revealed how mitochondrial adaptation and nuclear receptor tune inflammatory responses. Collectively, these studies outline a metabolically driven paradigm for macrophage activation.

Figure 2 Macrophage Inflammatory Response and Immunometabolic Landscape Under Metabolic Regulation



Tricarboxylic Acid Cycle as a Hub for Immunometabolic Regulation

The tricarboxylic acid (TCA) cycle also exerts immunoregulatory effects. Succinate, an intermediate, stabilizes HIF-1α and amplifies proinflammatory gene expression.[e29] Bailey et al.[e33] demonstrated that nitric oxide regulates succinate levels, thereby influencing inflammation. In addition, itaconate—a recently discovered immunometabolite—inhibits succinate dehydrogenase (SDH), reducing reactive oxygen species (ROS) and proinflammatory cytokines.[39,e34] These findings establish as both an energy provider and immune modulator.

Itaconic Acid as a Central Metabolite in Inflammation and Resolution

Itaconic acid, generated by immune response gene 1 (IRG1), is a pivotal regulator in macrophage metabolism. Michelucci et al.[e35] found that itaconate suppresses SDH, decreases succinate, and inhibits inflammation.[39] As a promising target for anti-inflammatory therapy, it represents a novel bridge between immune signaling and metabolism.

Crosstalk Between the Kynurenine Pathway and TREM2 in Neuroimmune Regulation

In addition to glucose and lipid metabolism, amino acid catabolism also exerts a profound influence on immune regulation. The kynurenine pathway, as the principal route of tryptophan degradation, generates metabolites such as kynurenine, quinolinic acid, and kynurenic acid, which act not only as metabolic intermediates but also as signaling molecules shaping microglial and macrophage phenotypes.[40] Through indoleamine 2,3-dioxygenase (IDO1)–mediated tryptophan depletion and downstream aryl hydrocarbon receptor (AhR) activation,[e36] this pathway establishes an immunoregulatory axis that often counterbalances glycolysis-driven inflammation. Emerging evidence indicates that TREM2 signaling may directly modulate key enzymes of the kynurenine pathway, thereby influencing the production of neuroactive metabolites and shaping the immune microenvironment. Conversely, kynurenine-derived ligands acting via AhR may also feedback to fine-tune TREM2-dependent microglial responses. This bidirectional crosstalk plays a pivotal role in maintaining microglial homeostasis and limiting excessive neuroinflammation. Recent findings further suggest that such convergence is particularly relevant in neurodegenerative diseases, including Alzheimer disease and Parkinson disease, where the coordinated regulation of TREM2 and kynurenine pathway activity determines the balance between neuroprotection and chronic neuroinflammation.[e37]

TREM2 as a Master Regulator of Immunometabolic Adaptation

Molecular Signaling Mechanisms Linking TREM2 to Glycolytic Flux

The regulation of glycolysis by TREM2 represents a conserved mechanism that shapes macrophage function. Although the following examples span various diseases, from wound healing to sepsis, they are included specifically to illuminate fundamental immunometabolic processes that directly inform microglial behavior and CNS neuroinflammation. On stimulation, TREM2 enhances glycolytic activity, stabilizes HIF-1α, and promotes lactylation, thereby supporting M1 polarization and proinflammatory responses in contexts such as wound healing and sepsis.[41,e38]

Conversely, TREM2 can promote M2 differentiation by suppressing the NF-κB/CXCL3 axis, enhancing markers such as Arg1 and Ym1, and maintaining immune balance in conditions such as osteoarthritis and schistosomiasis.[31,42] TREM2 deficiency exacerbates inflammation, as observed in liver ischemia-reperfusion injury and CCl_4-induced hepatic damage[e39,e40] (Table 3).

Across diverse disease contexts, including myocardial infarction, hepatocellular carcinoma, and tuberculosis, TREM2 orchestrates glycolysis and macrophage polarization to regulate tissue repair, immune evasion, and host defense.[e41-e43]

Mechanistically, TREM2 regulates glycolysis through HIF-1α stabilization and lactylation[41,e38] and supports M2 phenotypes via NF-κB/CXCL3 suppression.[31] It also cooperates with p53 to regulate lipid metabolism and phagocytosis. Of interest, some studies report that TREM2 deficiency may simultaneously enhance M1 and M2 responses, indicating context-dependent roles (Table 3).

