Role of microglia in neuromyelitis optica (Review)

YUAN ZHANG[1*], JIAN-BIN HONG[2*], MING-WEI LIU[3] and LIN-MING ZHANG[1]

[1]Department of Neurology, The First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan 650032, P.R. China;
[2]Department of Orthopedics, The First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan 650032, P.R. China;
[3]Department of Emergency, People's Hospital of Dali Bai Autonomous Prefecture, Dali, Yunnan 671000, P.R. China

Received March 31, 2026; Accepted October 9, 2026

DOI: 10.3892/ijmm.2026.6036

Abstract. Neuromyelitis optica spectrum disorder (NMOSD) is an antibody-mediated autoimmune disease of the central nervous system (CNS), typically characterized by optic neuritis and myelitis. Aquaporin-4 antibodies initiate astrocyte injury, although the factors triggering their production are unclear. Subsequent interactions among astrocytes, microglia, complement and peripheral immune cells drive neuroinflammation, demyelination and axonal damage. Microglia amplify tissue injury through the release of inflammatory mediators and cytotoxic factors, while contributing to debris clearance and tissue repair. The present review examines the roles of microglia in NMOSD, with a focus on complement, cytokine and interferon signaling, lipid metabolism and metabolic reprogramming. It further discusses therapeutic strategies for modulating microglial activity and the challenges of translating experimental findings into clinical practice. Elucidating the context-dependent balance between inflammatory and reparative microglial states may facilitate the development of strategies that limit immune-mediated injury while promoting CNS recovery.

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Correspondence to: Professor Ming-Wei Liu, Department of Emergency, People's Hospital of Dali Bai Autonomous Prefecture, 35 Renmin South Road, Xiaguan Street, Dali, Yunnan 671000, P.R. China
E-mail: lmw2004210@163.com

Professor Lin-Ming Zhang, Department of Neurology, The First Affiliated Hospital of Kunming Medical University, 295 Xichang Road, Wuhua, Kunming, Yunnan 650032, P.R. China
E-mail: zlmeek@163.com

*Contributed equally

Key words: microglia, neuromyelitis optica, interleukin, therapeutic strategy

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing autoimmune disease of the central nervous system (CNS) that predominantly affects female patients and typically manifests as optic neuritis and myelitis, often resulting in disability (1). Its annual incidence in China is ~0.278/100,000 individuals (2). Binding of aquaporin (AQP)4-IgG to astrocytic end-feet triggers complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC), leading to astrocyte injury, blood-brain barrier (BBB) disruption and secondary damage to oligodendrocytes and neurons (3,4) (Fig. 1). Astrocytic injury releases damage-associated molecular patterns (DAMPs), including ATP, high mobility group B1 (HMGB1) and mitochondrial DNA, which activate microglial pattern recognition receptors and NF-κB signaling (5,6). The mechanisms underlying the initial production of AQP4-IgG are incompletely understood, with genetic and environmental factors potentially contributing to its development. Subsequent AQP4-IgG attacks involve complement activation, IL-6 signaling and BBB disruption (7).

Microglia are not primary targets of AQP4-IgG but contribute to the amplification of astrocyte-initiated injury (Fig. 1; Table I) (8-11). Complement signals, Fc receptor engagement and DAMPs stimulate microglia to release TNF-α, IL-1β, IL-6, chemokines, reactive oxygen species (ROS) and MMPs. These mediators further compromise the BBB, promote peripheral immune cell recruitment and contribute to oligodendrocyte and axonal injury. Activated microglia also upregulate major histocompatibility complex class II and costimulatory molecules, potentially sustaining autoreactive T cell responses through antigen presentation (12).

Serum from patients with NMOSD impairs astrocytic glutamate uptake and glutamine synthetase activity, contributing to secondary oligodendrocyte injury (13). Under physiological conditions, astrocytes and microglia exchange trophic and immunoregulatory signals that maintain cell homeostasis (14).

In NMOSD, injured astrocytes release complement fragments, ATP, DAMPs and cytokines that activate microglia, whereas microglial inflammatory mediators exacerbate astrocyte injury. This reciprocal amplification loop promotes persistent neuroinflammation, demyelination and axonal damage (15).

The present review aimed to examine how complement, IL, IFN and metabolic pathways shape microglial responses in NMOSD and how these responses may be modulated to limit inflammation and support tissue repair. The present study aimed to distinguish mechanistic opportunities from the experimental and translational limitations that constrain the development of microglia-targeted therapies.

2. Microglia functions and phenotypes

As the resident immune cells of the CNS, microglia provide continuous surveillance of the brain through dynamic interactions with neurons and other cell components. Upon detecting pathogens or tissue injury, microglia respond by phagocytosing cellular debris and releasing cytokines and chemokines, thereby enabling timely recognition and containment of threats within the CNS (16). Microglia are key for synaptic maintenance and remodeling. During neurodevelopment, they mediate synaptic pruning, facilitate synaptogenesis and myelination and contribute to the maturation and synchronization of neuronal activity (17). In addition, microglia support neuronal survival and repair through the release of neurotrophic factors (NFs), such as brain-derived NF (BDNF) (18).

Rather than existing as a simple pro-inflammatory or reparative binary, microglia occupy a continuous spectrum of functional states (Table II) (19-27). These states encompass homeostatic, inflammatory, immunoregulatory and disease-associated microglial (DAM) phenotypes and are shaped by local signals and disease stage (Fig. 2) (28). In AQP4-IgG-driven pathology, complement, FcγR, NF-κB and STAT1 signaling can amplify tissue injury (12), whereas triggering receptor expressed on myeloid cells (TREM)2, PPARγ, STAT6 and Nrf2 pathways may promote phagocytosis, trophic support and barrier repair (29-31). Complement fragments, glutamate, metabolic substrates, iron, myelin debris and apoptotic cell signals further influence microglial states across lesion cores, peri-lesional regions and distinct stages of injury. Accordingly, therapeutic strategies should aim to restrain detrimental microglial responses while preserving their reparative function, rather than treating microglial activation as uniformly harmful. The timing and cell specificity of such interventions are therefore key determinants of their therapeutic potential.

3. Role of microglia in NMOSD

Microglia integrate complement, cytokine, IFN and metabolic signals in NMOSD (Fig. 2; Table III) (30,32-40). Following AQP4-IgG-mediated injury to astrocytes, complement-responsive microglia become activated at the damage site and serve as the central innate immune effector in this pathological cascade (32). Guided by opsonization from complement proteins activated via the classical AQP4-IgG pathway, these microglia efficiently phagocytose necrotic cell debris released from dying astrocytes (41). While this phagocytic process clear tissue damage, it concurrently triggers intracellular inflammatory signaling, driving the microglia to secrete pro-inflammatory mediators, including cytokines such as TNF-α and IL-1β, chemokines, and reactive oxygen species (42). These mediators not only amplify local inflammation but also disrupt the integrity of the blood-brain barrier, which facilitates the recruitment and infiltration of peripheral immune cells such as neutrophils, monocytes, and T cells that are normally excluded from the central nervous system (CNS) (42). IFN signaling, from both type I IFN produced by resident CNS cells and type II IFN secreted by infiltrating T cells, acts to lock microglia in a sustained pro-inflammatory activated state, preventing their transition to an anti-inflammatory repair phenotype (43). In addition to signaling regulation, metabolic reprogramming reinforces this pro-inflammatory response: activated microglia shift from oxidative phosphorylation to increased aerobic glycolysis to meet the high energy and biosynthetic demands of continuous activation, while altered lipid metabolism leads to accumulation of pro-inflammatory lipid intermediates that amplify inflammatory signaling (44). Together, these interconnected interactions between initial astrocyte damage, complement-dependent microglial activation, sustained IFN signaling, and metabolic rewiring create a self-reinforcing pathological loop that explains how a focal autoimmune response initially targeting astrocytes progressively spreads to cause broader, multifocal CNS injury.

Complement-mediated microglial activation in NMOSD. The complement system is a notable component of innate immunity (45). Microglia express complement receptors, including C3aR and C5aR, and produce complement components such as C1q and C3 (45). Microglia-derived complement contributes to neuroinflammation and neurodegeneration, with increased C1q and C3 expression associated with microglial synaptic phagocytosis in neuropathological conditions, including depression and neurodegenerative disease (46). Under physiological conditions, microglia produce complement components while expressing regulatory proteins such as CD55 and CD59 to constrain excessive complement activation (47). Following CNS injury or disease, damage-associated signals induce increased complement production by microglia, thereby promoting local complement activation (47).

Complement C3 is a key component of the complement cascade and a convergence point for the classical, alternative and lectin pathways in NMOSD, with key effects on microglial activation and function (Fig. 2) (48). Dysregulated C3 expression sustains microglial activation and contributes to synaptic dysfunction and cognitive impairment. Systemic inflammation, for example, promotes microglial activation through increased C3 expression, leading to synaptic loss and cognitive deficit (8). In NMOSD, excessive C3 activation is associated with optic nerve and spinal cord injury, whereas C3 inhibition decreases complement deposition and demyelination and improves motor function in experimental models (49,50).

Under physiological conditions, astrocytes express little or no C3. In pathological states, NMO-IgG induces robust C3 production by astrocytes (51), followed by its cleavage into C3a and C3b. C3a binds C3aR and promotes NLRP3 inflammasome assembly, facilitating the maturation and release of IL-1β and IL-18 and enhancing microglial inflammatory responses

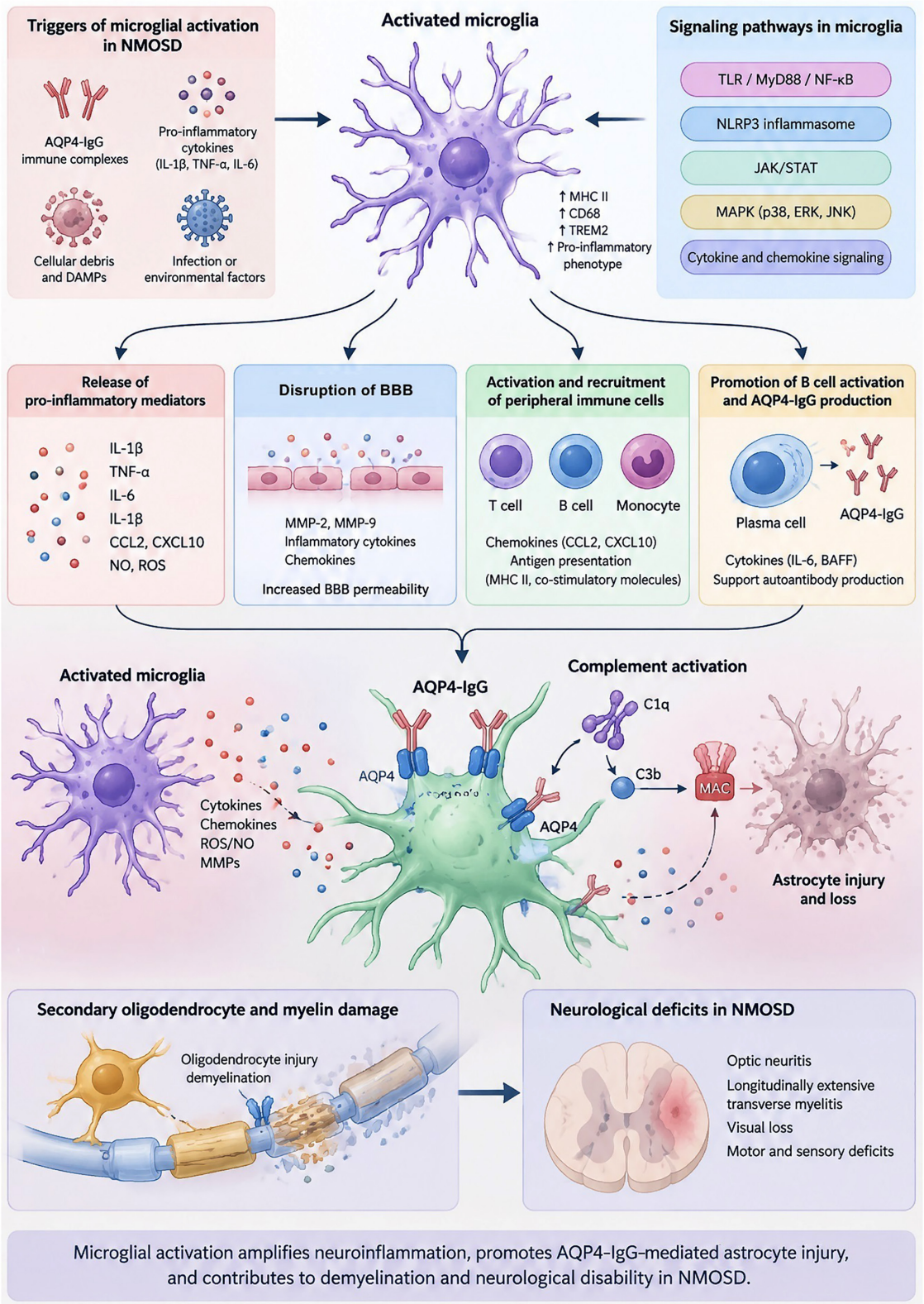


Figure 1. Mechanism of microglia induced NMOSD. AQP4-IgG crosses the compromised BBB and binds AQP4 on astrocytic end-feet, activating the classical complement pathway. Astrocyte injury releases DAMPs, which engage microglial TLR4, RAGE and P2X7, triggering NF-κB, MAPK, JAK/STAT and NLRP3 inflammasome signaling. This drives M1-like polarization and the release of TNF-α, IL-1β, IL-6, CXCL10, CCL2 and NOX-derived ROS, establishing a self-amplifying inflammatory loop. Protective regulators (TREM2, ApoE, CD200R, PPARγ, miR-124, AMPK/PGC-1α) are suppressed. The resulting milieu injures OPCs and oligodendrocytes via complement opsonization, cytokine cytotoxicity and oxidative stress, leading to demyelination and neuronal loss. Targeted interventions include anti-C5, anti-IL-6R, JAK inhibitors and TREM2/CSF1R modulation. NMOSD, neuromyelitis optica spectrum disorder; BBB, blood-brain barrier; AQP4-IgG, aquaporin-4 immunoglobulin G; CCL2, C-C motif chemokine ligand 2; CXCL10, C-X-C motif chemokine ligand 10; NO, nitric oxide; ROS, reactive oxygen species; BAFF, B cell activating factor; MHC II, major histocompatibility complex class II; TREM2, triggering receptor expressed on myeloid cells 2; TLR, toll-like receptor; MyD88, myeloid differentiation primary response 88; NLRP3, NOD-like receptor protein 3; RAGE, receptor for advanced glycation end products; P2X7, P2X purinoceptor 7; NOX, NADPH oxidase; ApoE, apolipoprotein E; CD200R, CD200 receptor; miR, microRNA; PGC, peroxisome proliferator-activated receptor gamma coactivator 1α; OPC, Oligodendrocyte precursor cell; CSF1R, Colony stimulating factor 1 receptor.

Table I. Cell and molecular interactions centered on microglia in neuromyelitis optica spectrum disorder.

