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Review

Microenvironmental Regulation of Central Nervous System Myelination and Remyelination

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Abstract

Both myelination and remyelination in the central nervous system (CNS) rely on the differentiation of oligodendrocyte precursor cells (OPCs) into mature oligodendrocytes (OLs). However, the microenvironment and underlying mechanisms of these two processes are significantly different. Myelination is driven by intrinsic developmental programs, whereas remyelination is triggered as a response to demyelinating injury. These distinct origins shape unique microenvironmental conditions that critically influence the respective processes. The microenvironment comprises, the extracellular matrix (ECM) and cellular components. Neurons, microglia, and astrocytes play stage-specific roles, ensuring proper myelin turnover under physiological conditions and regeneration after demyelination. Dysregulation of the microenvironment represents a critical driver of aberrant myelination and remyelination failure, as well as a key limitation of current pro-regenerative strategies. In this review, we discuss the cellular and molecular basis of microenvironmental regulation, recent advances in pathological microenvironmental alterations across demyelinating diseases (multiple sclerosis and neuromyelitis optica spectrum disorder) and myelin-associated disorders (Alzheimer's disease and ischemic stroke), and emerging pro-remyelination strategies targeting the microenvironment, such as Bruton's tyrosine kinase (BTK) inhibitors and microglia replacement strategies. We provide a non-cell autonomous perspective to advance the understanding of OLs differentiation and CNS remyelination.

Keywords: myelination; remyelination; microenvironment; neuron; microglia; astrocyte; multiple sclerosis; Alzheimer's disease; ischemic stroke

1. Introduction

Myelin, a fundamental structural component in the central nervous system (CNS), facilitates saltatory conduction of action potentials and provides metabolic support of in the CNS [1]. Oligodendrocyte precursor cells (OPCs) constitute a progenitor population that differentiates into mature oligodendrocytes (OLs) to form myelin sheaths [2]. Physiological myelination begins in infancy and involves continuous structural remodelling [2]. The microenvironment, composed of cellular components and the extracellular matrix (ECM), is essential for myelin formation and maintenance [3]. Neurons, microglia, and astrocytes interact with OPCs/OLs to maintain myelination homeostasis [4]. Following pathological demyelination, remyelination emerges as a critical neuroprotective mechanism to mitigate disease progression and neurodegeneration [5]. When the CNS encounters external stress such as inflammation or disrupted blood-brain barrier (BBB) integrity, the brain enables peripheral immune cells to infiltrate the CNS, and the microenvironment exhibits significant challenge [6]. These interactions alter microenvironmental conditions, ultimately determining the success or failure of remyelination [6]. Impaired remyelination represents a pivotal driver of neuronal damage and a central therapeutic challenge in regenerative therapy [5].

CNS myelinopathies include neurodevelopmental disorders (e.g., X-linked adrenoleukodystrophy (X-ALD), metachromatic leukodystrophy (MLD)) and demyelinating diseases (e.g., multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD)) [1]. Emerging studies have

identified myelin defects as critical engineers of neurodegenerative diseases—including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD)—as well as neurovascular pathologies such as ischemic stroke [7,8]. These findings expand the spectrum of demyelination-associated pathologies and provide novel therapeutic perspectives for incurable CNS disorders through myelin-targeting strategies. Current therapeutic strategies are evolving from inflammatory modulation towards remyelination-promoting approaches, particularly to address progressive disability in chronic MS [9]. However, many pro-remyelination therapies are unable to overcome the detrimental effects of pathological microenvironmental factors and fail to achieve therapeutic outcomes [10]. Thus, understanding microenvironmental alterations is crucial for advancing knowledge of CNS disease mechanisms and developing novel therapies.