TREM2-Dependent Regulation of Macrophage Glycolysis and Polarization States

In recent years, TREM2 has emerged as a critical regulator of immunometabolism, particularly in microglia and peripheral macrophages. TREM2 modulates glycolytic flux and lipid metabolism through multiple downstream signaling cascades, helping maintain metabolic homeostasis under stress conditions. Notably, during chronic myelin phagocytosis, TREM2 deficiency leads to cholesterol accumulation and ER stress, which aggravates inflammation.[7,43] In sepsis, TREM2 has been shown to inhibit FAO via the Src homology region 2 domain-containing phosphatase-1-Bruton tyrosine kinase (SHP1-BTK) signaling axis, thereby reshaping macrophage metabolic responses and enhancing host defense.[8] These findings position TREM2 not only as an immune receptor but also as a key modulator of macrophage energy metabolism.

Beyond metabolism, TREM2 promotes efferocytosis and tissue repair, limiting necrotic core formation and fibrosis in atherosclerosis, hepatic injury, and demyelinating diseases such as multiple sclerosis.[6,7,e44-e46]

In neuroinflammation, TREM2 supports Aβ phagocytosis, modulates inflammatory gene expression, and coordinates metabolic adaptation to facilitate neurorepair.[9,e47] It also activates MAPK and PI3K/Akt pathways, which are closely linked to glycolytic regulation and immune cell survival.[10,e48]

Collectively, these findings underscore TREM2's central role in bridging metabolic cues with immune function, highlighting its potential as a therapeutic target in both metabolic and neuroinflammatory diseases.

Functional and Pathologic Consequences of TREM2-Mediated Metabolic Control

TREM2-mediated glycolytic control affects macrophage activation, metabolic homeostasis, and inflammation. In tissue repair, TREM2 boosts facilitate wound healing and angiogenesis. Its deficiency impairs HIF-1α lactylation and vascular remodeling.[41] In MASLD, TREM2 aggravates macrophage pyroptosis via the PI3K/AKT pathway.[22]

In tumors, $TREM2^+$ macrophages upregulate IL-1β and glycolysis-related genes (e.g., PKM2), while suppressing $CD8^+$ T cells, promoting immune evasion.[e42] In pancreatic cancer, TREM2 deficiency amplifies the NLRP3/NF-κB/IL-1β axis, exacerbating inflammation.[44]

In neurodegeneration, TREM2 supports glucose and lipid metabolism. Its absence disrupts sphingolipid metabolism and genes such as lipoprotein lipase (LPL) , accelerating neurodegeneration.[e49] It also modulates tau pathology via the PI3K/Akt/GSK-3β pathway.[23]

TREM2 further mediates glycolytic reprogramming via the mTOR/HIF-1α axis[45] and inhibits BTK-dependent fatty acid oxidation.[8] In obesity, TREM2 loss disrupts lipid handling and augments macrophage inflammation, suggesting tissue-specific metabolic effects.[e50,e51]

Glycolysis as a Metabolic Driver of Neural Repair

Metabolic Reprogramming of Immune Cells in Axonal Regeneration

Neural repair constitutes a highly orchestrated biological process that integrates diverse cellular interactions and dynamic metabolic adaptations. Within this regenerative cascade, macrophages emerge as central players (Table 4, eTable 2), performing dual roles in immune regulation and metabolic support that are indispensable for axonal regrowth and functional recovery.[46]

After nerve injury, macrophages are recruited to the injury site, where their phenotypic transition from proinflammatory M1 to anti-inflammatory M2 states is essential for axon

Table 3 TREM2 Signaling and Glycolysis: Regulatory Mechanisms

	Axis/target/pathway	M1 and M2 polarization
TREM2	HIF-1α lactylation	Promotes M2 (angiogenesis support)
	Suppression of SETD2 → HIF-1α upregulation	Drives M1 polarization
	NF-κB/CXCL3 axis suppression	Promotes M2 differentiation
	Arg1, Ym1 upregulation; CD86 inhibition	Enhances M2, inhibits M1
	Mitochondrial DAMP amplification (in TREM2 deficiency)	Exacerbates M1 inflammation
	Glycolysis and phagocytosis regulation	Supports M2 repair; deficiency worsens repair
	IL-1β secretion → tumor glycolysis (PKM2 activation)	Tumor-associated macrophages shift to immunosuppressive M2
	Regulation of M1/M2 balance	Modulates M1 and M2 responses

Abbreviations: Arg = arginase 1; CD86 = cluster of differentiation 86; CXCL3 = C-X-C motif chemokine ligand 3; DAMP = damage-associated molecular pattern; IL-1β = interleukin-1 beta; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; PKM2 = pyruvate kinase muscle isozyme M2; TREM2 = triggering receptor expressed on myeloid cells 2; Ym1 = chitinase 3-like protein 3.