Interaction axis	Upstream input signals (activating microglia)	Core microglial response	Downstream output effects affecting other cells/structures	Final pathological outcomes	(Refs.)
Astrocyte-microglia axis	AQP4-IgG$^+$ complement: Astrocyte damage, release of DAMPs such as ATP and HMGB1; astrocyte-derived C3a: Directly acts on microglial C3aR.	Pattern recognition receptors (such as TLR4) are activated; C3aR signal drives polarization towards M1; NLRP3 inflammasome activation	Release of IL-1β, TNF-α and IL-6 damage astrocytes/oligodendrocytes; release of CCL2 and CXCL10 recruits monocytes/neutrophils	Inflammatory cascade amplification, demyelination	(8)
Peripheral immune-microglia axis	Th1 cells secrete IFN-γ; Th17 cells secrete IL-17A; infiltrating macrophages/neutrophils release pro-inflammatory cytokines	IFN-γ induces M1 phenotype via the JAK/STAT1 pathway; inflammatory environment promotes M1 polarization	Following M1 transformation of microglia, feedback release factors maintain Th1/Th17 response; blood-brain barrier disruption	Persistent autoimmune attack, chronic inflammation	(9)
Lipid metabolism-microglia axis	Damage to myelin sheath fragments; serum LDL enters via damaged BBB; ApoE EVs derived from astrocytes	TREM2 senses lipid signals, promoting phagocytosis and M2 repair programs; in the absence of TREM2 or ApoE dysregulation, lipid overload leads to dysfunction and inflammation	Effective clearance: Secretion of PDGF-BB promotes OPC differentiation and remyelination; clearance impairment: Lipid accumulation exacerbates toxicity and inhibits repair	Determines whether the injury leads to repair or chronic degeneration	(10)
Intrinsic metabolic reprogramming	Microenvironment inflammatory signals (LPS, IFN-γ)	Shift from oxidative phosphorylation to glycolysis (M1 metabolic signature)	Metabolic changes stabilize the pro-inflammatory phenotype, generating large amounts of metabolites such as lactate that affect the microenvironment	Maintains the pro-inflammatory state, resisting transition to a repair phenotype	(11)

AQP4-IgG, aquaporin-4 immunoglobulin G; DAMP, damage-associated molecular pattern; LDL, low-density lipoprotein; BBB, blood-brain barrier; ApoE, apolipoprotein E; EV, extracellular vesicle; LPS, lipopolysaccharide; TLR4, toll-like receptor 4; NLRP3, NOD-like receptor protein 3; CCL2, C-C motif chemokine ligand 2; CXCL10, C-X-C motif chemokine ligand 10; PDGF-BB, platelet-derived growth factor-BB; OPC, oligodendrocyte precursor cell.

(Fig. 2) (8). CDC and ADCC are also established mechanisms of astrocyte injury in NMOSD (52,53). Complement activation promotes macrophage recruitment, while macrophage-derived cytokines and ROS injure neurons and oligodendrocytes, contributing to astrocyte damage and secondary demyelination (54).

C5a is an inflammatory effector molecule (55). Elevated C5a levels in NMOSD are associated with disease activity and increased concentrations of IL-6 and TNF-α (56,57). C5a/C5aR1 signaling promotes microglial chemotaxis, proliferation and cytokine production (58), whereas astrocytic C5a receptors may enhance reactive astrogliosis and local complement production (59). These effects reinforce reciprocal astrocyte-microglia activation. C5aR1 blockade is neuroprotective in experimental neuroinflammatory settings, although its microglia-specific contribution to NMOSD remains to be defined (60). Complement cleavage also generates C5b, which initiates assembly of the C5b-9 membrane attack complex (MAC) following AQP4-IgG binding (61). MAC disrupts astrocyte membranes and contributes to tissue injury (62), distinguishing terminal complement-mediated cytotoxicity from C5a-mediated inflammatory signaling.

AQP4-IgG promotes AQP4 internalization and astrocyte injury through CDC and ADCC (63). Activated microglia

Table II. Microglia functions and phenotypes.

Authors, year	Phenotype/State	Key markers	Main functions	Relevance in NMOSD	(Refs.)
Guzmán-Ruíz *et al*, 2024	Homeostatic/ Surveillant	P2RY12, TMEM119, CX3CR1, Tmem119, Siglec-H, Ramified morphology	Continuous process extension/retraction; synaptic monitoring; release of neurotrophic factors (e.g., BDNF); maintenance of CNS homeostasis.	Baseline state before lesion formation. Loss of P2RY12/TMEM119 expression occurs with activation. In NMOSD, early microglial reactivity may precede or accompany astrocyte damage	(19)
Baligács *et al*, 2024	Activated/ reactive (general)	Iba1 upregulation, CD68, MHC-II, amoeboid morphology	Rapid response to injury; proliferation; migration to lesion; phagocytosis of debris; cytokine/ chemokine secretion.	Observed in NMOSD lesions, especially around perivascular areas with AQP4 loss and complement deposition. Microglial activation is associated with lesion activity.	(20)
Felice *et al*, 2024	Pro-inflammatory (M1-like/ Neurotoxic)	CD86, CD16/32, iNOS, TNF-α, IL-1β, IL-6, ROS production, MHC-II	Release of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6); production of reactive oxygen/nitrogen species; antigen presentation; potentiation of neuroinflammation.	AQP4-IgG and complement trigger microglial release of IL-1β, TNF-α, and IL-6, which can amplify astrocyte injury, recruit other immune cells, and contribute to oligodendrocyte damage.	(21)
Stojanović *et al*, 2024	Anti-inflammatory/repair (M2-like/ neuroprotective)	CD206, Arg1, Ym1, TGF-β, IL-10, IGF-1	Secretion of anti-inflammatory cytokines (IL-10, TGF-β); phagocytosis of myelin/cell debris; promotion of tissue repair; secretion of neurotrophic factors.	Microglia acquire a reparative phenotype, clearing myelin debris and releasing IL-10 or TGF-β, which limit lesion extension and support remyelination. However, evidence in NMOSD is limited	(22)
Ajoolabady *et al*, 2025	Disease-associated microglia (DAM)/ Neurodegenerative phenotype	TREM2, APOE, LPL, Clec7a, CD9, down regulation of homeostatic genes (P2RY12, TMEM119)	Phagocytosis of apoptotic cells, myelin and amyloid-like debris; lipid metabolism; transition state associated with chronic neurodegeneration.	Emerging single-cell studies suggest a DAM-like signature may appear in NMOSD lesions and models, especially with secondary demyelination and neurodegeneration. The role is unclear-may be protective or pathogenic depending on context.	(23)

Table II. Continued.

Authors, year	Phenotype/State	Key markers	Main functions	Relevance in NMOSD	(Refs.)
Miyake *et al*, 2026	Phagocytic/ foamy microglia	CD68, MERTK, AXL, TREM2, lipid-laden vacuoles	Engulfment of myelin debris, dead cells, and complement opsonized material; lipid clearance and processing	In NMOSD lesions, microglia/macrophages phagocytose damaged astrocytes, myelin, and debris. Foamy macrophages are common in active lesions. Impaired clearance may prolong inflammation	(24)
	Antigen-presenting microglia	MHC-II, CD80/ CD86, CD40	Processing and presentation of antigens to T cells; potential to activate infiltrating autoreactive T cells and support B cell response	In NMOSD, $CD4^+$ Th1 and Th17 cell involvement is recognized; microglia expressing MHC-II present CNS antigens, helping sustain the autoimmune response. CNS professional APCs are mainly dendritic cells and macrophages	(25)
Huang *et al*, 2022	Complement-related microglia	C3, C1q, C3aR, C5aR, CR3 (CD11b/CD18)	Production of complement components; response to complement activation; phagocytosis via complement receptor	AQP4-IgG activates complement, leading to C5b-9 deposition and astrocyte damage. Microglia express complement receptors (e.g., C3aR, C5aR) and can be activated by anaphylatoxins, contributing to inflammation and demyelination.	(26)
Corbali *et al*, 2023	Migratory/ perivascular microglia	CCR2 (low), CX3CR1, CD11b	Migration toward chemokine gradients (e.g., CCL2, CXCL10); accumulation around blood vessels and lesion edges.	In NMOSD lesions, microglia/macrophages accumulate in perivascular spaces and around astrocytes with AQP4 loss. Their migration may be driven by chemokines released from injured astrocytes and endothelium.	(27)

TMEM11, transmembrane protein 11; P2RY12, P2Y purinoceptor 12; CX3CR1, C-X3-C motif chemokine receptor 1; TREM2, triggering receptor expressed on myeloid cells 2; SAL1, senescence-associated lectin 1; P16INK4a, cyclin-dependent kinase inhibitor 2A; LAMP1, lysosomal-associated membrane protein 1; iNOS, Inducible Nitric Oxide Synthase; MHCII, Major Histocompatibility Complex Class II; COX-2, cyclooxygenase-2; BST2, bone Marrow Stromal Cell Antigen 2; Ym1 (CHI3L3), Chitinase-Like Protein 3 (Chitinase 3-Like 3); FIZZ1 (RELMα), Found in Inflammatory zone 1/Resistin-Like Molecule Alpha; APOE, Apolipoprotein E; SPP1, Secreted Phosphoprotein 1; IFITM3, Interferon-Induced Transmembrane Protein 3; LPL, Lipoprotein Lipase; ISG15, Interferon-Stimulated Gene 15 (Ubiquitin-Like Modifier); MX1, IFN-Induced GTP-Binding Protein Mx1; OAS1, 2'-5'-Oligoadenylate synthetase 1.

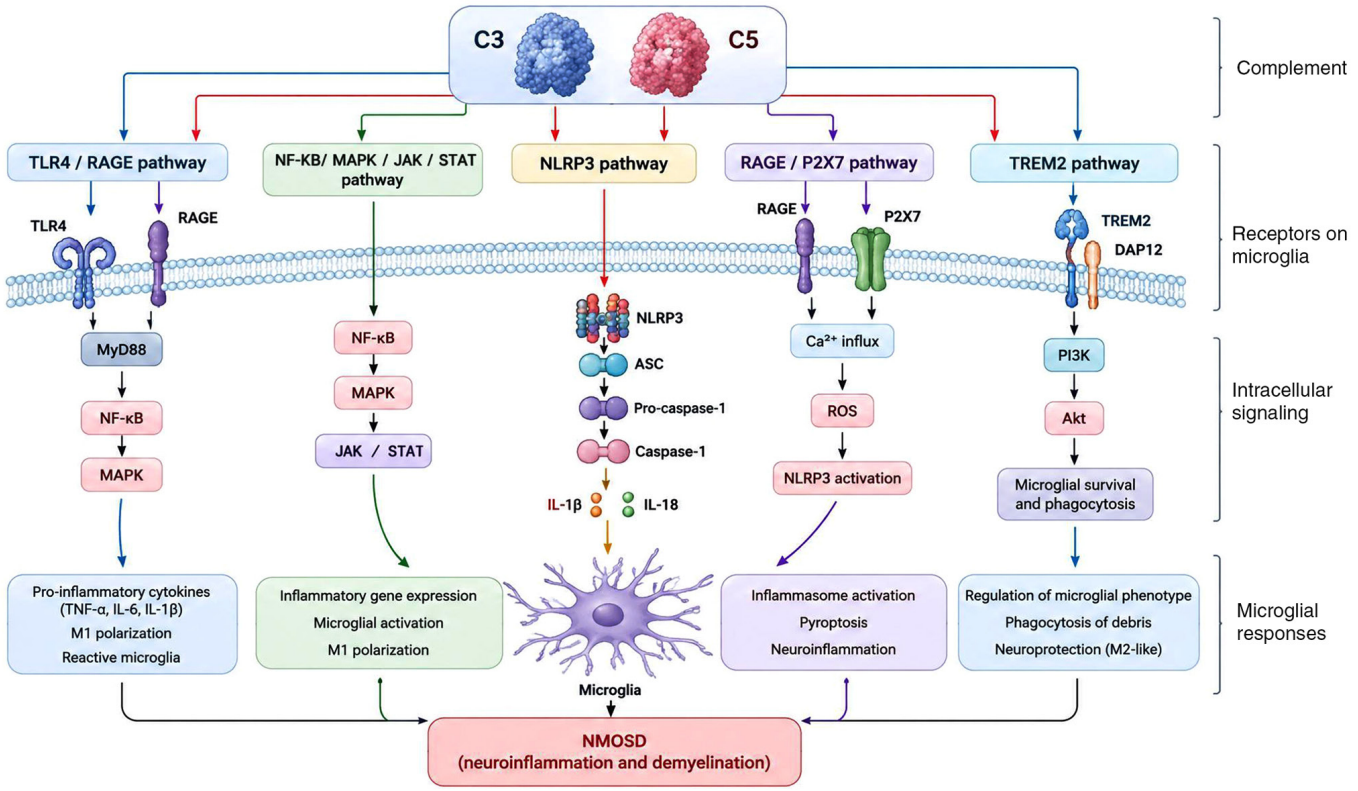


Figure 2. Complement C3 and C5 mediate NMOSD by regulating microglia. AQP4-IgG-mediated classical complement activation (C1q, C3, C5) generates C3a/C3aR and C5a/C5aR signals that activate microglial NF-κB, MAPK, JAK/STAT and NLRP3 signaling, inducing TNF-α, IL-1β, IL-6, CCL2, CXCL10, ROS and MMP-2/9. C3b/inactivated C3b opsonization via CR3 (CD11b/CD18) amplifies phagocytosis and inflammasome activation, while C5b-9 membrane attack complex damages astrocytes and oligodendrocytes. Homeostatic regulators (TREM2, apolipoprotein E, C-X3-C motif chemokine receptor 1, purinergic receptor P2Y) are suppressed, sustaining microglial dysfunction, oligodendrocyte precursor cell injury, demyelination and blood-brain barrier breakdown. Therapeutic targets include C3/C5 inhibitors and C3aR/C5aR antagonists. NLRP3, NOD-like receptor protein 3; TREM2, triggering receptor expressed on myeloid cells 2; DAP12, DNAX-activation protein 12; RAGE, receptor for advanced glycation end products; P2X7, P2X purinoceptor 7; TLR4, toll-like receptor 4; MyD88, myeloid differentiation primary response 88; ASC, apoptosis-associated speck-like protein containing a CARD; ROS, reactive oxygen species; NMOSD, neuromyelitis optica spectrum disorder.

secrete C1q, contributing to local neuronal and oligodendrocyte injury (64). Astrocyte-derived ATP, HMGB1 and S100B activate microglial receptors, including P2Y12 and TLR4/receptor for advanced glycation end products (RAGE), whereas microglial IL-1α, TNF and ROS can further impair astrocyte function (65). Complement signaling also regulates microglial processing of myelin debris (66). Excessive complement activation may compromise effective debris clearance and sustain demyelination, potentially via NF-κB signaling (66). Thus, complement-dependent phagocytosis should be considered in the context of both tissue injury and repair.

Several key questions remain unresolved, including the interplay between C3a and C5a signaling, their relevance to AQP4-IgG-seronegative disease and their potential utility as biomarkers. Longitudinal studies are needed to define their association with relapse and treatment response, while pathway-selective interventions should distinguish detrimental inflammatory signaling from the protective functions of complement.