While myelination and remyelination share fundamental cellular developmental pathways, they are regulated by distinct microenvironmental signals and mechanisms. Previous reviews have predominantly characterized the static components of myelination and remyelination microenvironments, focusing largely on inflammatory demyelinating diseases. To broaden understanding, this review examines the cellular and molecular mechanisms of microenvironmental modulation in both processes and investigates their pathogenic roles across various CNS disorders. Notably, we highlight emerging insights into myelinopathies beyond inflammatory demyelination, including Alzheimer's disease and ischemic stroke. Finally, we evaluate innovative strategies targeting microenvironmental modulation to promote myelin regeneration.

2. Myelin Structure, Function, and Formation

Myelin is a multilayered membrane structure formed by OLs processes wrapping around axonal segments [1]. It consists primarily of lipids (≈70% of its dry weight), with cholesterol making up 40% and sphingomyelin 20% of the total lipid content [1]. The remaining 30% consists of proteins, including various myelin-specific proteins that are essential for maintaining its structural integrity [1].

Myelin sheaths segmentally insulate axons, creating distinct electrophysiological domains along the neural fiber [11]. The exposed nodal regions, known as the Node of Ranvier, are enriched with voltage-gated sodium channels, enabling efficient action potential propagation through saltatory conduction [12]. Conversely, the myelinated internodal regions exhibit reduced membrane potential fluctuations below the excitation threshold [12]. The conduction velocity in myelinated fibers is influenced by factors such as myelin thickness, internode length, and axon diameter, which are represented by the g-ratio (the ratio of axon diameter to fiber diameter) [11]. An optimal g-ratio (approximately 0.6–0.7) maximizes saltatory conduction efficiency [13]. Additionally, axons face energetic challenges due to their long distance from the cell body and high metabolic demand [14]. Myelin supports these needs by enabling metabolic coupling through monocarboxylate transporters (MCTs), which transfer lactate and pyruvate from OLs to axons for oxidative phosphorylation [15]. Apart from the effects on conduction and metabolic support, potassium buffering mechanisms, involving Kir4.1 channels, paranodal gap junctions, and Na^+/K^+-ATPase on myelin, help maintain extracellular K^+ balance and prevent neuronal hyperexcitability [16,17].

The CNS contains an abundant population of long-lived, proliferative OPCs that continuously differentiate into mature oligodendrocytes. During this process, OLs undergo an immense expansion of membrane surface area—up to several thousandfold—enabling them to myelinate multiple axons. This remarkable growth is achieved with relatively high metabolic demands on the vascular supply [2,18,19]. The progress involves a series of precisely regulated myelination stages [2]. Initially, OPCs are recruited to axonal domains, where they extend processes to establish selective axonal contact [2]. Once stable contact is made, polarized redistribution of proteins and reorganization of the cytoskeleton drive the morphological transformation into pre-myelinating OLs [2]. Finally, terminal maturation culminates in the concentric wrapping of axons and compaction of the myelin sheath [2]. Specific transcriptional regulators govern each stage, with sequential expression of Sox2 (promoting OPC proliferation), Olig2/Sox10 (lineage commitment), Sox2/Tcf7l2/Nkx2.2 (OLs maturation), and Myrf (terminal differentiation) [20–24]. Moreover, myelination is bidirectionally influenced by microenvironmental factors: Neuronal electrical activity and gliogenic growth factors promote myelination, while axonal surface, such as Jagged1, and inhibitory ECM components like chondroitin sulfate proteoglycans (CSPGs) help prevent excessive myelination [3,25,26].

Human myelination follows distinct spatiotemporal patterns. It progresses rapidly in early life and adolescence, stabilizes in adulthood, and declines with aging [27]. Spatially, myelination occurs in a specific sequence: projection fibers complete myelination first, followed by commissural fibers, and ultimately association fibers [27]. Notably, even after myelination is complete, structural remodeling continues throughout life, involving dynamic adjustments to myelin sheath quantity, length, thickness, and internode properties [27]. This ongoing plasticity plays a key role in neural circuit refinement and supports advanced neurological functions, including motor skill acquisition and memory consolidation [28–30].