regeneration.[47] In addition, macrophages facilitate neural repair by activating the mTOR pathway and exerting paracrine regulatory effects.[e52] These cells also enhance tissue remodeling by secreting neurotrophic factors and attenuating inflammation-driven apoptosis, extracellular matrix degradation, and impaired axon growth.[e53]

The metabolic state of macrophages is intimately linked to their functional phenotype. After nerve injury, their metabolic profile undergoes significant shifts that correlate with their activation status.[48] For instance, accumulation of succinyl-CoA has been shown to inhibit mTORC1 activity in macrophages, thereby affecting regenerative outcomes.[e54] Furthermore, macrophage polarization is tightly regulated by metabolic programming: M1 macrophages depend on glycolysis to support inflammatory responses, whereas M2 macrophages rely on OXPHOS and FAO to promote tissue repair.[e55]

TREM2-Orchestrated Immunometabolic Modulation in CNS Repair and Remyelination

Emerging evidence highlights the role of TREM2 in promoting neural regeneration by modulating both immune responses and cellular metabolism. In an experimental autoimmune encephalomyelitis (EAE) model, IV delivery of bone marrow–derived, TREM2-overexpressing myeloid progenitors significantly reduced tissue damage and enhanced CNS repair.[49] These cells mediated their effects through enhanced clearance of cellular debris and the induction of an anti-inflammatory cytokine milieu.

Microglia—the resident phagocytes of the CNS—express TREM2 and have been shown to play a central role in neurorepair after injury or inflammation. Consequently, TREM2 has emerged as a promising therapeutic target for facilitating neural regeneration and resolving inflammation in diseases such as multiple sclerosis (MS).[49]

Other studies[e56] underscore the significance of white matter repair in poststroke recovery. TREM2 upregulation after ischemic injury contributes to neuroprotection and supports remyelination, which is crucial for functional recovery.

Mechanistically, TREM2 regulates the immunometabolic state of macrophages and microglia by modulating glycolytic activity, promoting their transition to prorepair, anti-inflammatory phenotypes. TREM2-expressing macrophages display enhanced debris clearance, reduced inflammatory burden, and increased support for axonal regeneration after CNS injury.

Role of TREM2 in Neuroinflammation

Neuroinflammation: Cellular and Molecular Characteristics

Neuroinflammation is an immune response of the CNS to injury or disease, characterized by glial activation, cytokine

Table 4 Glycolysis and Cellular Mechanisms in Neural Repair

	Axis or target	Related diseases	References
Metabolic reprogramming during nerve regeneration	mTOR pathway, glycolysis, OXPHOS, FAO	Nerve injury and regeneration	46-48
TREM2-mediated immunometabolic modulation in neurorepair	Regulation of glycolytic activity	EAE, MS, poststroke repair	49

Abbreviations: EAE = experimental autoimmune encephalomyelitis; FAO = fatty acid oxidation; MS = multiple sclerosis; mTOR = mammalian target of rapamycin; OXPHOS = oxidative phosphorylation.

Table 5 Role of TREM2 in Neuroinflammation

	Axis or target	Related diseases	References
Neuroinflammation: cellular and molecular characteristics	NF-κB, NLRP3	Neurodegenerative diseases (general), chronic neuroinflammation	[50,52,53]
Role of TREM2 in macrophages and microglial cells in neuroinflammation	TREM2/NF-κB, TREM2/PI3K/Akt	AD; TBI; SAH; NMOSD	[24,53,54]

Abbreviations: AD = Alzheimer disease; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3 = nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing protein 3; NMOSD = neuromyelitis optica spectrum disorder; PI3K/Akt = phosphoinositide 3-kinase/protein kinase B; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury; TREM2 = triggering receptor expressed on myeloid cells 2.

release, oxidative stress, and blood-brain barrier disruption.[50,e57] This response is protective in acute phases but contributes to pathology if sustained,[51,e58] while astrocytes regulate blood-brain barrier permeability and metabolic adaptation.[e59-e61] However, prolonged cytokine release (e.g., TNF-α and IL-1β) promotes neurodegeneration.[52] Pathways such as NF-κB and NLRP3 mediate proinflammatory gene expression and inflammasome activation, linking chronic inflammation to neuronal injury[e62,e63] (Table 5).