Role of IL in microglia in NMOSD. ILs are multifunctional cytokines that regulate immune responses and contribute to microglial activation and neuroinflammation (Fig. 3). IL-6 is involved in the initiation and regulation of NMOSD and can modulate microglial activation (67). IL-17A activates microglia and astrocytes, inducing the production of inflammatory mediators and exacerbating neuronal injury and dysfunction (68). The IL-20 family regulates BBB integrity, oxidative stress and autophagy partly through effects on microglial activation, linking these processes with neuroinflammatory and neurodegenerative pathology (69). IL-2 exhibits region- and cell type-specific changes across neurological diseases, including multiple sclerosis (MS), Alzheimer's disease (AD), ischemic stroke and encephalitis (70). By contrast, IL-10 is a key anti-inflammatory regulator that suppresses glial activation and protects against inflammation-associated neuronal degeneration (71). Collectively, these findings underscore the complex and context-dependent functions of ILs in NMOSD.

IL-6. IL-6 is produced by microglia, lymphocytes, macrophages, fibroblasts and endothelial cells in response to infection, tissue damage and inflammatory stimuli (72) (Fig. 4). Its effects on immune cell survival, inflammatory signaling and barrier function make it particularly relevant to NMOSD.

IL-6 is produced by microglia, lymphocytes, macrophages, fibroblasts and endothelial cells in response to infection, tissue injury and inflammatory stimuli (72) (Fig. 4). Its effects on plasmablast survival, stimulates AQP4 antibody production and perpetuates an autoimmune cycle make it particularly relevant

Table III. Key factors regulating microglial M1/M2 phenotypes and their roles in neuromyelitis optica spectrum disorder.

Factor	Microglia phenotype	Role in myelin phagocytosis	Role in myelin regeneration	Role in neurons	Role in oligodendroglia cells	(Refs.)
C3a	Pro-inflammatory	Inhibition of phagocytosis leads to abnormal accumulation of myelin fragments	Inhibits OPC migration and differentiation	Promotes axonal damage	Increases oligodendroglia cell apoptosis	(30)
C5a	Pro-inflammatory	Recruits inflammatory cells and promotes pathological myelin phagocytosis	Suppression of remyelination	Indirect inflammatory injury	Increases oligodendroglia cells apoptosis	(32)
C5b	Pro-inflammatory	MAC deposition leads to myelinolysis	Destroys the regeneration microenvironment	Indirect injury	Direct lysis of oligodendrocytes	(33)
IL-6	Pro-inflammatory	Inhibition of effective phagocytosis	Inhibits OPC differentiation	Excitatory toxicity	Inhibition of proliferation and differentiation	(34)
IL-1β	Pro-inflammatory	Inflammatory phagocytosis disorder	Inhibition of OPC maturation	Pyroptosis	Inhibition of survival	(35)
IFN-β	Pro-inflammatory	Inhibitor of efficient phagocytosis	Deterioration of demyelination	Aggravate damage to neurons	Suppression of oligodendrocyte repair	(36)
IFN-γ	Pro-inflammatory	Inhibits phagocytosis	Inhibition of myelin regeneration	Axonal damage	Apoptosis	(37)
TREM2	Anti-inflammatory	Promotes efficient phagocytosis	Promotes OPC differentiation	Protect neurons from damage	Promotes migration and differentiation	(38)
ApoE3	Anti-inflammatory	Enhances phagocytic clearance efficiency of microglia for myelin debris	Promotes the differentiation of OPCs and myelin regeneration	Supports synaptic repair	Promotes oligodendrocyte maturation via cholesterol supply	(39)
ApoE4	Pro-inflammatory	Impairment of debris clearance and promotion of lipid accumulation.	Inhibits myelin repair and increases the lipid-toxic microenvironment	Loss of dendritic spines and excitotoxicity	Lipid accumulation leads to cell dysfunction	(40)

C5b, complement component 5b; TREM2, triggering receptor expressed on myeloid cells 2; ApoE3, apolipoprotein E3; MAC, membrane attack complex; OPC, oligodendrocyte precursor cell.

to NMOSD (73). IL-6 is a regulator of neuroinflammation, with key effects on microglial activation and function (74). In microglia, IL-6 signals via the JAK/STAT pathway to regulate proliferation and inflammatory responses (74). IL-6 receptor engagement activates downstream signaling pathways that enhance microglial migration and phagocytic activity (75) (Fig. 4).

Elevated IL-6 levels during NMOSD relapses suggest its potential use as a biomarker of disease activity (76). IL-6 may promote disease progression by modulating other cytokines and immune cell populations (76). For example, IL-6 and IL-17A impair BBB integrity, thereby exacerbating CNS inflammation (77). Increasing evidence implicates dysregulated microglial activation and IL-6 production in NMOSD pathogenesis (78-80). Elevated serum and cerebrospinal fluid (CSF) IL-6 levels during relapse are associated with disease severity and brain atrophy, suggesting that IL-6 may serve not only as a marker of disease activity but also as a mediator of pathological progression (81). IL-6 promotes plasmablast survival and AQP4 antibody production, thereby sustaining the autoimmune response in NMOSD (82). It can also work with TNF-α to increase the expression of endothelial adhesion molecules, including intercellular adhesion molecule (ICAM)-1, facilitating neutrophil infiltration across the BBB (83). This compromises BBB integrity (84), while neutrophil-derived MMP-9 disrupts myelin structure (85).

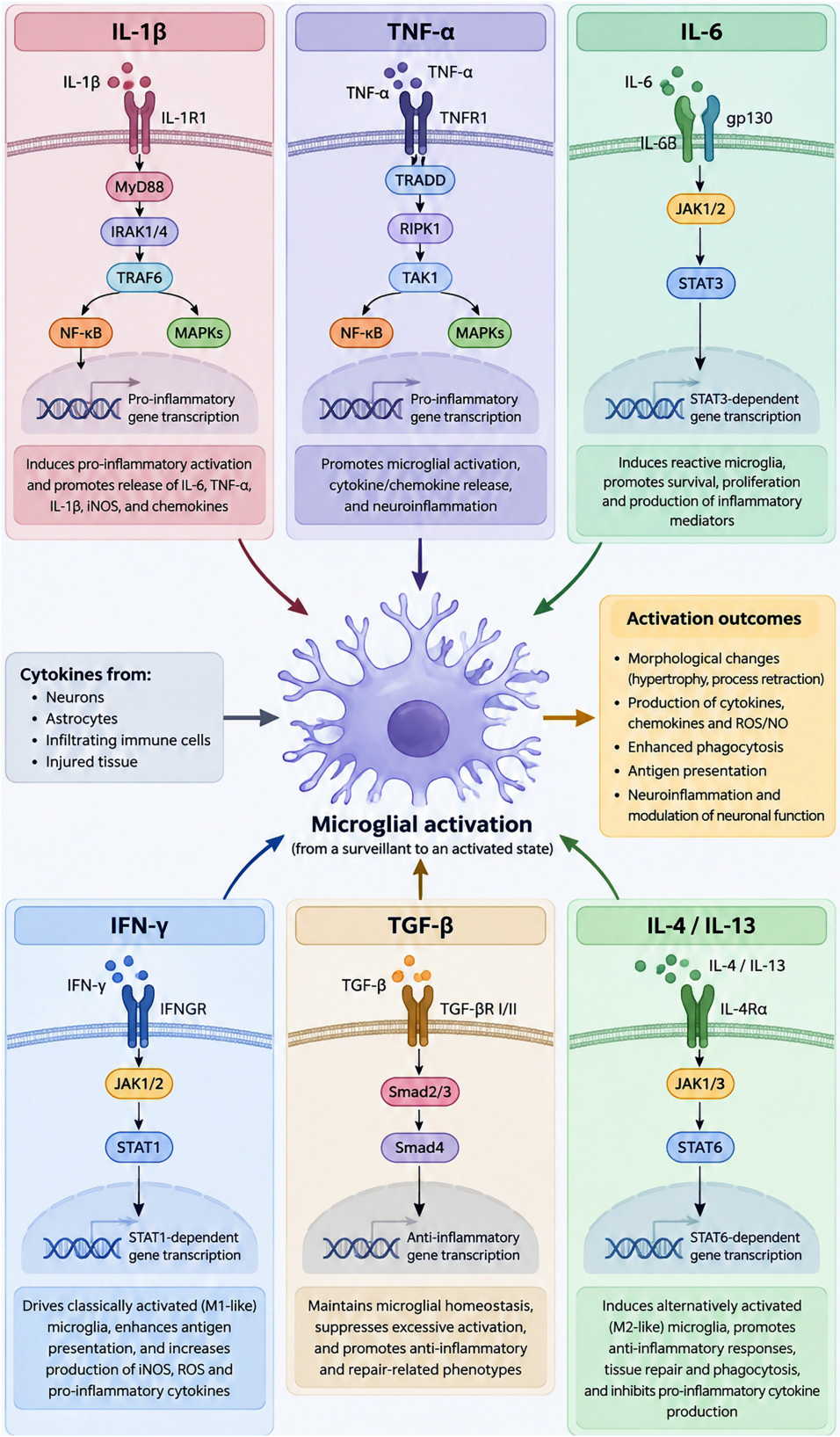


Figure 3. Functional roles of microglia induced by cytokines. TNF-α activates NF-κB/MAPK by regulating TRADD/RIPK1 to induce pro-inflammatory mediators. IL-1β engage TNFR/IL-1R/MyD88/NF-κB/MAPK, inducing M1 polarization and pro-inflammatory mediators (CCL2, CXCL10, iNOS, COX-2). IL-6 activates gp130/JAK/STAT3, sustaining M1 and impairing phagocytosis. IFN-γ signals via JAK/STAT1, enhancing major histocompatibility complex II antigen presentation. IL-4/IL-13 trigger JAK/STAT6/PPARγ, promoting M2 polarization (CD206, Arg1, IL-10, TGF-β). TGF-β/IL-10 activate SMAD/STAT3, restraining inflammation. CX3CL1/CX3CR1 sustains homeostatic microglia (purinergic receptor P2Y, transmembrane protein 119), dampening overactivation. Dysregulated signaling (dominance of NF-κB/MAPK over STAT6/PPARγ) shifts microglia toward pathogenic states in neuromyelitis optica spectrum disorder and multiple sclerosis. TRADD, TNFR1-associated death domain protein; RIPK1, receptor-interacting serine/threonine-protein kinase 1; CCL2, C-C motif chemokine ligand 2; CXCL10, C-X-C motif chemokine ligand 10; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; TRAF6, TNF receptor-associated factor 6; Arg1, arginase 1; MyD88, myeloid differentiation primary response 88; IRAK1/4, IL-1 receptor-associated kinase 1/4; TAK1, TGF-β-activated kinase 1; gp, glycoprotein.

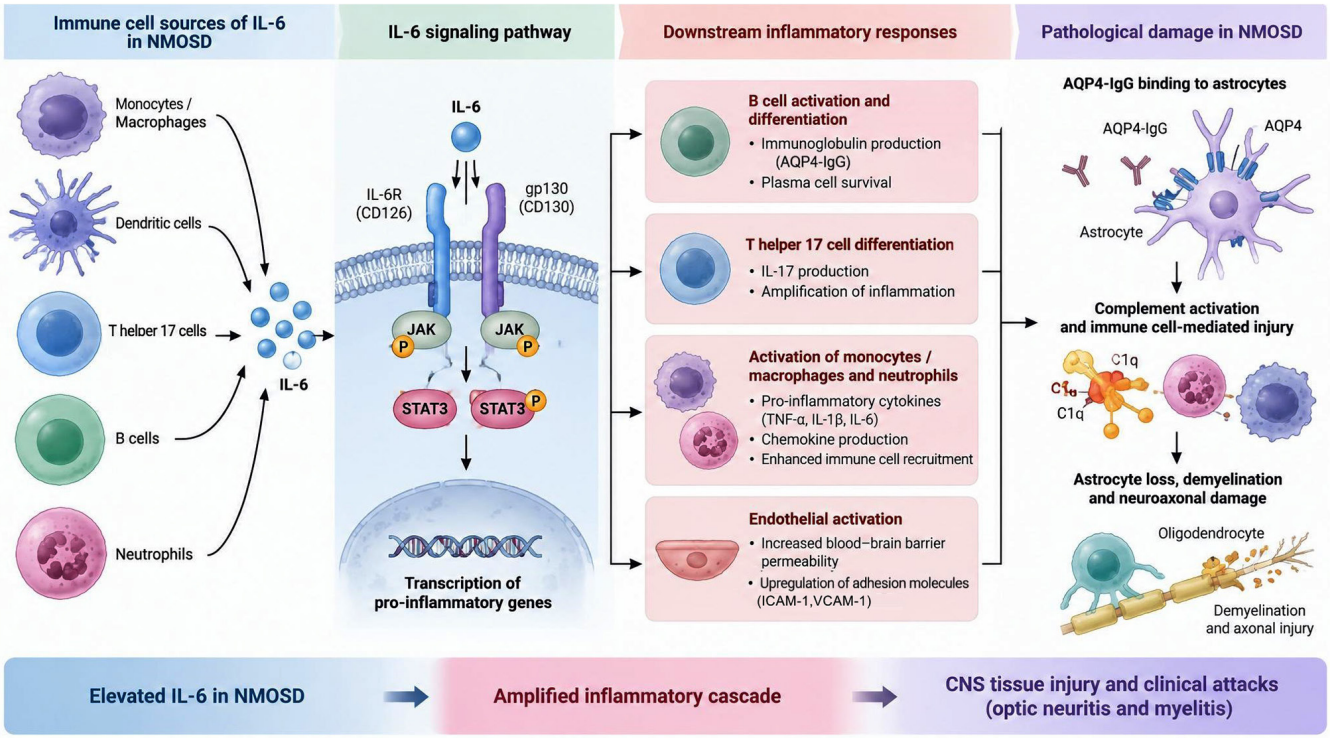


Figure 4. Inflammatory cascade effect of IL-6 mediated by regulating microglia in NMOSD. Circulating and CNS-resident IL-6 (from astrocytes, T and B cells) engages the microglial IL-6R/gp130 complex, activating JAK1/2/STAT3 and MAPK/PI3K/Akt signaling. STAT3 induces M1 polarization, upregulating NF-κB-driven pro-inflammatory mediators (TNF-α, IL-1β, CCL2, CXCL10, MMP-2/9, iNOS) while suppressing homeostatic genes (P2RY12, CX3CR1). The resulting ROS/NO burst and AQP4-IgG production by B cells promote a feed-forward loop, amplifying astrocyte injury, BBB breakdown and OPC demyelination. Therapeutic blockade (anti-IL-6R: tocilizumab/satralizumab) disrupts this cascade. IL-6R, IL-6 Receptor; AQP4, aquaporin-4; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; gp, glycoprotein; C1, complement component 1; NMOSD, neuromyelitis optica spectrum disorder.