3. Microenvironmental Regulation of Myelination

The formation and maintenance of CNS myelin depend on both the intrinsic properties of OLs and the bal-

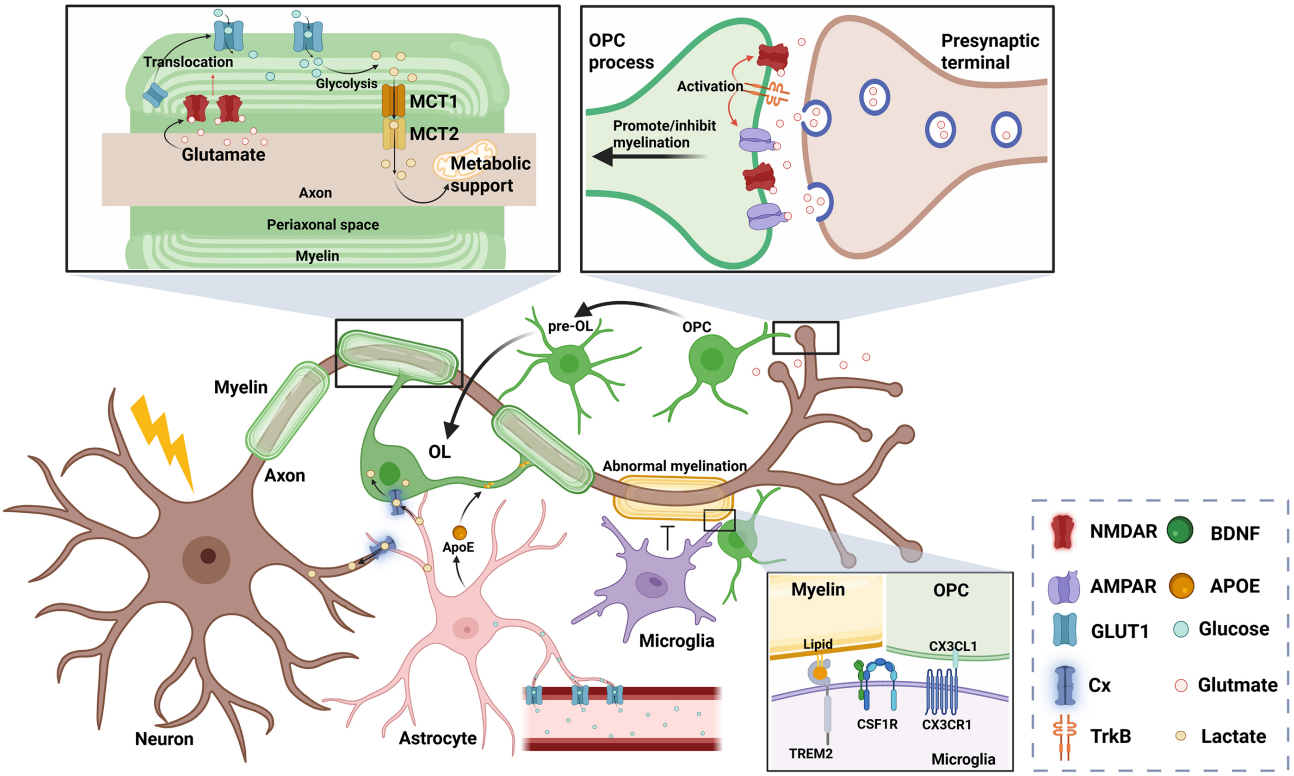

Fig. 1. Physiological myelination microenvironment. Neurons, microglia, and astrocytes regulate myelin structural stability and normal turnover. Neurons mediate neurotransmitter and BDNF release through electrical activity to initiate and regulate myelination. Glutamatergic signaling exerts differential effects at distinct sites: Axonal terminals release glutamate onto OPC processes to modulate their proliferation/differentiation, while glutamate from the periaxonal space acts on NMDARs to regulate myelin-mediated metabolic support for axons. Microglia phagocytose excessive/misplaced myelin sheaths and OPCs through TREM2 or CX3CR1 to prevent aberrant myelination. Astrocytes uptake glucose from the vasculature, supply energy substrates to neurons and OLs via connexin-mediated metabolic coupling, and provide cholesterol for myelination through APOE-mediated lipid transport. Cx, connexin; BDNF, brain-derived neurotrophic factor; OPC, oligodendrocyte precursor cell; NMDAR, N-methyl-D-aspartate receptor; TREM2, triggering receptor expressed on myeloid cells 2; CX3CR1, CX3C chemokine receptor 1; OLs, oligodendrocytes; APOE, Apolipoprotein E; MCT, monocarboxylate transporter; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GLUT1, glucose transporter 1; CSF1R, Colony-stimulating factor 1 receptor; TrkB, tropomyosin receptor kinase B. The figure was drawn using Biorender (https://www.biorender.com).

ance of microenvironmental factors [3]. Recent research has shown that disrupting meningeal lymphatic vessels in adult mice alters the CNS microenvironment, affecting glial cell function and cytokine profiles, leading to reduced populations of mature OLs and impaired myelination [31]. The microenvironment comprises cellular elements and ECM, with key contributors including neurons, astrocytes, and microglia (Fig. 1) [32–34]. The ECM contains inhibitory molecules such as CSPGs and hyaluronic acid, which can also influence myelination. While this review emphasizes cellular interactions, a detailed examination of ECM components can be found in Su *et al.*'s [26] comprehensive review.

3.1 Neurons Regulate Adaptive Myelination