Role of TREM2 in Macrophages and Microglial Cells in Neuroinflammation

TREM2 modulates neuroinflammation by influencing microglial polarization, phagocytosis, survival, and metabolism. It promotes M2 polarization via the TREM2/NF-κB signaling pathway, reducing proinflammatory cytokines in AD and sepsis models[53,e64] (eTable 1).

It enhances phagocytosis of Aβ and neuronal debris in traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH),[e65-e67] while its deficiency leads to myelin accumulation in neuromyelitis optica spectrum disorder (NMOSD).[54]

TREM2 enhances survival via the PI3K/Akt signaling pathway, maintaining CNS immune homeostasis.[55] Collectively, these mechanisms position TREM2 as a molecular checkpoint, balancing inflammatory containment with tissue repair in the injured CNS (Table 5).

Therapeutic Potential and Translational Applications of TREM2 in Neurologic Disorders

TREM2 regulates neuroinflammation in diabetes and CNS repair. LCN2 (lipocalin-2) deficiency reduces TREM2 expression and may worsen inflammation.[56] TREM2 inhibits NLRP3 activation in hyperglycemia, reducing neuroinflammation.[34] In Schwann cells (SCs), TREM2 maintains metabolic function and myelin protein expression, supporting regeneration in peripheral neuropathy.[54]

In obesity and diabetes, it modulates lipid metabolism and promotes wound repair by limiting NETs and inflammation.[e68] Preclinical studies support TREM2 as a therapeutic target in AD, diabetes, and chronic inflammation, particularly via inflammasome suppression.[e69] Its dynamic expression suggests value as a biomarker for disease severity and therapeutic response.[e70]

Conclusions and Future Prospects

TREM2 as a Context-Specific Modulator of Macrophage Glycolysis

TREM2 plays a central role in regulating macrophage glycolysis, representing a fundamental immunometabolic mechanism rather than a disease-specific effect. It orchestrates metabolic reprogramming through multiple pathways, including HIF-1α, NF-κB/CXCL3, and PI3K/AKT/mTOR, thereby supporting diverse physiologic and pathologic processes. During tissue repair, TREM2 enhances glycolysis to meet bioenergetic demands while promoting an immunosuppressive microenvironment. In neurodegenerative contexts, it maintains metabolic homeostasis, regulates lipid metabolism, and modulates tau phosphorylation, contributing to neuroprotection. It is important to note that TREM2 functions are highly context-dependent, and its deficiency often results in metabolic dysregulation and exacerbated inflammation. Collectively, TREM2 serves as a master regulator of macrophage adaptation, integrating immune regulation with tissue repair.

Future research should focus on delineating the context-specific determinants of TREM2 function, including microenvironmental cues, epigenetic regulation, and metabolic substrate availability. Dissecting these factors will help clarify why TREM2 exerts protective roles in neurodegeneration yet contributes to immunosuppression in tumor settings. In addition, integrating single-cell multiomics with metabolic flux analysis will provide deeper insights into how TREM2 governs macrophage heterogeneity across tissues and disease states.

TREM2-Mediated Modulation of Neuroinflammation and Glial Homeostasis

TREM2 modulates neuroinflammation by shaping microglial polarization, phagocytosis, and survival, maintaining the balance between neuroprotection and neurotoxicity. It promotes anti-inflammatory phenotypes via NF-κB regulation, limits proinflammatory cytokine release, and enhances neuroimmune tolerance, while facilitating clearance of Aβ and necrotic debris to reduce secondary inflammation. In neurodegeneration and brain injury models, TREM2 activation lowers pathologic burden and supports immune resolution, whereas its deficiency intensifies inflammasome activity, amplifies proinflammatory signaling, and impairs repair. These observations establish TREM2 as a central immunometabolic checkpoint, controlling glial function and neuronal survival.

Looking ahead, a key direction is the development of TREM2-targeted interventions that selectively promote reparative microglial states while minimizing the risk of excessive immunosuppression. Preclinical strategies, such as TREM2 agonistic antibodies and small-molecule modulators, require refinement to optimize tissue specificity and minimize off-target effects. Furthermore, longitudinal biomarker studies are needed to evaluate whether fluctuations in sTREM2 levels can reliably reflect disease progression, treatment response, or neuroinflammatory resolution.