In addition, IL-6 inhibits nuclear translocation of oligodendrocyte transcription factor 2 in oligodendrocyte precursor cells (OPCs), impairing their differentiation into mature oligodendrocytes and decreasing myelin basic protein (MBP) synthesis (86,87). IL-6 also activates suppressor of cytokine signaling 3 in OPCs (88), interfering with insulin-like growth factor-1 (IGF-1)-mediated repair signaling (89) and restricting OPC differentiation and remyelination. Because OPC proliferation and differentiation are key for myelin regeneration, impaired microglia-OPC interactions may further compromise repair in the inflamed CNS (90). IL-6 is directly involved in inflammatory signaling (91). Binding of IL-6 to IL-6R promotes gp130 homodimerization and formation of the functional receptor complex, leading to activation of JAK1 and JAK2 and subsequent phosphorylation and activation of STAT3. Activated STAT3 translocates to the nucleus and regulates the expression of inflammation-associated genes (Fig. 4) (92). In activated microglia, IL-6 signaling via the IL-6R/gp130 complex induces downstream pro-inflammatory mediators, including TNF-α and IL-1β, establishing a positive feedback loop that sustains inflammation and neuronal injury (93). This pathway increases microglial expression of inducible nitric oxide synthase and cyclooxygenase-2, promoting the production of ROS and prostaglandin E2 and thereby aggravating oxidative stress (93). IL-6 may cooperate with TGF-β to promote differentiation of $CD4^+$ T cells toward the T helper (Th)17 lineage, enhancing autoimmune responses, increasing BBB permeability and intensifying inflammation in NMOSD (94).

Key questions remain regarding the interaction between IL-6 signaling and AQP4-IgG-mediated injury, its relevance to seronegative NMOSD and the determinants of treatment response. Longitudinal comparative studies and biomarker-guided patient stratification are needed to refine IL-6-targeted therapy and assess combination approaches for refractory disease.

IL-1β. IL-1β primarily promotes inflammation by activating immune cells and inducing the release of additional inflammatory mediators (95). IL-1β stimulates astrocytes and microglia to produce chemokines, thereby recruiting peripheral immune cells to sites of inflammation and amplifying neuronal injury (Fig. 3) (95). IL-1β levels are notably elevated during the acute phase of inflammatory demyelinating disease, including myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and AQP4-IgG-positive NMOSD (96,97). This increase is particularly pronounced during acute attacks, suggesting a role for IL-1β in early disease pathology. CSF IL-1β levels are elevated in NMOSD and associated with disease severity, supporting its involvement in NMOSD pathogenesis (98). IL-1β can act in concert with other inflammatory mediators to reinforce microglial activation. It promotes the production of pro-inflammatory cytokines, including TNF-α and IL-6, and chemokines such as CCL2 and CXCL10, thereby intensifying local inflammation (99). IL-1β may promote steroid resistance through activation of T helper 17 cells, further sustaining inflammatory responses (100). In astrocytes, IL-1β binding to IL-1 receptor activates NF-κB and MAPK

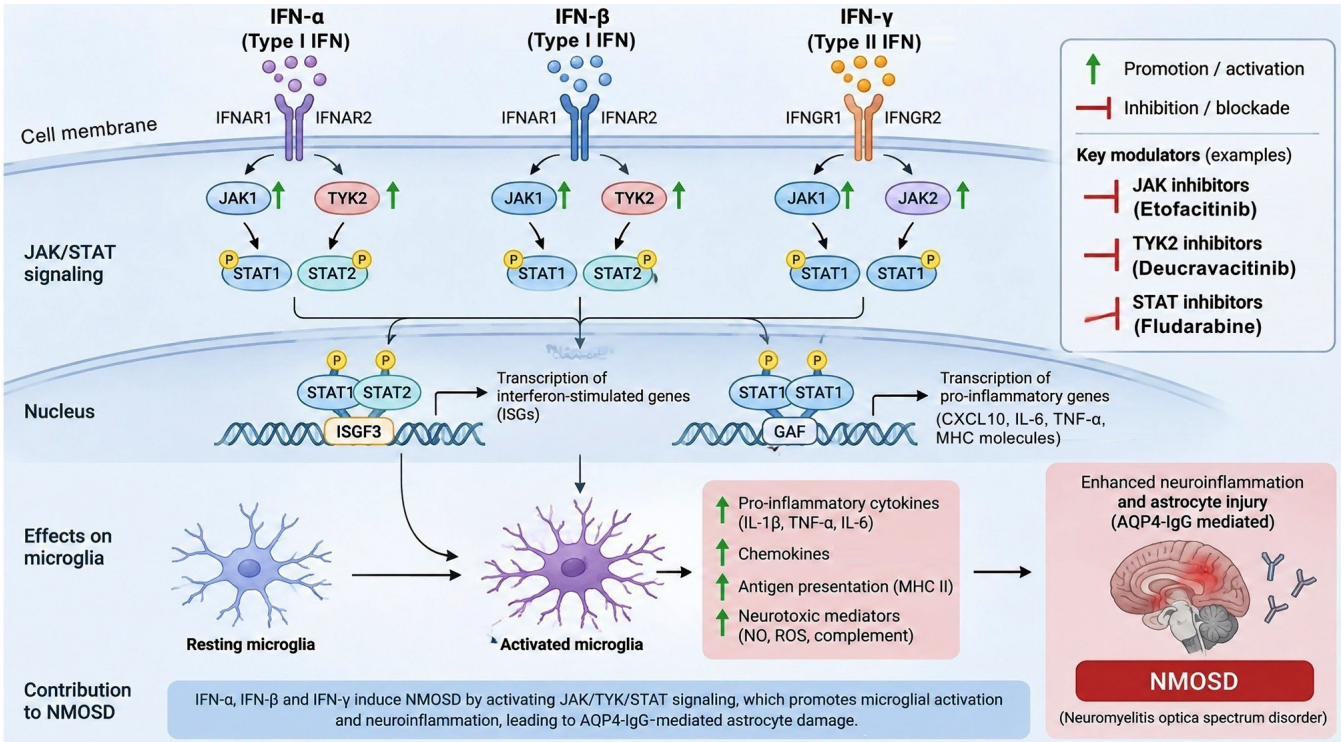


Figure 5. IFN induces NMOSD by regulating microglia. IFN binds IFNAR on microglia, activating JAK/STAT signaling and polarizing microglia toward a pro-inflammatory (M1-like) phenotype. Activated microglia release pro-inflammatory cytokines (IL-6, TNF-α, IL-1β), chemokines (CCL2, CXCL10) and ROS, which increase blood-brain barrier permeability and facilitate the entry of circulating AQP4-IgG and inflammatory cells into the CNS. Within the CNS, AQP4-IgG binds AQP4 on astrocyte end-feet, triggering complement-dependent astrocyte injury. Microglia-derived inflammatory mediators amplify complement-mediated astrocyte damage, leading to secondary oligodendrocyte injury, demyelination and neuronal loss, which contribute to NMOSD pathogenesis. AQP4-IgG, aquaporin-4 immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder; IFNAR1, IFN α/β receptor subunit 1; ISGF3, IFN-stimulated gene factor 3; GAF, γ-activated factor; CXCL10, C-X-C motif chemokine ligand 10; MHC II, major histocompatibility complex class II; NO, nitric oxide; ROS, reactive oxygen species; CNS, central nervous system; TYK, tyrosine kinase.

signaling, inducing the production of CXCL10 and CCL2. These chemokines facilitate the recruitment of peripheral neutrophils and monocytes to the CNS, thereby amplifying inflammation and contributing to IL-1β-associated neuronal and oligodendrocyte injury (101). This cytokine-driven cascade may promote NMOSD pathology. Beyond its inflammatory effects, IL-1β influences tissue repair and cellular differentiation (102). Increased BBB permeability facilitates peripheral immune cell infiltration, while experimental evidence linking IL-1β with caspase-1 activation, pyroptosis and synaptic dysfunction suggests additional mechanisms of neuronal injury (103). The relative contribution of these pathways to human NMOSD remains to be established. IL-1β may contribute to NMOSD by regulating immune cell activation and trafficking. It enhances T and other immune cell activation (104) and increases the expression of endothelial adhesion molecules, including vascular CAM-1 and ICAM-1, facilitating transendothelial immune cell migration and compromising BBB integrity (105). IL-1β may promote the production of AQP4-targeting autoantibodies, potentially reinforcing the autoimmune response characteristic of NMOSD. IL-1β can inhibit OPC proliferation and differentiation through the microRNA-202-3p/β-catenin/glioma-associated oncogene 1 pathway, decreasing the expression of myelin proteins such as MBP and impairing remyelination (106). In neurons, IL-1β induces calcium overload and mitochondrial ROS production, contributing to axonal degeneration (107). It may also act with TNF-α to increase neutrophil-derived MMP-9, disrupting myelin integrity and promoting neuronal injury (108). Evidence supporting a role for IL-1β in NMOSD is predominantly preclinical or based on cross-sectional observations (96). Its association with AQP4-IgG-mediated astrocyte injury and seronegative disease requires further clarification. Longitudinal biomarker studies and controlled evaluations of pathway-specific inhibition are needed to determine whether IL-1β serves as a reliable marker of disease activity or a viable therapeutic target.

Role of IFN in NMOSD via Microglia. IFNs regulate antimicrobial defense, antigen presentation and immune cell activation (109,110). Their effects in NMOSD vary according to IFN subtype, cell context and experimental model, with potential roles in either inflammatory amplification or maintenance of immune tolerance (111) (Fig. 5).

IFN-β. IFN-β, a type I IFN, is key for antiviral defense and is produced by various resident CNS cells, including microglia, astrocytes, neurons and endothelial cells (28). Microglia are responsive to type I IFN signaling in the CNS (112). Type I IFNs have been investigated in immune-mediated demyelinating disease, particularly MS (113), in which IFN-β exerts therapeutic effects by modulating immune cell functions (108). However, excessive or context-dependent type I IFN signaling may produce adverse effects. In a mouse model

of NMOSD lesions, IFN-β exacerbates NMO-like pathological changes, including increased AQP4 and glial fibrillary acidic protein expression and expansion of the $CD11c^+$ microglial subset (114). Transcriptomic analysis have identified notable type I IFN signatures in affected tissue and microglial populations (115). Microglial depletion attenuates these pathological changes without substantially altering IFN-β expression, supporting a key role for microglia as downstream responders to type I IFN signaling (116). Type I IFN-responsive microglia may contribute to the inflammatory milieu and aggravate CNS injury (116). In NMOSD, type I IFN may exacerbate disease by suppressing Th1 cell function (117).

Experimental findings, however, are not consistent across models (118,119). Type I IFN receptor deficiency improves outcomes in an induced lesion model, whereas IFN-β has limited effects in organotypic slice cultures and improved disease in an active-immunization rat model (120). These discrepancies may reflect differences between T cell- and antibody/complement-mediated mechanisms of injury. Both $CD11c^+$ and $CD11c^-$ microglia exhibit IFN response signatures, whereas IFN-β-associated expansion of $CD11c^+$ microglia is associated with greater pathology in induced lesions (121). Clinically, IFN-β treatment is associated with NMOSD exacerbations, including severe optic neuritis and myelitis (108,122-124). Proposed mechanisms include AQP4-IgG- and astrocyte injury-dependent microglial programming (125), altered STAT1/STAT2 signaling (Fig. 5) (126) and cooperation between astrocyte-derived DAMPs and microglial TLR4/NLRP3 activation (127). Th17 responses and AQP4-specific T cells may reinforce these pathways (108). IFN-β-responsive microglia produce IL-6, TNF-α and IL-1β (128), while IL-6 promotes Th17 differentiation and supports AQP4-IgG-producing plasmablasts (129), potentially accounting for effects opposite to those observed in MS (108,130). Other proposed mechanisms include increased C1q/C3 and Fcγ receptor expression (131), MMP-9/VEGF-associated BBB disruption (132) and CXCL9, CXCL10, and CCL2-mediated leukocyte recruitment (133). Microglial production of B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) may support autoreactive B cell survival, linking IFN signaling with persistent antibody production and astrocyte injury (134). The relative contribution of these pathways to human NMOSD lesions is uncertain.

The aforementioned findings support further investigation of the disease-specific IFN-microglia axis. Single-cell and spatial transcriptomic approaches may identify IFN-responsive microglial populations, whereas epigenetic analyses may clarify persistent inflammatory programming. CNS-penetrant JAK inhibitors and IL-6 antagonists are potential mechanistic interventions, although proposed CSF biomarkers, including IL-6 and BAFF, require independent validation.

IFN-β engages microglia through the cyclic GMP-AMP synthase/stimulator of interferon genes/type I interferon (IFN-I) signaling pathway and plays a paradoxical role in NMOSD (135), in contrast to its therapeutic effect on multiple sclerosis. Activated microglia-derived IFN-β promotes expansion and infiltration of AQP4-specific autoreactive T cells, exacerbates astrocyte injury and inflammatory pathology in NMOSD (133). Nevertheless, the functional heterogeneity of microglial subsets, species differences between rodent and human systems and stage-dependent effects of IFN signaling must be resolved before pathway modulation can be translated into NMOSD therapy.

IFN-γ. IFN-γ is the sole member of the type II IFN family and is a notable regulator of inflammatory responses. Dysregulated IFN-γ signaling is implicated in several autoinflammatory and autoimmune diseases such as MS and NMOSD, reflecting its dual immunostimulatory and immunoregulatory functions (136). Primarily produced by Th1, $CD8^+$ T and natural killer cells, IFN-γ promotes the polarization of microglia toward an inflammatory state (137). In NMOSD, IFN-γ is typically considered pathogenic due to its role in enhancing inflammatory responses and activating immune pathways targeting the CNS (Fig. 5) (108). Th1-derived IFN-γ promotes inflammatory microglial polarization via JAK1/STAT1 signaling, suppresses reparative markers such as arginase-1 and CD206 and increases the expression of pro-inflammatory cytokines and chemokines, thereby aggravating NMOSD-associated pathology (138). IFN-γ can activate the NLRP3 inflammasome through STAT1, intensifying microglial inflammatory responses (139). In addition, IFN-γ promotes $CD8^+$ T cell and monocyte recruitment through the CXCL10/CXCR3 pathway, facilitating inflammatory cell accumulation within lesions and potentially exacerbating optic nerve and spinal cord injury (140). IFN-γ may induce Fas expression on oligodendrocytes, enhancing FasL-mediated apoptotic signaling (141), while activating NADPH oxidase 2 in microglia and increasing superoxide production, which contribute to myelin injury (142). IFN-γ-associated BBB disruption may facilitate the entry of autoantibodies and peripheral immune cells into the CNS, thereby promoting demyelination and neuronal injury (143).

Recent findings, however, indicate that type I and II IFNs may exert opposing effects in $AQP4^{201-220}$-induced disease (138). In this model, type II IFN decreases disease incidence and severity, challenging the predominant view of IFN-γ as pathogenic (144). Further studies suggest IFN-γ contributes to immune tolerance toward AQP4, whereas its deficiency promotes autoimmune inflammation (108,145). Decreased IFN-γ signaling may increase IL-6 expression and enhance Th17 responses, thereby facilitating autoimmune activation (136). The effects of IFN-γ are associated with peripheral immune-tolerance mechanisms that regulate autoreactive B and T cell activation (146). These observations suggest IFN-γ may exert protective effects under specific immunological conditions and highlight the context dependence of IFN signaling in NMOSD.