Neuronal activity plays a crucial role in regulating OPCs proliferation, axonal selection, and myelin structural dynamics through adaptive myelination, a process fundamental to CNS development and circuit remodeling [32,35]. Mechanistically, experience-driven neuronal depolarization triggers patterned action potentials that release signaling molecules, which in turn modulate OPCs lineage progression [35].

Neurotransmitters, particularly glutamate, mediate axoglial communication by binding to receptors on both OPCs and myelin, with emerging evidence highlighting the roles of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and N-methyl-D-aspartate receptor (NMDAR) in myelination [36,37]. Bergles *et al.* [38] reveal axoglial synaptic connections between axonal terminals and OPC processes, which induce inward currents in OPCs via AMPARs. Notably, AMPARs display divergent effects *in vitro* versus *in vivo* [39,40]. In cerebellar slice cultures, AMPAR activation

inhibits OPC proliferation and differentiation [39]. However, genetic deletion of AMPAR functional subunits (GluA2/A3/A4) in mice spares OPCs proliferation and differentiation but reduces post-differentiation OLs survival, suggesting AMPARs primarily regulate myelination at later stages [40]. It is important to note that pharmacological modulation of AMPARs *in vitro* affects not only OPCs but also neurons, triggering the release of factors that indirectly influence myelination, which may explain the discrepancies between in vitro and *in vivo* findings [40]. NMDARs are localized in both axoglial synaptic and periaxonal space, with varying evidence regarding their roles in myelination [37,41]. While primary culture studies suggest that NMDAR activation promotes OPCs migration and differentiation, NMDAR knockout mice display intact OPCs development and myelination [42–44]. More recent studies, however, indicate that NMDARs serve as metabolic regulators in myelinated axons [45]. Periaxonal glutamate release activates NMDARs on the inner myelin sheaths. This activation recruits GLUT1 (glucose transporter 1) to oligodendrocyte membranes, facilitating glucose uptake. The imported glucose is then metabolized into lactate via glycolysis, which is then exported through monocarboxylate transporters (MCT1/2) to support axonal bioenergetic needs [45]. Notably, compensatory upregulation of calcium-permeable AMPARs in NMDAR-deficient OPCs suggests an interaction between these receptors [44]. Further experimental validation is required to clarify how neuronal activity-mediated alterations involving these two receptors regulate myelination.