Therapeutic Potential of TREM2 in Neural Regeneration and Metabolic Disorder

TREM2 plays a crucial role in neural repair by regulating macrophage phenotype and metabolic activity. After neural injury, its activation promotes clearance of cellular debris, enhances glycolytic metabolism, and stimulates neurotrophic factor release, supporting tissue regeneration. In the context of diabetes-related complications, TREM2 mitigates inflammation, modulates glial energy homeostasis, and contributes to functional recovery. Moreover, clinical studies indicate that TREM2 expression reflects the severity of metabolic and inflammatory disorders, highlighting its potential as both a biomarker and a therapeutic target in conditions where immune and metabolic processes intersect.

Future therapeutic exploration should address three interrelated aspects:

Precision targeting: clarifying cell-type and context-specific effects of TREM2 in macrophages, microglia, and Schwann cells to avoid conflicting outcomes across different diseases.

Drug development: advancing TREM2 agonists, metabolic modulators, and gene-editing approaches to clinical testing, with emphasis on CNS penetration and immune selectivity.

Biomarker identification: establishing standardized assays for sTREM2 and related metabolic markers to guide patient stratification, treatment monitoring, and prognosis prediction.

Author Contributions

Y. Che: drafting/revision of the manuscript for content, including medical writing for content. Z. Yu: Data curation and visualization. S. Ji: Writing–review & editing. D. Yang: Conceptualization, supervision, review and editing. All authors have read and approved the final manuscript.

Study Funding

This work was supported by the National Natural Science Foundation of China (No. 82004182) and Medical Research Union Found for High-quality health development of Guizhou Province (2024GZYXKYJJXM0134), Guizhou Provincial Natural Science Foundation (qiankehejichu-ZK [2024] syiban581) and Technology Achievement Transformation and Industrialization Program Project (Clinical Special Project) (Qian Ke He Cheng Guo-LC [2025] General 163).

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NN for full disclosures.

Publication History

Received by *Neurology® Neuroimmunology & Neuroinflammation* June 4, 2025. Accepted in final form October 22, 2025. Submitted and externally peer reviewed. The handling editor was Dennis L. Kolson, MD, PhD.

References

1. Wu Y, Wu M, Ming S, et al. TREM-2 promotes Th1 responses by interacting with the CD3ζ-ZAP70 complex following Mycobacterium tuberculosis infection. *J Clin Invest.* 2021;131(17):e137407. doi:10.1172/JCI137407
2. Wang S, Mustafa M, Yuede CM, et al. Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model. *J Exp Med.* 2020;217(9):e20200785. doi:10.1084/jem.20200785
3. Song WM, Joshita S, Zhou Y, Ulland TK, Gilfillan S, Colonna M. Humanized TREM2 mice reveal microglia-intrinsic and -extrinsic effects of R47H polymorphism. *J Exp Med.* 2018;215(3):745-760. doi:10.1084/jem.20171529
4. Jaccard A, Wyss T, Maldonado-Pérez N, et al. Reductive carboxylation epigenetically instructs T cell differentiation. *Nature.* 2023;621(7980):849-856. doi:10.1038/s41586-023-06546-y