The divergent effects of IFN-γ underscore the limitations of extrapolating findings across experimental models and disease stages. Regional microglial heterogeneity, species differences, interactions with other cytokines and limited access to human lesion tissue complicate interpretation. Spatial profiling and functional studies are needed to distinguish inflammatory effects within CNS lesions from peripheral mechanisms by which IFN-γ contributes to AQP4-specific immune tolerance.

Role of microglial lipid metabolism in NMOSD. Disrupted lipid metabolism promotes oxidative stress and neuroinflammation (147,148). Acyl-coA synthetase long chain family

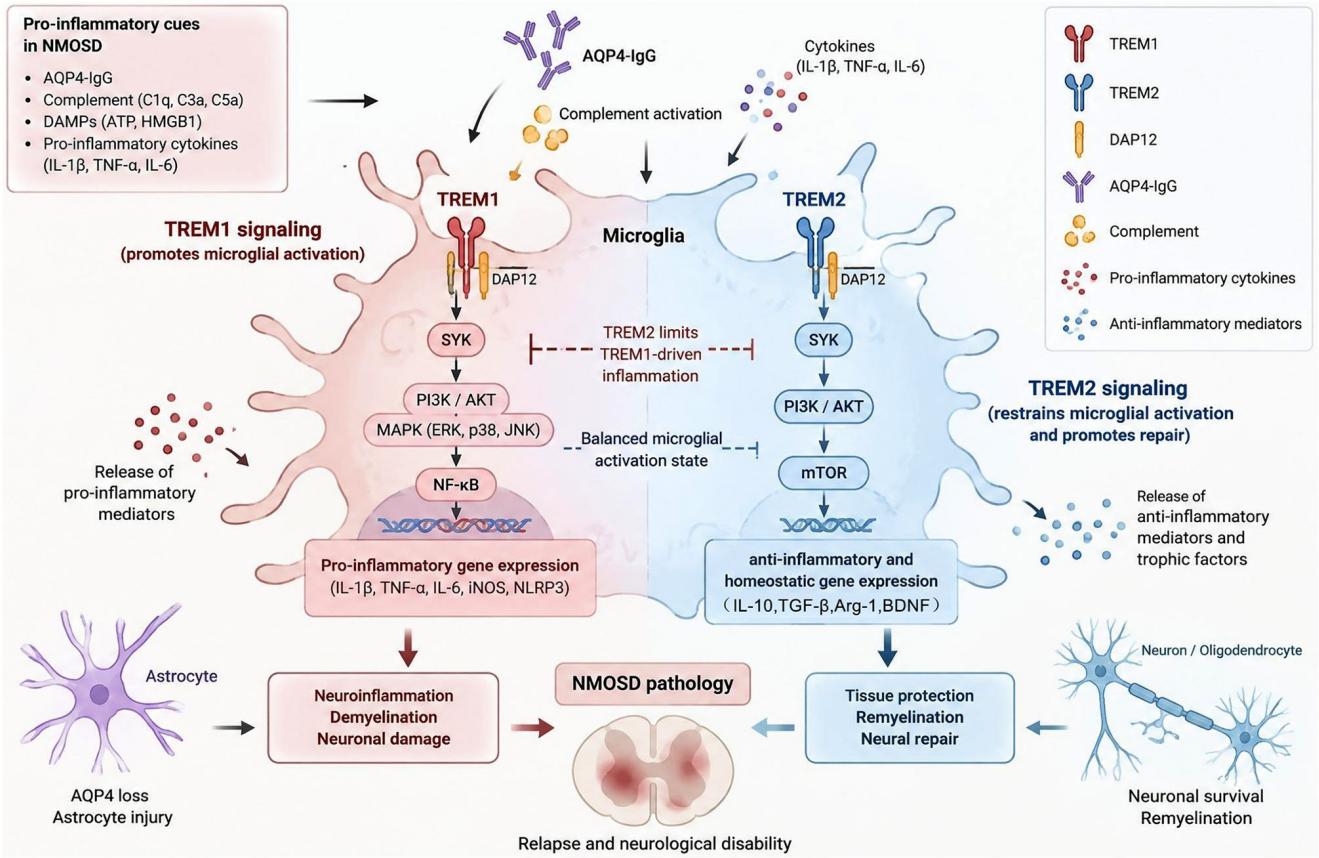


Figure 6. TREM induces NMOSD by regulating microglia. In NMOSD, binding of AQP4-IgG to astrocytic AQP4 activates the complement cascade, generating C3a/C5a and DAMPs that engage microglial TREM1 and TREM2. TREM1, signaling via DAP12, amplifies pro-inflammatory microglial activation and increases NF-κB-dependent production of TNF-α, IL-6, IL-1β and reactive oxygen species, thereby exacerbating blood-brain barrier disruption and neuroinflammation. TREM2 signaling via DAP12/DAP10 normally promotes phagocytosis of myelin debris and apoptotic cells and restrains excessive inflammation. However, in the chronic NMOSD milieu, sustained IFN-γ, IL-6 and complement activation suppress or dysregulate TREM2 expression and signaling, impairing microglial clearance and anti-inflammatory functions. The resulting TREM1/TREM2 imbalance drives persistent microglial activation, complement-mediated astrocyte injury, demyelination and neurodegeneration. NMOSD, neuromyelitis optica spectrum disorder; AQP4-IgG, aquaporin-4 immunoglobulin G; TREM2, triggering receptor expressed on myeloid cells 2; DAP12, DNAX-activation protein 12; SYK, spleen tyrosine kinase; PI3K, phosphoinositide 3-kinase; iNOS, inducible nitric oxide synthase; NLRP3, NOD-like receptor protein 3; Arg, arginase 1; BDNF, brain-derived neurotrophic factor; HMGB, high mobility group box 1.

member 4/vestigial like family member 4(VGLL4)-associated signaling is one example of lipid-dependent regulation of microglial function (149). In NMOSD, altered lipid handling may influence microglial response and myelin integrity (150), although much of the mechanistic evidence derives from other types of neurological disorders, particularly AD and MS (10). Lipid metabolic pathways should therefore be considered potential contributors to NMOSD pathology rather than established disease-specific mechanisms.

TREM. TREM family regulates inflammation, immune response and tissue homeostasis. TREM1 and TREM2 are of particular interest because they link myeloid cell activation with inflammatory signaling, phagocytosis and metabolic adaptation (151).

TREM1 signals through the adaptor protein tyrosine kinase-binding protein 12 (DAP12) to activate spleen tyrosine kinase (SYK) and NF-κB, promoting the release of IL-1β and TNF-α (152) (Fig. 6). TREM1 contributes to inflammatory signaling and macrophage polarization in numerous types of inflammatory disorder such as NMOSD, MS, and ankylosing spondylitis (153). By contrast, TREM2 recognizes lipid-associated signals and damaged cell material and supports microglial survival and phagocytosis (154). Through DAP12 and PI3K/Akt signaling, TREM2 enhances phagocytic activity and favors reparative microglial responses (Fig. 6) (155). Microglia in these states produce IL-10 and TGF-β, which restrain inflammation and support neuronal survival (156). Recognition of myelin debris activates SYK/PI3K-dependent lysosomal programs, facilitating debris processing in demyelinated regions and limiting the accumulation of potentially toxic lipid material (157). TREM2 may suppress TLR4/NF-κB signaling and IL-1β production, linking debris clearance with control of excessive inflammation (158). These functions are relevant to tissue repair because effective phagocytosis requires not only recognition and uptake of damaged material but also the metabolic capacity to process its lipid content (159). However, TREM2 expression alone does not define a uniform reparative state and its functional effects depend on lesion stage and the surrounding inflammatory milieu.

TREM2 is a transmembrane receptor predominantly expressed by microglia and serves as an important regulator of cell metabolism and inflammatory responses through extracellular lipid sensing (160). In AD, TREM2 signaling enhances

the metabolic adaptability and survival of microglia, thereby shaping the response to amyloid-β plaques (161). TREM2 is implicated in other neurodegenerative disease; in AD and MS, it contributes to the balance between protective and detrimental inflammatory responses (162). Its effects extend to lipid metabolism, through which TREM2 maintains cell energy homeostasis and functional adaptation (163). TREM2 deficiency causes metabolic abnormality characterized by autophagosome accumulation and impaired mitochondrial function (20). TREM2 regulates mTOR signaling, thereby influencing microglial metabolism and autophagy, processes that are essential for cellular energy production and biosynthetic activity (164). In NMOSD, TREM2 deficiency impairs microglial response and exacerbates demyelinating injury (165). Acute TREM2 inhibition decreases the population of v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog B-expressing microglia and impairs remyelination (166). Loss of this microglial population is associated with decreased oligodendrocyte generation, an essential process for myelin restoration (167). During NMOSD pathology, TREM2 expression is associated with microglial aggregation, proliferation and phagocytic activity (157). TREM2 deficiency aggravates tissue injury and neurological dysfunction while decreasing microglial accumulation and impairing myelin debris clearance (157), supporting a neuroprotective role for TREM2 during demyelination. TREM2-activated microglia promote OPC differentiation into mature oligodendrocytes through the release of platelet-derived growth factor BB, while enhancing the synthesis and secretion of myelin proteins such as proteolipid protein and MBP, thereby facilitating remyelination (168). TREM2-dependent debris clearance and secretion of NFs, including BDNF and glial cell line-derived neurotrophic factor (GDNF), may also contribute to extracellular matrix remodeling, reduce glial scar formation and provide a permissive environment for OPC migration and remyelination (169). TREM2 is associated with microenvironmental changes in NMOSD. Elevated CSF levels of soluble TREM2 (sTREM2) are associated with neuronal injury and other neuroinflammatory markers (neurofilament light chain, intercellular adhesion molecule 1 and IFN-γ) in patients with NMOSD (170). sTREM2 may influence microglial dysfunction through NF-κB signaling, potentially contributing to disease progression (31,171). In animal models of NMOSD, TREM2 deficiency decreases microglial phagocytic activity and myelin debris degradation, supporting its role in maintaining microglial function during demyelination (165,166,172). The interaction between TREM2 and apolipoprotein (Apo)E is key for microglial activation and lipid handling. A biphasic TREM2 response is associated with microglial state transitions, raising the possibility that TREM2 may support inflammatory responses during early inflammation while promoting repair and inflammation resolution at later stages (173). TREM1 may similarly regulate microglial activity through interconnected inflammatory pathways, but its specific contribution to NMOSD is poorly defined. TREM2 signaling in AQP4-IgG-mediated astrocyte injury and seronegative NMOSD is incompletely characterized. Larger longitudinal cohorts are needed to determine associations between TREM2 expression, sTREM2 levels, genetic variation, disease activity and prognosis. Whether TREM2 activation or inhibition is therapeutically beneficial may depend on disease stage and the specific microglial function being targeted.

ApoE. ApoE is a major regulator of lipid and cholesterol transport in the CNS. Its three notable alleles, ε2, ε3 and ε4, differ in their effects on lipid handling and disease susceptibility, with ε4 associated with late-onset AD (174,175). These established functions in lipid metabolism and neuroinflammation provide a rationale for investigating ApoE in NMOSD, although genetic associations established in AD cannot be directly extrapolated to optic-spinal autoimmunity.

ApoE modulates CNS inflammatory responses in experimental MS (176) and may influence NMOSD through lipid metabolic pathways (Fig. 7) (177). Studies of astrocyte-derived extracellular vesicles and mouse models implicate the APOE/low density lipoprotein receptor-related protein 1 pathway in limiting microglial reactivity, complement activation and tissue injury (178,179). ApoE serves as a ligand for TREM2 and supports microglial survival, lesion-associated clustering and transition toward DAM states, although these responses may have inflammatory consequences (31). ApoE interactions with C1q and C3b may influence opsonization (180), whereas ATP-binding cassette transporter A1 (ABCA1)/ABCG1-dependent cholesterol efflux facilitates the removal of damaged membrane lipids (181). ApoE regulates T cell proliferation and Th1/Th17 response (182), potentially influencing the inflammatory milieu in NMOSD (183). Following astrocyte injury, increased microglial ApoE expression may partially compensate for impaired astrocytic lipid support and facilitate tissue repair (184). Associations between ApoE4 and ischemic optic nerve injury provide an additional potential mechanism but do not establish an equivalent effect in NMOSD (185). The identification of APOE/TREM2/lipoprotein lipase-expressing microglial subsets (186), alterations in CSF or serum ApoE levels (187) and early ApoE/TREM2 upregulation in experimental NMOSD (188) connect this pathway with microglial phagocytosis and lipid metabolism. ApoE/TREM2 functional and clinical value, however, requires validation.

The timing and direction of APOE/TREM2 signaling in NMOSD are uncertain. Independent human cohorts should examine associations between ApoE genetic variation, pathway activity, relapse risk and disease severity, including in seronegative NMOSD. Stage-specific therapeutic strategies require evidence that modifying lipid handling enhances debris clearance and repair without sustaining detrimental inflammatory responses. TREM2/DAP12/Syk signaling connects recognition of damaged material with phagocytosis, metabolic adaptation and regulation of complement and inflammatory pathways (Fig. 8) (189). Its protective capacity may be insufficient under intense AQP4-IgG-driven inflammation (189). AQP4-IgG-triggered complement cascade and rapid infiltration of neutrophils/eosinophils generate tissue destruction far exceeding the pathway's physiological clearance and anti-inflammatory threshold; the highly oxidative NMOSD lesion microenvironment induces excessive TREM2 ectodomain shedding, depleting functional membrane TREM2 and abrogating downstream Syk signaling; and the pathway's myeloid-restricted regulatory scope cannot directly counteract the core pathological drivers of AQP4-IgG-mediated astrocyte

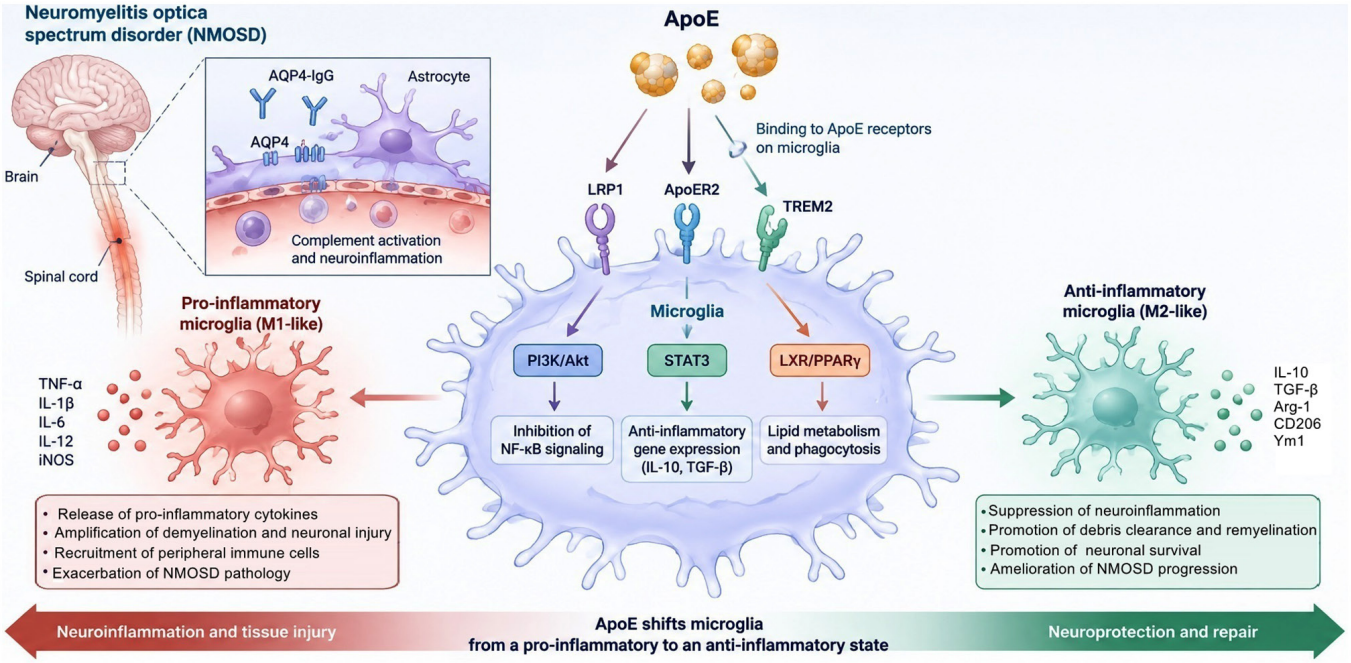


Figure 7. ApoE regulates microglia in NMOSD. In NMOSD, AQP4-IgG4 binds to AQP4 on astrocytes, activating complement and triggering neuroinfiammation. ApoE, secreted by glial cells and neurons, binds its receptors on microglia, including LRP1, ApoER2 and TREM2, and activates downstream signaling pathways such as PI3K/Akt, STAT3 and LXP/PPARγ. These pathways inhibit NF-κB-mediated inflammatory responses, promote anti-inflammatory gene expression (IL-10, TGF-β) and enhance lipid metabolism and phagocytosis, thereby driving microglia from a pro-inflammatory (M1-like) to an anti-inflammatory (M2-like) phenotype. ApoE suppresses neuroinflammation, facilitates debris clearance and remyelination, supports neuronal survival and may ameliorate the progression of NMOSD. ApoER, apolipoprotein E receptor; NMOSD, neuromyelitis optica spectrum disorder; AQP4-IgG, aquaporin-4 immunoglobulin G; PI3K, phosphoinositide 3-kinase; LXR, liver X receptor; PPARγ, peroxisome proliferator-activated receptor γ; iNOS, inducible nitric oxide synthase; TREM, triggering receptor expressed on myeloid cells; Arg, arginase; LRP, low-density lipoprotein receptor-related protein; Ym, chitinase-like protein 3.

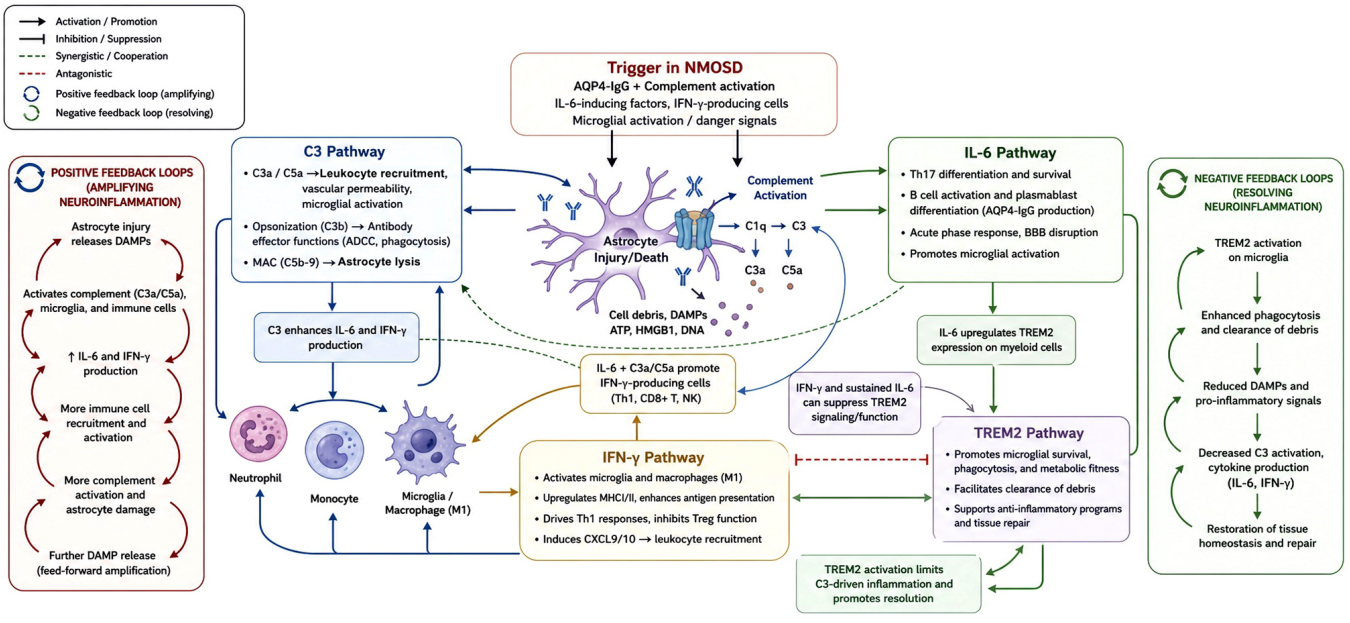


Figure 8. Crosstalk between C3, IL-6, IFN-γ and TREM2 in NMOSD. In NMOSD, binding of AQP4-IgG to astrocytic AQP4 activates the classical complement cascade, leading to C3 cleavage and generation of C3a and C3b. C3a acts via C3aR on microglia and macrophages, promoting their activation and release of IL-6. IL-6 amplifies neuroinflammation, enhances T cell effector function and contributes to increased production of IFN-γ by infiltrating Th1 cells. IFN-γ activates microglia via IFNGR/JAK/STAT signaling, stimulating pro-inflammatory cytokine release and altering microglial phagocytic and homeostatic functions. TREM2 on microglia serves as a key regulator of phagocytosis and inflammatory restraint; chronic exposure to IFN-γ and IL-6 suppresses or dysregulates TREM2 signaling, impairing clearance of myelin debris and apoptotic cells. Decreased TREM2-mediated control exacerbates complement-driven injury and sustains microglial activation, creating a feed-forward loop that amplifies astrocyte damage, demyelination and neurodegeneration in NMOSD. NMOSD, neuromyelitis optica spectrum disorder; DAMP, damage-associated molecular pattern; C3aR, complement component 3a receptor; MAC, membrane attack complex; ADCC, antibody-dependent cell-mediated cytotoxicity; HMGB1, high mobility group box 1; Th1, T helper; NK, natural killer; TREM2, triggering receptor expressed on myeloid cells 2; AQP4-IgG, aquaporin-4 immunoglobulin G; BBB, blood-brain barrier; IFNGR, IFN γ receptor; MHC, major histocompatibility complex; Treg, T regulatory.

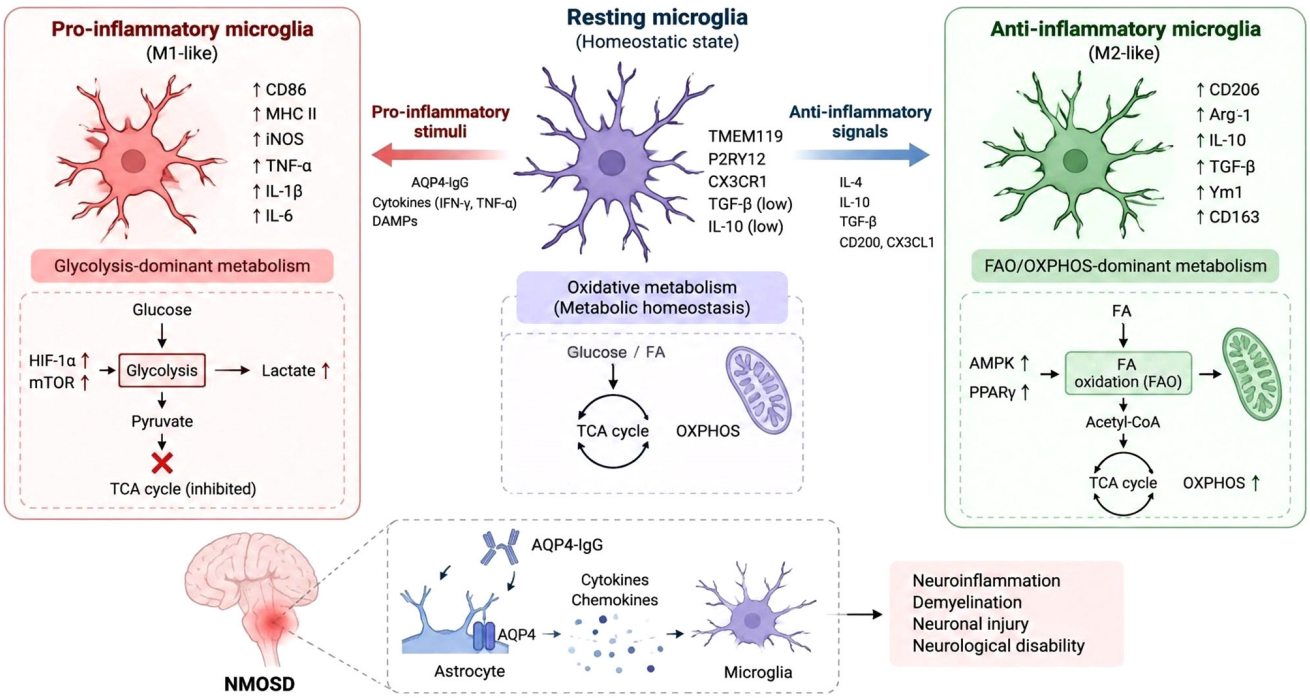


Figure 9. Metabolic reprogramming drives microglial functional polarization in NMOSD. In the resting state, microglia maintain homeostasis through balanced oxidative metabolism with an active TCA cycle and OXPHOS. In NMOSD, AQP4-IgG and inflammatory stimuli (IFN-γ, TNF-α, DAMPs) trigger metabolic reprogramming toward glycolysis-dominant metabolism, characterized by HIF-1α and mTOR activation, leading to pro-inflammatory (M1-like) microglial polarization and production of inflammatory mediators. Anti-inflammatory signals (IL-4, IL-10, TGF-β, CD200, CX3CL1) promote fatty acid oxidation and OXPHOS through AMPK and PPARγ, driving anti-inflammatory (M2-like) microglial polarization and release of immunoregulatory factors. Microglial metabolic reprogramming contributes to neuroinflammation, demyelination and neurological disability in NMOSD. MHCII, major histocompatibility complex class II; Arg-1, arginase 1; iNOS, inducible nitric oxide synthase; Ym1, chitinase-like protein 3; DAMP, damage-associated molecular pattern; TMEM119, transmembrane protein 119; P2RY12, P2Y purinoceptor 12; CX3CR1, C-X3-C motif chemokine receptor 1; OXPHOS, oxidative phosphorylation; TCA, tricarboxylic acid cycle; AQP4-IgG, aquaporin-4 immunoglobulin G; CX3CL1, C-X3-C motif chemokine ligand 1; AMPK, AMP-activated protein kinase; PPARγ, peroxisome proliferator-activated receptor γ; NMOSD, neuromyelitis optica spectrum disorder; FAO, fatty acid oxidation; HIF, hypoxia-inducible factor.

cytotoxicity and persistent autoantibody production. Defining the conditions under which TREM2 signaling supports recovery and determining whether genetic or metabolic factors modify these effects in NMOSD is key for evaluating its therapeutic potential.

Metabolic reprogramming. Metabolic reprogramming is a key determinant of microglial functional state and has emerged as an important focus in neuroscience (Fig. 9) (190,191). Pro-inflammatory microglia typically exhibit increased glycolytic metabolism, whereas reparative microglia rely more heavily on oxidative phosphorylation (OXPHOS) to meet their energetic demands (192). These metabolic states are coupled to microglial function: Glycolysis provides rapid ATP production and biosynthetic intermediates to support inflammatory activation, whereas OXPHOS provides sustained energy for phagocytosis, tissue repair and homeostatic functions. The mTOR signaling pathway is a key metabolic regulator that connects cellular energy status with microglial functional phenotype (193). Modulation of mTOR-associated metabolic pathways promotes the transition from inflammatory toward reparative microglial states and may alleviate neuroinflammation and neurodegenerative pathology (193). Lipid metabolism is key for CNS homeostasis and myelin maintenance; its disruption can increase myelin vulnerability and contribute to neurological dysfunction (194). In NMOSD, impaired lipid handling may further compromise myelin integrity and nerve conduction. Microglial metabolic reprogramming may contribute to remyelination failure in NMOSD through interconnected alterations in energy metabolism, inflammatory state persistence and intercellular signaling (195). In acute NMOSD lesions, AQP4-IgG-mediated astrocyte injury activates microglial purinergic receptor P2X 7 (P2X7) and RAGE) receptors, promoting glycolytic metabolism via NF-κB and hypoxia-inducible factor (HIF)-1α signaling (196,197). Increased glycolytic activity and lactate accumulation may impair OPC differentiation and enhance inflammatory gene expression through lactylation, thereby reinforcing local inflammation (198). At later stages, mitochondrial dysfunction and impaired OXPHOS may decrease ATP availability and compromise the efficient clearance of myelin debris, limiting OPC maturation (199). Persistent metabolic imbalance may stabilize a glycolysis-dependent inflammatory state through epigenetic mechanisms, including histone lactylation and DNA methylation, restricting the transition toward an OXPHOS-supported reparative phenotype (200). Metabolic reprogramming may alter microglia-oligodendrocyte and microglia-astrocyte communication. Lactate released by glycolytic microglia activates G protein-coupled receptor 81 on OPCs and inhibits differentiation through ERK and PI3K/Akt signaling, whereas CXCL10/CXCR3 signaling between microglia and reactive astrocytes may promote glial scar formation and restrict OPC migration (201,202). Together, these metabolic and intercellular alterations may