5. Freemerman AJ, Johnson AR, Sacks GN, et al. Metabolic reprogramming of macrophages: glucose transporter 1 (GLUT1)-Mediated glucose metabolism drives a proinflammatory phenotype. *J Biol Chem.* 2014;289(11):7884-7896. doi:10.1074/jbc.M113.522037
6. Cignarella F, Filipello F, Bollman B, et al. TREM2 activation on microglia promotes myelin debris clearance and remyelination in a model of multiple sclerosis. *Acta Neuropathol.* 2020;140(4):513-534. doi:10.1007/s00401-020-02193-z
7. Gouna G, Klose C, Bosch-Queralt M, et al. TREM2-dependent lipid droplet biogenesis in phagocytes is required for remyelination. *J Exp Med.* 2021;218(10):e20210227. doi:10.1084/jem.20210227
8. Ming S, Li X, Xiao Q, et al. TREM2 aggravates sepsis by inhibiting fatty acid oxidation via the SHP1/BTK axis. *J Clin Invest.* 2024;135(1):e159400. doi:10.1172/JCI159400
9. Zhong R, Xu Y, Williams JW, Li L. Loss of TREM2 diminishes CAA despite an overall increase of amyloid load in Tg-SwDI mice. *Alzheimers Dement.* 2024;20(11):7595-7612. doi:10.1002/alz.14222
10. Schapansky J, Grinberg YY, Osiecki DM, et al. MEK1/2 activity modulates TREM2 cell surface recruitment. *J Biol Chem.* 2021;296:100218. doi:10.1074/jbc.RA120.014352
11. Gao H, Di J, Clausen BH, et al. Distinct myeloid population phenotypes dependent on TREM2 expression levels shape the pathology of traumatic versus demyelinating CNS disorders. *Cell Rep.* 2023;42(7):112773. doi:10.1016/j.celrep.2023.112773
12. Yu C, Lad EM, Mathew R, et al. Microglia at sites of atrophy restrict the progression of retinal degeneration via galectin-3 and Trem2. *J Exp Med.* 2024;221(3):e20231011. doi:10.1084/jem.20231011
13. Sudom A, Talreja S, Danao J, et al. Molecular basis for the loss-of-function effects of the Alzheimer's disease-associated R47H variant of the immune receptor TREM2. *J Biol Chem.* 2018;293(32):12634-12646. doi:10.1074/jbc.RA118.002352
14. Zhao Y, Wu X, Li X, et al. TREM2 is a receptor for β-Amyloid that mediates microglial function. *Neuron.* 2018;97(5):1023-31.e7. doi:10.1016/j.neuron.2018.01.031
15. Kober DL, Stuchell-Brereton MD, Kluender CE, et al. Functional insights from biophysical study of TREM2 interactions with apoE and Aβ. *Alzheimers Dement.* 2020;16(10):1534-1542. doi:10.1002/alz.12194
16. Liu Y, Theil S, Ibach M, Walter J. DAP12 interacts with RER1 and is retained in the secretory pathway before assembly with TREM2. *Cell Mol Life Sci.* 2024;81(1):302. doi:10.1007/s00018-024-05298-w
17. Fremuth LE, Hu H, Van De Vlekkert D, Annunziata I, Weesner JA, Alessandra d'Azzo . Neuraminidase 1 regulates neuropathogenesis by governing the cellular state of microglia via modulation of Trem2 sialylation. *Cell Rep.* 2025;44(1):115204. doi:10.1016/j.celrep.2024.115204
18. Zhao P, Xu Y, Jiang LL, et al. LILRB2-mediated TREM2 signaling inhibition suppresses microglia functions. *Mol Neurodegener.* 2022;17(1):44. doi:10.1186/s13024-022-00550-y
19. Fan Z, Su D, Li ZC, Sun S, Ge Z. Metformin attenuates central sensitization by regulating neuroinflammation through the TREM2-SYK signaling pathway in