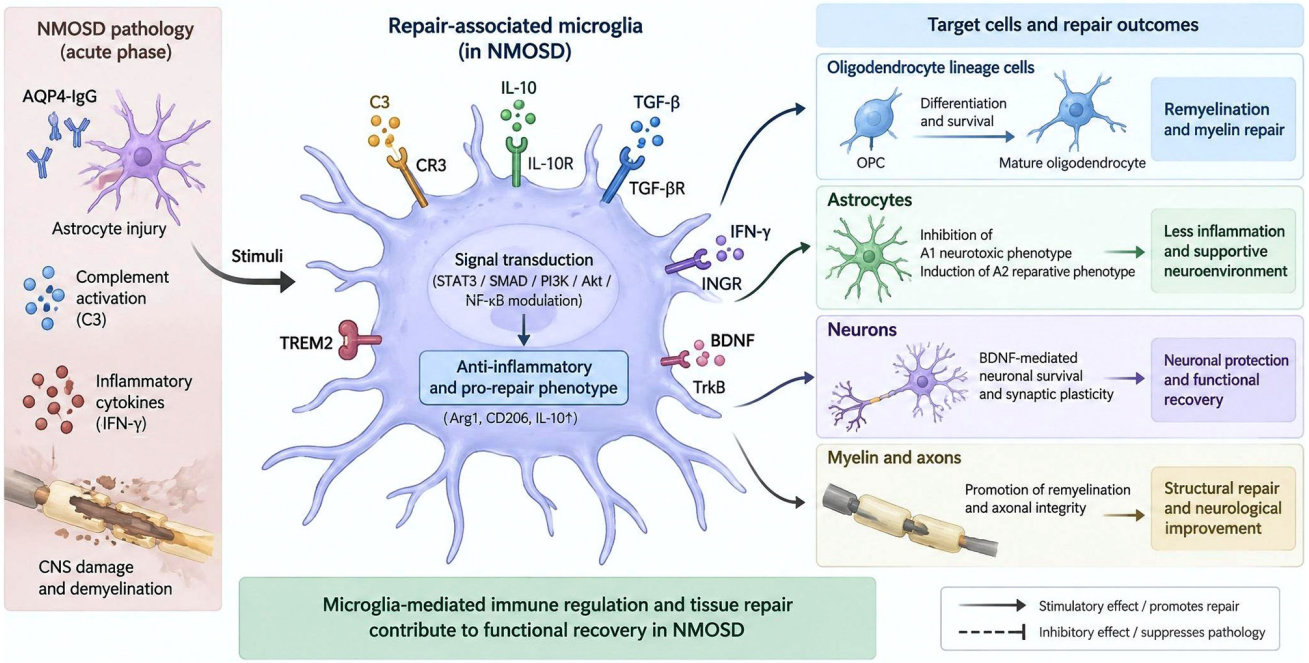


Figure 10. Mechanisms of microglia-mediated promotion of repair in NMOSD. During the resolution phase of NMOSD, microglia shift from a pro-inflammatory state toward a reparative phenotype. TREM2 signaling is upregulated and enhances microglial phagocytosis of C3-opsonized myelin debris and apoptotic cells, facilitating clearance of complement-damaged material. This TREM2-dependent phagocytosis promotes lipid metabolism and prevents accumulation of myelin debris that inhibits remyelination. Microglial responses to IFN-γ and IL-6 are attenuated, reducing sustained pro-inflammatory activation. Reparative microglia secrete anti-inflammatory cytokines, such as IL-10 and TGF-β, which restrain residual T cell and macrophage activity, and produce neurotrophic factors, including BDNF, IGF-1 and GDNF, that support OPC survival and differentiation. These microglial functions contribute to astrocyte recovery, blood-brain barrier repair and partial remyelination in NMOSD. NMOSD, neuromyelitis optica spectrum disorder; AQP4-IgG, aquaporin-4 immunoglobulin G; CNS, central nervous system; TREM2, triggering receptor expressed on myeloid cells 2; CR3, complement receptor 3; Arg-1, arginase 1; PI3K, phosphoinositide 3-kinase; INGR, IFN-γ receptor; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin-related kinase receptor B; IGF, insulin-like growth factor; GDNF, glial cell line-derived neurotrophic factor; OPC, oligodendrocyte precursor cell.

establish a persistent inflammatory microenvironment that limits remyelination in NMOSD. Direct characterization of microglial metabolism in NMOSD remains limited, with evidence derived from MS, AD and spinal cord injury models (191,203). Current experimental systems incompletely reproduce AQP4-IgG-mediated astrocytopathy (30,204), while lesion-stage heterogeneity (202,206), static metabolic measurement (207), difficulty in distinguishing resident microglia from infiltrating macrophages (208) and limited access to human lesion tissue (209) constrain mechanistic interpretation. Future studies should stratify NMOSD by disease phenotype and lesion stage and distinguish NMOSD from MOGAD rather than assuming shared metabolic mechanisms (210). Single-cell and spatial profiling, metabolic-flux analysis, induced pluripotent stem cell (iPSC)-derived models, and neurovascular co-culture systems may provide more direct evidence of cell-specific metabolic changes. Candidate interventions include itaconate derivatives, HIF-1α modulation, AMPK activation, PPARγ agonism and TREM2 modulation (211). Their therapeutic potential depends on disease stage, cell specificity and compatibility with existing immunotherapies, which require investigation in NMOSD.

4. Mechanisms of microglia promotion of repair in NMOSD

Microglia contribute to tissue repair and recovery in addition to their roles in acute inflammatory injury (Fig. 10; Table IV) (165,212-223). TREM2-, CR3- and MER proto-oncogene tyrosine kinase-mediated phagocytosis facilitates the removal of myelin and cell debris that impede tissue regeneration (165,224-227). IL-33/growth stimulation expressed gene 2, TGF-β/Smad3 and PPARγ signaling may promote homeostatic or reparative microglial states and support oxidative metabolism, although these phenotypes are heterogeneous and context-dependent (228-230). Microglia release trophic mediators, including BDNF, GDNF, IGF-1, fibroblast growth factor 2, ciliary neurotrophic factor and stromal cell-derived factor 1(SDF-1), which support neuronal and glial survival and recovery (231-235). Efficient debris clearance, OPC recruitment and metabolic support may facilitate oligodendrocyte maturation and remyelination (235,236). Microglia may contribute to neurovascular repair by promoting endothelial junction restoration, supporting pericyte function, limiting MMP-9 activity and facilitating recovery of astrocytic end-feet (237,238). Through synaptic pruning and trophic support for axonal growth, microglia may participate in circuit remodeling and functional recovery (239). In addition, microglia modulate adaptive immunity through regulatory T cell (Treg) recruitment and signals that regulate B cell responses (240). These reparative functions are shaped by interactions with other immune cells: Th1/Th17-derived cytokines typically favor inflammatory activation (241), whereas Th2/Treg-associated signals may promote reparative responses (242,243). Direct cell-cell contact provides an additional mode of reciprocal regulation between microglia

Table IV. Regulators of microglial phenotypes and their roles in neuromyelitis optica spectrum disorder.

Authors, year	Key regulators	Mechanistic pathways	Roles in NMOSD	(Refs.)
A, Pro-inflammatory (M1-like)				
Liu *et al*, 2025; Kumar *et al*, 2021	IL-1β, TNF-α, IFN-γ	NF-κB, JAK/STAT, MAPK activation	Drive microglial proliferation and pro-inflammatory cytokine release (IL-6, CXCL10), exacerbate astrocyte lysis and demyelination	(212,213)
Given *et al*, 2025	AQP4-IgG immune complexes	Fcγ receptor signaling, complement cascade activation	Trigger microglial chemotaxis and phagocytosis of damaged astrocytes, amplifying lesion formation	(214)
Fan *et al*, 2021	Myelin debris, ATP, HMGB1	TLR4, P2X7, RAGE receptor activation	Initiate sterile inflammation at lesion sites, promoting neurotoxic microglial activation	(215)
Tastan *et al*, 2025; Asl *et al*, 2025	miR-155, lncRNA NEAT1	Post-transcriptional regulation of anti-inflammatory gene expression	Maintain pro-inflammatory phenotype by silencing M2-associated genes (Arg-1, IL-10)	(216,217)
B, Pro-repair (M2-like)				
Cao *et al*, 2025	L-4, IL-13, IL-10	STAT6, PI3K/Akt activation	Induce microglial polarization toward reparative phenotype, releasing anti-inflammatory mediators	(218)
You *et al*, 2023; Zhao *et al*, 2019	TREM2, CD200R	Syk, PI3K signaling	Enhance phagocytosis of myelin debris and apoptotic cells, supporting tissue repair	(165,219)
Ma *et al*, 2026; Wang *et al*, 2024	miR-124, PPAR-γ	Transcriptional regulation of pro-inflammatory gene suppression	Shift microglial phenotype from pro-inflammatory to reparative, promoting remyelination	(220,221)
Zhou *et al*, 2025; Jin *et al*, 2023	Estrogen, ketone bodies	ERα/β signaling, AMPK/PGC-1α metabolic pathway	Modulate microglial metabolic state, enhancing oxidative phosphorylation and repair capacity	(222,223)

AQP4-IgG, aquaporin-4 immunoglobulin G; HMGB1, high mobility group box 1; miR-155, microRNA-155; lncRNA NEAT1, long non-coding RNA nuclear-enriched abundant transcript 1; TREM2, triggering receptor expressed on myeloid cells 2; TLR4, toll-like receptor 4; P2X7, P2X purinoceptor 7; RAGE, receptor for advanced glycation end products; Syk, spleen tyrosine kinase; PI3K, phosphoinositide 3-kinase; ER, estrogen receptor; AMPK, AMP-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1 α; CSF1R, colony-stimulating factor 1 receptor; Arg-1, arginase 1.

and neighboring cells (244). Therapeutic strategies should preserve beneficial debris clearance and trophic function while limiting cytotoxic activation. However, mechanisms established in other types of CNS injury should not be regarded as definitive restorative pathways in human NMOSD without disease-specific validation. Repair-oriented studies face many of the same model and species limitations as investigations of inflammatory microglial responses. Phagocytosis and synaptic pruning exert beneficial or detrimental effects depending on their target, timing and cellular context (245). Human-relevant and spatially resolved studies should therefore assess functional recovery alongside inflammatory and repair-associated markers and distinguish protective microglial responses from excessive removal of viable neural elements.

5. Targeting microglia in NMOSD treatment strategies

Potential microglia-directed strategies include colony-stimulating factor 1 receptor inhibition, modulation of NF-κB/NLRP3 signaling, disruption of C3-C3aR or

Table V. Microglia-targeting strategies in NMOSD.

Authors, year	Strategy	Targets/agents	Advantages	Disadvantages	Research progress	Clinical prospects	(Refs.)
Chadarevian *et al*, 2023	Inhibition of microglial survival/ proliferation	CSF1R inhibitors (PLX3397, BLZ945)	Rapid depletion of activated microglia; strong anti-inflammatory effect	Long-term use leads to microglial loss, impaired immune surveillance and tissue repair; potential effects on peripheral monocytes	Preclinical studies in NMO/EAE models show decreased lesion severity; no NMOSD clinical trials	Potential short-term adjunct in acute phase; long-term safety is a notable concern	(246,247)
Martín-Colomo *et al*, 2026	Modulation of inflammatory signaling pathways	NF-κB, JAK/STAT and NLRP3 inflammasome inhibitors	Preserves microglial viability; decreases pro-inflammatory cytokine release (TNF-α, IL-1β, IL-6)	Limited specificity; systemic side effects; variable blood-brain barrier penetration	Preclinical data support efficacy in EAE (NLRP3 inhibitors); clinical evidence in NMOSD lacking	May serve as adjuncts with other immunomodulators; need brain-targeted formulations	(248)
Gong *et al*, 2026	Blockade of microglia-astrocyte crosstalk	C3aR antagonists, anti-IL-1α, anti-TNF, anti-C1q	Targets the key pathogenic loop in NMOSD; disrupts astrocyte-to-microglia activation and microglia-to-astrocyte toxicity	Complement/cytokine blockade may increase infection risk; potential interference with physiological phagocytosis	C3aR antagonists show benefit in NMO animals; no clinical trials in NMOSD	May work with terminal complement inhibitors (eculizumab); needs long-term safety evaluation	(249)
Hu *et al*, 2026.	Promotion of anti-inflammatory/ reparative microglial phenotype	TREM2 and PPARγ agonists, IL-4/IL-13, M2-polarizing agents	Physiologically oriented; promotes debris clearance and tissue repair	May be insufficient alone in acute severe inflammation; TREM2 agonists have shown mixed results in other neurodegenerative disease	TREM2 agonists are in clinical trials for Alzheimer's disease; no NMOSD-specific studies	Suitable for recovery phase or relapse prevention; requires NMOSD-specific validation	(251)
Brown *et al*, 2026; Hu *et al*, 2026.	Inhibition of microglial phagocytosis/ oxidative stress	P2X7 receptor antagonists, NADPH oxidase inhibitors, ROS scavengers	Decreases oxidative damage and excessive phagocytosis of viable tissue	Impaired clearance of myelin/necrotic debris may delay repair	P2X7 antagonists and NOX inhibitors decrease injury in neuroinflammation models; no NMOSD clinical data	Potential neuroprotective adjunct; needs balance between phagocytosis and tissue preservation	(252,253)

CSF1R, colony-stimulating factor 1 receptor; EAE, experimental autoimmune encephalomyelitis; NMOSD, neuromyelitis optica spectrum disorder; NLRP3, NOD-like receptor protein 3; C3aR, complement component 3a receptor; P2X7, P2X purinoceptor 7; ROS, reactive oxygen species; NOX, NADPH oxidase.

Table VI. Development of microglial research in NMOSD.

Authors, year	Research phase	Key questions	Dominant Techniques	Major Findings	Limitations	Future directions	(Refs.)
Saadoun *et al*, 2010	Phase 1: Histopathological era (2000s–2010s)	Activation and distribution of microglia in NMOSD lesions remain to be characterized	Immunohistochemistry (Iba-1, CD68, MHC-II); light/electron microscopy	Microglia are extensively activated in perivascular and periaqueductal lesions; amoeboid morphology indicates strong activation; macrophage-like transformation observed	Descriptive only; no functional or molecular characterization; cannot distinguish microglia from infiltrating macrophages reliably	Re-analyze archived NMOSD tissues using spatial transcriptomics and multiplex immunohistochemistry to retrospectively identify microglial subsets and spatial niches; develop more specific markers to distinguish resident microglia from monocyte-derived macrophages	(258)
Wingerchuk *et al*, 2025	Phase 2: Molecular & Cytokine Era (2010s)	Cytokines and signaling pathways used by microglia in NMOSD remain to be fully defined.	RT-PCR, ELISA, Western blot, flow cytometry (bulk); *in vitro* cell culture	Microglia produce pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) in response to AQP4-IgG; complement pathway (C1q, C3) implicated; NF-κB and NLRP3 inflammasome activation identified	Bulk techniques mask cellular heterogeneity; *in vitro* models may not reflect *in vivo* complexity; cannot distinguish disease stages	Validate key pathways in human samples at single-cell resolution; develop more physiologically relevant models; investigate non-canonical inflammasome and complement-independent mechanisms	(259)
Jiang *et al*, 2025	Phase 3: Single-Cell & Omics Era (2018–present)	Microglial subsets present in NMOSD and their dynamic changes across disease stages remain to be fully defined	Single-cell RNA-seq (scRNA-seq), single-nucleus RNA-seq (snRNA-seq), CyTOF, spatial transcriptomics, proteomics, metabolomics	Microglia exhibit significant heterogeneity with distinct transcriptional states; identified disease-associated microglia (DAM) signatures; ApoE and TREM2 show biphasic expression; metabolic reprogramming (glycolysis ↔ OXPHOS) linked to functional states	High cost and technical complexity; snRNA-seq may miss cytoplasmic transcripts; limited human longitudinal samples; functional validation of identified subsets lacking	Conduct longitudinal single-cell profiling across disease stages and treatment courses; integrate spatial and single-cell data to localize pathogenic subsets; perform functional screens (*in vivo* perturbations) to validate candidate genes; combine multi-omics (transcriptomics,	(260)

Table VI. Continued.