a mouse model of chronic migraine. *J Neuroinflammation.* 2024;21(1):318. doi:10.1186/s12974-024-03313-2

20. Liu J, Luo S, Wang G, Hu X, Chen G, Xu Q. Molecular cloning, tissue distribution and antiviral immune response of duck src. *Genes (Basel).* 2024;15(8):1044. doi:10.3390/genes15081044
21. Wang Q, Zheng K, Tan D, Liang G. TREM2 knockdown improves the therapeutic effect of PD-1 blockade in hepatocellular carcinoma. *Biochem Biophys Res Commun.* 2022;636(Pt 1):140-146. doi:10.1016/j.bbrc.2022.10.079
22. Yu W, Zhang Y, Sun L, et al. Myeloid Trem2 ameliorates the progression of metabolic dysfunction-associated steatotic liver disease by regulating macrophage pyroptosis and inflammation resolution. *Metabolism.* 2024;155:155911. doi:10.1016/j.metabol.2024.155911
23. Peng X, Guo H, Zhang X, et al. TREM2 inhibits tau hyperphosphorylation and neuronal apoptosis via the PI3K/Akt/GSK-3β signaling pathway in vivo and in vitro. *Mol Neurobiol.* 2023;60(5):2470-2485. doi:10.1007/s12035-023-03217-x
24. Chen S, Peng J, Sherchan P, et al. TREM2 activation attenuates neuroinflammation and neuronal apoptosis via PI3K/Akt pathway after intracerebral hemorrhage in mice. *J Neuroinflammation.* 2020;17(1):168. doi:10.1186/s12974-020-01853-x
25. Qiao X, Wang H, He Y, et al. Grape seed proanthocyanidin ameliorates LPS-induced acute lung injury by modulating M2a macrophage polarization via the TREM2/PI3K/Akt pathway. *Inflammation.* 2023;46(6):2147-2164. doi:10.1007/s10753-023-01868-5
26. Li C, Hou X, Yuan S, et al. High expression of TREM2 promotes EMT via the PI3K/AKT pathway in gastric cancer: bioinformatics analysis and experimental verification. *J Cancer.* 2021;12(11):3277-3290. doi:10.7150/jca.55077
27. Li D, Pan L, Chen M, Zhang X, Jiang Z. TREM2 protects against LPS-induced murine acute lung injury through suppressing macrophage ferroptosis. *Int Immunopharmacol.* 2025;150:114247. doi:10.1016/j.intimp.2025.114247
28. Jiang Y, Yu W, Hu T, et al. Unveiling macrophage diversity in myocardial ischemia-reperfusion injury: identification of a distinct lipid-associated macrophage subset. *Front Immunol.* 2024;15:1335333. doi:10.3389/fimmu.2024.1335333
29. Wang J, Du L, Zhang T, et al. Edaravone dexborneol ameliorates the cognitive deficits of APP/PS1 mice by inhibiting TLR4/MAPK signaling pathway via upregulating TREM2. *Neuropharmacology.* 2024;255:110006. doi:10.1016/j.neuropharm.2024.110006
30. Tian Y, Xiao X, Liu W, et al. TREM2 improves microglia function and synaptic development in autism spectrum disorders by regulating P38 MAPK signaling pathway. *Mol Brain.* 2024;17(1):12. doi:10.1186/s13041-024-01081-x
31. Fang C, Zhong R, Lu S, et al. TREM2 promotes macrophage polarization from M1 to M2 and suppresses osteoarthritis through the NF-κB/CXCL3 axis. *Int J Biol Sci.* 2024;20(6):1992-2007. doi:10.7150/ijbs.91519
32. Jiang C, Chen Z, Wang X, et al. Curcumin-activated olfactory ensheathing cells improve functional recovery after spinal cord injury by modulating microglia polarization through APOE/TREM2/NF-κB signaling pathway. *J Neuroimmune Pharmacol.* 2023;18(3):476-494. doi:10.1007/s11481-023-10081-y
33. Yan Y, Bai S, Han H, et al. Knockdown of trem2 promotes proinflammatory microglia and inhibits glioma progression via the JAK2/STAT3 and NF-κB pathways. *Cell Commun Signal.* 2024;22(1):272. doi:10.1186/s12964-024-01642-6
34. Huang P, Zhang Z, Zhang P, et al. TREM2 deficiency aggravates NLRP3 inflammasome activation and pyroptosis in MPTP-induced parkinson's disease mice and LPS-induced BV2 cells. *Mol Neurobiol.* 2024;61(5):2590-2605. doi:10.1007/s12035-023-03713-0
35. Haensel D, Daniel B, Gaddam S, et al. Skin basal cell carcinomas assemble a pro-tumorigenic spatially organized and self-propagating Trem2+ myeloid niche. *Nat Commun.* 2023;14(1):2685. doi:10.1038/s41467-023-37993-w
36. Zhou Y, Tada M, Cai Z, et al. Human early-onset dementia caused by DAP12 deficiency reveals a unique signature of dysregulated microglia. *Nat Immunol.* 2023;24(3):545-557. doi:10.1038/s41590-022-01403-y
37. Li W, Liao LP, Song N, et al. Natural product 1,2,3,4,6-penta-O-galloyl-β-D-glucopyranose is a reversible inhibitor of glyceraldehyde 3-phosphate dehydrogenase. *Acta Pharmacol Sin.* 2022;43(2):470-482. doi:10.1038/s41401-021-00653-0
38. Van Den Bossche J, Baardman J, Otto NA, et al. Mitochondrial dysfunction prevents repolarization of inflammatory macrophages. *Cell Rep.* 2016;17(3):684-696. doi:10.1016/j.celrep.2016.09.008