Authors, year	Research phase	Key questions	Dominant Techniques	Major Findings	Limitations	Future directions	(Refs.)
						metabolomics, epigenomics) to decode metabolic reprogramming and its regulators	
Elosua-Bayés *et al*, 2026	Phase 4: Functional and Therapeutic Era (current and future)	Unknown which microglial subsets are pathogenic vs. protective and whether they can be therapeutically targeted.	Conditional knockout models, lineage tracing, cell-specific depletion (CSF1R inhibitors), metabolic flux analysis, organoids, advanced imaging (two-photon)	Emerging evidence that targeting microglial metabolism (e.g., glycolysis inhibition) or specific receptors (TREM2, ApoE) modulates disease severity; stage-specific therapeutic windows proposed	Need for NMOSD-specific animal models; human relevance of murine findings uncertain; long-term safety of microglial modulation unknown	Develop robust NMOSD animal models (e.g., AQP4 autoimmunity models) for preclinical testing; evaluate metabolic modulators (2-DG, metformin) and TREM2/ApoE pathway agents in human-relevant systems; establish patient-derived organoid or organ-on-chip platforms for personalized drug screening; define optimal therapeutic time windows and companion biomarkers.	(79)

NMOSD, neuromyelitis optica spectrum disorder; C3a/C3aR, complement component 3a receptor; TREM2, triggering receptor expressed on myeloid cells 2; ApoE, aquaporin-4 immunoglobulin G; Apo, apoplipoprotein.

Table VII. Limitations and future perspectives of microglia in neuromyelitis optica spectrum disorder research.

Authors, year	Key limitations	Challenges	Future perspectives	(Refs.)
A, Model system				
Huang *et al*, 2024;	Species differences between rodents and humans	Rodent microglia do not fully recapitulate human transcriptional profiles and functional responses	Develop humanized mouse models (iPSC-derived microglia engraftment, CRISPR gene editing)	(261)
Seok *et al*, 2023	Incomplete disease modeling	Fail to replicate chronic, relapsing NMOSD pathology and persistent microglial activation	Establish chronic relapsing models with persistent microglial activation	(262)
B, Mechanistic understanding				
Li *et al*, 2021	Oversimplified phenotype classification	M1/M2 framework ignores microglial heterogeneity and dynamic phenotype shifts during disease progression	Use single-cell/spatial transcriptomics to identify microglial subpopulations	(12)
Liu *et al*, 2025	Unclear cell-cell interaction mechanisms	Signaling pathways between microglia and astrocytes, neurons or immune cells in NMOSD are not fully elucidated	Integrate multi-omics to determine epigenetic regulation and signaling pathways	(188)
C, Technical methods				
Zhang *et al*, 2024;	Limited *in vivo* imaging resolution	Limited *in vivo* imaging resolution	Advance high-resolution imaging (two-photon microscopy, novel PET radiotracers)	(263)
Xu *et al*, 2025	Single-cell analysis for NMOSD microglia research is constrained by limited access to active-stage human lesion biopsies, sample processing-induced artificial activation artifacts, low recovery of rare pathogenic microglial subsets, poor detection of low-abundance signaling molecules, missing spatial context of AQP4-associated lesions, inconsistent cross-study annotation standards, high cost that blocks large-cohort validation, and the inability to directly distinguish causal from correlative microglial pathological signatures.	Single-cell analysis for NMOSD microglia research faces key challenges including restricted access to active-stage human lesion biopsies, tissue dissociation-induced artificial activation artifacts, low recovery of rare pathogenic microglial subsets, insufficient detection of low-abundance signaling molecules, loss of spatial lesion context, inconsistent cross-study cell annotation standards, high cost limiting large-cohort validation, and the inability to distinguish causal microglial pathological signatures from bystander changes.	Develop functional assays and microglial-specific biomarkers	(264)

Table VII. Continued.

D, Therapeutic translation				
Authors, year	Key limitations	Challenges	Future perspectives	(Refs.)
Zhang *et al*, 2025;	Lack of specific microglial targets	Overlap in signaling pathways makes it difficult to selectively target pro-inflammatory subsets	Design targeted therapies (small molecule inhibitors, cell-based transplantation)	(265)
Wang *et al*, 2021	Insufficient biomarkers for clinical trials	No reliable tools to monitor microglial activity or treatment response in patients	Conduct biomarker-driven clinical trials with adaptive designs	(266)
E, Ethical/practical concerns				
Zakani *et al*, 2023;	Limited access to human tissue	Post-mortem samples are scarce and typically obtained at advanced disease stages	Establish human tissue biobanks; optimize iPSC-derived microglia protocols	(99)
Chan *et al*, 2021	High cost and slow progress	Advanced techniques (scRNA-seq, primate models) are expensive and time-consuming	Promote international collaboration and data sharing	(267)

CRISPR, clustered regularly interspaced short palindromic repeats; iPSC, induced pluripotent stem cell; PET, positron emission tomography; scRNA-seq, single-cell RNA sequencing.

cytokine-mediated astrocyte-microglia communication and promotion of reparative responses through TREM2 or PPARγ (Table V) (246-253). Inhibition of P2X7 or NADPH oxidase may attenuate inflammatory activation and oxidative stress (246-248). These approaches must be balanced against potential impairment of immune surveillance following microglial depletion, systemic effects of broadly expressed signaling pathways, increased infection risk and delayed clearance of cell debris. Most evidence is preclinical and the therapeutic relevance of these pathways to human NMOSD requires validation (254,255). Current therapies targeting complement (C3aR antagonists and anti-C1q), IL-6R or B cells primarily act on upstream immune mechanisms rather than selectively modulating microglial response (249-251). Future microglia-directed adjunctive therapy should demonstrate adequate CNS exposure, cellular specificity and long-term safety while preserving key phagocytic and reparative functions. Candidate monitoring approaches, including 18 kDa translocator protein-positron emission tomography (256,257) and sTREM2, require validation because their signals do not reliably distinguish beneficial from detrimental microglial states.

6. Limitations and prospects of microglia in NMOSD research

Limitations. Despite increasing interest in microglial function and immune-regulatory mechanisms in NMOSD (Table VI) (79,258-260), several limitations remain in disease modeling, cell resolution, functional assessment and clinical translation. Rodent microglia differ notably from their human counterparts, while passive transfer and active immunization models do not fully reproduce the chronic, relapsing features of NMOSD (Table VII) (12,99,188,261-266). The conventional M1/M2 framework oversimplifies microglial heterogeneity and fails to capture dynamic interactions with astrocytes, neurons and peripheral immune cells. MRI and PET provide valuable information at the tissue level but lack sufficient spatial resolution to resolve individual cell responses, whereas single-cell sequencing may underrepresent rare populations or low-abundance transcripts. Shared molecular pathways between resident microglia and infiltrating myeloid cells complicate cell attribution and target specificity. Reliable biomarkers that reflect microglial function and treatment response are limited, and available human tissue samples typically represent advanced or end-stage lesions. These constraints restrict causal interpretation and indicate that decreased inflammatory markers alone cannot establish neuroprotection or tissue repair.

Future studies should integrate human iPSC-derived microglia, neurovascular co-culture systems and improved chronic or relapsing models with single-cell and spatial multi-omics. Such approaches may resolve microglial subsets, characterize their interactions with neighboring cells and define the temporal transition from inflammatory activation to tissue repair. Longitudinal imaging and functional assays should be combined with patient-derived samples to validate candidate biomarkers rather than infer microglial activity from non-specific inflammatory signals. Translational studies should prioritize selective intervention with adequate CNS

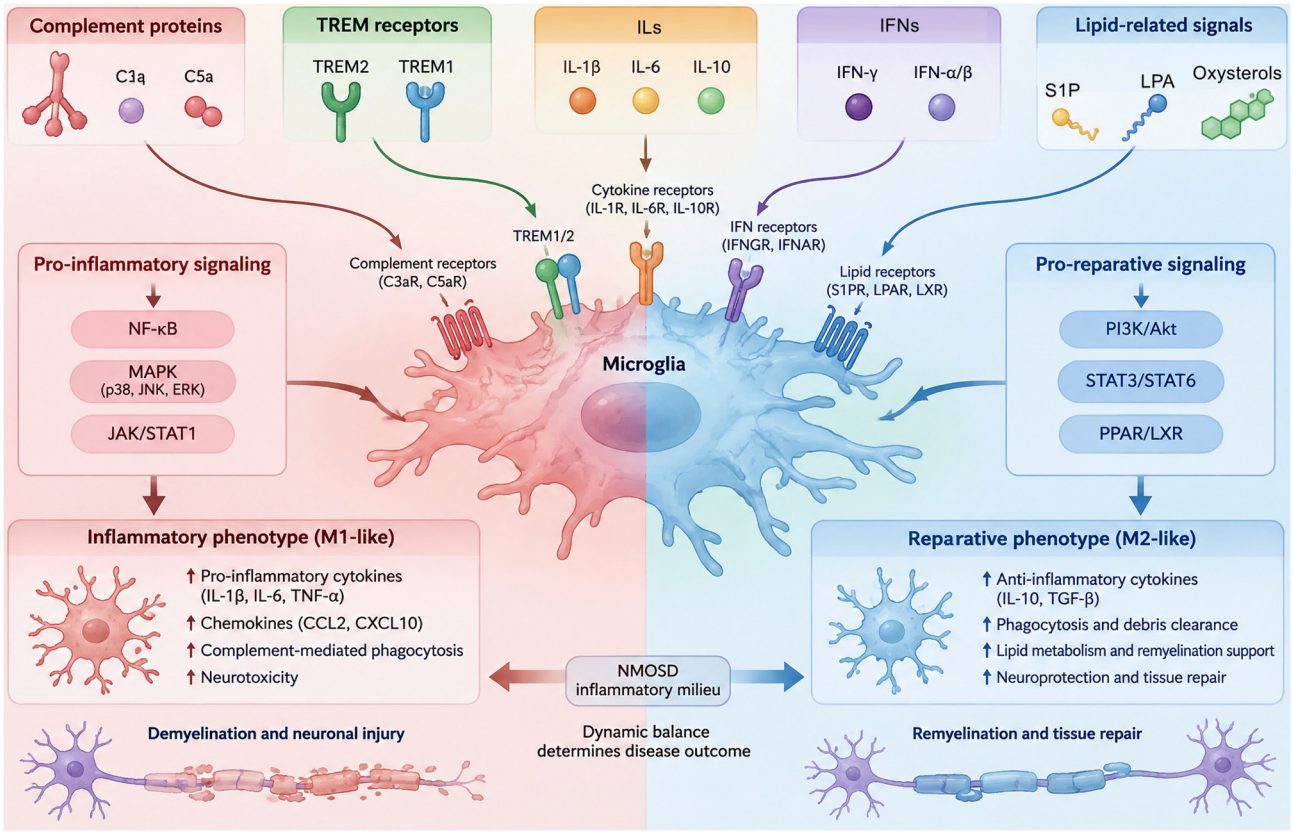


Figure 11. Complement proteins, ILs, IFNs and lipid-associated signals shape inflammatory and reparative microglial function in NMoSD. During NMOSD pathogenesis, circulating anti-AQP4) autoantibodies breach the blood-brain barrier and engage astrocytic AQP4, triggering complement activation (C1q-C3-C5-C9 membrane attack complex) that drives astrocyte injury and liberates damage-associated molecular patterns (DAMPs). These cues are sensed by microglia through an integrated receptor network: TREM2 signaling promotes phagocytic clearance and a tissue-reparative transcriptional state, while TREM1/DAP12 pathways amplify pro-inflammatory output. Classical (IL-1β, IL-6, IL-17) and anti-inflammatory (IL-10, IL-33/ST2) interleukins fine-tune the balance between microglial activation and resolution. Type I (IFN-α/β) and type II (IFN-γ) interferons, often produced locally by infiltrating lymphocytes and plasmacytoid dendritic cells, shift microglia toward antigen-presenting and neurotoxic phenotypes. Concurrently, lipid-associated signals-including lyso-phosphatidylcholine, oxidized phospholipids, ceramide, and resolvin/protectin mediators-act via TLRs, LXR/PPAR pathways and specialized pro-resolving receptors to remodel membrane dynamics, lipid droplet accumulation and efferocytosis. The convergence of these pathways determines whether microglia adopt a deleterious inflammatory state that sustains complement-mediated demyelination and oligodendrocyte loss, or transition toward a reparative phenotype supporting remyelination and astrocytic recovery. Therapeutic targeting of these complement, cytokine, IFN and lipid signaling axes offers a precision strategy to recalibrate microglial responses and promote repair in NMOSD. C5a, complement component 5a; TREM, triggering receptor expressed on myeloid cells; S1P, sphingosine-1-phosphate; LPA, lysophosphatidic acid; CCL2, C-C motif chemokine ligand 2; CXCL10, C-X-C motif chemokine ligand 10; PI3K, Phosphoinositide 3-kinase; LXR, liver X receptor.

exposure and assess outcomes that capture both relapse control and tissue recovery. Human tissue biobanks, standardized experimental protocols and collaborative data sharing may improve reproducibility and enable validation across independent cohorts. Metabolic interventions are promising, but direct evidence is needed to establish whether altering microglial energy metabolism can restore remyelination in NMOSD.

7. Conclusion

Complement- and IL-6R-directed therapy underscore the therapeutic relevance of targeting pathways involved in NMOSD pathogenesis. Microglia-directed approaches, including modulation of cytokine signaling and TREM2-dependent phagocytosis, are primarily experimental. Their development should complement control of pathogenic autoimmunity while preserving endogenous mechanisms of tissue repair.

Complement proteins, ILs, IFNs and lipid-associated signals shape inflammatory and reparative microglial function (Fig. 11). IL-6 and IL-1β can amplify inflammatory responses, whereas IFN effects vary with disease context; the association between IFN-β and NMOSD exacerbation cautions against extrapolating its therapeutic effects in MS. C3a/C5a signaling and C5b-9-mediated astrocyte injury provide links between complement activation and microglial response, whereas TREM2-associated lipid handling and phagocytosis may contribute to debris clearance and recovery. These pathways provide plausible therapeutic targets, but their stage-dependent effects and relevance to human NMOSD require validation.

Defining the temporal and molecular determinants of microglial transition between injury-promoting and reparative states may reveal biomarkers and therapeutic opportunities. Progress depends on NMOSD-specific experimental models, longitudinal human evidence and interventions that selectively limit detrimental inflammation while preserving the phagocytic, trophic and metabolic functions required for CNS repair.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant no. 32560188), Yunnan Revitalization Talent Support Program (grant no. XDYC-QNRC-2022-0328), 535 Talent Project of First Affiliated Hospital of Kunming Medical University (grant no. 2025535Q05), Yunnan Health Training Project of High Level Talents (grant no. D-2024038), Collaborative Innovation Special Project of Dali University Affiliated Hospital Alliance (grant no. ZDXM202602), Yunnan Clinical Research Center for Neurological Disease (grant no. 202505AJ310009) and Yunnan Clinical Center for Neurological and Cardiovascular Diseases (grant no. YNLCYXZX2023300077).

Availability of data and materials

Not applicable.

Authors' contributions

YZ, LMZ and MWL performed the literature review and drafted the manuscript. JBH and YZ edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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