39. Lampropoulou V, Sergushichev A, Bambouskova M, et al. Itaconate links inhibition of succinate dehydrogenase with macrophage metabolic remodeling and regulation of inflammation. *Cell Metab.* 2016;24(1):158-166. doi:10.1016/j.cmet.2016.06.004
40. Fathi M, Vakili K, Yaghoobpoor S, et al. Dynamic changes in kynurenine pathway metabolites in multiple sclerosis: a systematic review. *Front Immunol.* 2022;13:1013784. doi:10.3389/fimmu.2022.1013784
41. Wei W, Qu ZL, Lei L, Zhang P. TREM2-mediated macrophage glycolysis promotes skin wound angiogenesis via the Akt/mTOR/HIF-1α signaling axis. *Curr Med Sci.* 2024;44(6):1280-1292. doi:10.1007/s11596-024-2946-3
42. Zhu D, Huang M, Shen P, et al. TREM2 expression promotes liver and peritoneal M2 macrophage polarization in mice infected with Schistosoma japonicum. *J Cel Mol Med.* 2023;27(15):2261-2269. doi:10.1111/jcmm.17842
43. Nugent AA, Lin K, Van Lengerich B, et al. TREM2 regulates microglial cholesterol metabolism upon chronic phagocytic challenge. *Neuron.* 2020;105(5):837-54.e9. doi:10.1016/j.neuron.2019.12.007
44. Yang D, Sun X, Wang H, et al. TREM2 depletion in pancreatic cancer elicits pathogenic inflammation and accelerates tumor progression via enriching IL-1β(+) macrophages. *Gastroenterology.* 2025;168(6):1153-1169. doi:10.1053/j.gastro.2025.01.244
45. Zhong WJ, Liu T, Yang HH, et al. TREM-1 governs NLRP3 inflammasome activation of macrophages by firing up glycolysis in acute lung injury. *Int J Biol Sci.* 2023;19(1):242-257. doi:10.7150/ijbs.77304
46. Wang Y, Wan Y, Zhou X, Zhang P, Zhang J. OTULIN of exosomes derived from schwann cells promotes peripheral nerve injury repair by regulating macrophage polarization via deubiquitination of ERBB2. *Neurosci Lett.* 2024;833:137813. doi:10.1016/j.neulet.2024.137813
47. Oshima E, Hayashi Y, Xie Z, et al. M2 macrophage-derived cathepsin S promotes peripheral nerve regeneration via fibroblast-Schwann cell-signaling relay. *J Neuroinflammation.* 2023;20(1):258. doi:10.1186/s12974-023-02943-2
48. Gitik M, Elberg G, Reichert F, Tal M, Rotshenker S. Deletion of CD47 from schwann cells and macrophages hastens myelin disruption/dismantling and scavenging in schwann cells and augments myelin debris phagocytosis in macrophages. *J Neuroinflammation.* 2023;20(1):243. doi:10.1186/s12974-023-02929-0
49. Takahashi K, Prinz M, Stagi M, Chechneva O, Neumann H. TREM2-transduced myeloid precursors mediate nervous tissue debris clearance and facilitate recovery in an animal model of multiple sclerosis. *PLoS Med.* 2007;4(4):e124. doi:10.1371/journal.pmed.0040124
50. Chen X, Chen C, Fan S, et al. Omega-3 polyunsaturated fatty acid attenuates the inflammatory response by modulating microglia polarization through SIRT1-mediated deacetylation of the HMGB1/NF-κB pathway following experimental traumatic brain injury. *J Neuroinflammation.* 2018;15(1):116. doi:10.1186/s12974-018-1151-3
51. Cheng J, Zhang R, Xu Z, et al. Early glycolytic reprogramming controls microglial inflammatory activation. *J Neuroinflammation.* 2021;18(1):129. doi:10.1186/s12974-021-02187-y
52. Giacomello G, Otto C, Priller J, Ruprecht K, Böttcher C, Parr Mk. 1,2-(13)C(2)-Glucose tracing approach to assess metabolic alterations of human monocytes under neuroinflammatory conditions. *Curr Issues Mol Biol.* 2023;45(1):765-781. doi:10.3390/cimb45010051
53. Chiang YK, Lin YS, Chen CY, et al. Different splice isoforms of peripheral triggering receptor expressed on myeloid cells 2 mRNA expressions are associated with cognitive decline in mild dementia due to Alzheimer's disease and reflect central neuroinflammation. *Am J Alzheimers Dis Other Demen.* 2024;39:15333175241243183. doi:10.1177/15333175241243183
54. You YF, Chen M, Tang Y, et al. TREM2 deficiency inhibits microglial activation and aggravates demyelinating injury in neuromyelitis optica spectrum disorder. *J Neuroinflammation.* 2023;20(1):89. doi:10.1186/s12974-023-02772-3
55. Li L, Xu N, He Y, et al. Dehydroervatamine as a promising novel TREM2 agonist, attenuates neuroinflammation. *Neurotherapeutics.* 2025;22(2):e00479. doi:10.1016/j.neurot.2024.e00479
56. Shin HJ, Jin Z, An HS, et al. Lipocalin-2 deficiency reduces hepatic and hippocampal triggering receptor expressed on myeloid Cells-2 expressions in high-fat Diet/streptozotocin-induced diabetic mice. *Brain Sci.* 2022;12(7):878. doi:10.3390/brainsci12070878

eReferences are available as Supplementary Material at Neurology.org/NN.