Neuronal activity also induces the release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) [46,47]. Released via synaptic vesicles, BDNF binds to TrkB receptors on OPCs, driving their differentiation [48]. Additionally, BDNF enhances glutamatergic signaling by simultaneously activating NMDARs and AMPARs on OPCs. [49]. Geraghty *et al*. [50] reveal that OPC-specific TrkB deletion in mice exhibits impaired cortical projection myelination and leads to cognitive deficit. In contrast, axonal membrane proteins exert inhibitory control over myelination, including polysialylated neural cell adhesion molecule (PSA-NCAM), Jagged1, transient axonal glycoprotein-1 (TAG-1), and leucine-rich repeat and immunoglobulin domain-containing protein 1 (LINGO-1) [51–54]. Their structural features and inhibitory mechanisms are detailed in Almeida's review [55].

Interestingly, Fang *et al*. [56] reveal that OPCs regulate neuronal function through mechanisms independent of myelination. OPC processes establish activity-dependent contacts with neuronal somata, promoting lysosomal exocytosis in neurons, which protects against neuronal senescence and degeneration. However, further studies are needed to clarify the temporal sequence between cellular contact and lysosomal fusion [56].

3.2 Microglia Maintain Homeostasis and Orchestrate Myelin Formation

The CNS harbors two main macrophage populations: parenchymal microglia and non-parenchymal border-associated macrophages (BAMs) [57]. BAMs reside in perivascular spaces, meninges, and choroid plexus [57,58]. Under physiological conditions, microglia secrete neurotrophic factors and regulate synaptic pruning, refining neural circuits during development [59]. Perivascular macrophages maintain BBB integrity by restricting peripheral immune cell entry [60]. Meningeal macrophages may regulate meningeal lymphatic vessel dynamics and act as antigen-presenting cells (APC) [31]. Choroid plexus macrophages, located near microvilli, are thought to contribute to cerebrospinal fluid (CSF) homeostasis [61]. Collectively, BAM functions require further validation.

A specialized "microglial fountain" subset emerges postnatally in regions of active myelination, such as the corpus callosum and cerebellum. These cells express activation-associated markers, including CD11c, and are critical for early oligodendrogenesis and the maintenance of adult OPC pools [62]. Their lifespan coincides with the period of extensive myelination in healthy murine brains, and they represent a major source of insulin-like growth factor-1 (IGF-1), a potent pro-myelination signal [63,64]. Selective depletion of this subset impairs myelination, confirming their essential role in developmental myelinogenesis [63].

Microglia regulate OPC lineage development and myelination through phagocytosis, lipid metabolism regulation, and neurotrophic factor secretion [65]. Pioneering work by Schafer *et al*. [66] reveals their role in activity-dependent synaptic pruning in the developing retina. Subsequent studies revealed their ability to phagocytose excess OPCs and aberrant myelin in an activity-dependent manner, preventing hypermyelination [67,68]. The neuron-derived chemokine CX3CL1 plays a critical role by binding to the microglial receptor CX3C chemokine receptor 1 (CX3CR1), which triggers activity-dependent synaptic remodeling [69]. Beyond synaptic modulation, CX3CR1 signaling also enables microglia to recognize and phagocytose OPCs [68]. Loss of CX3CR1 not only disrupts synaptic pruning but also reduces myelin density in the corpus callosum, linking microglial-dependent oligodendrogenesis to neuronal circuit refinement [68].

Microglia express triggering receptor expressed on myeloid cells 2 (TREM2), a member of the immunoglobulin superfamily. TREM2 recognizes anionic myelin components, including sphingomyelin, phosphatidylcholine, and fatty acids, which regulate diverse microglial functions encompassing survival, migration, phagocytosis, and metabolic regulation [70,71]. It is activated in response to mild myelin injury or aging, coordinating microglial responses that stabilize neural networks [70]. Homozygous TREM2 mutations cause Nasu-Hakola disease, character-

ized by subcortical demyelination and early-onset dementia [72]. TREM2 also plays an important role in regulating microglial lipid metabolism [73–75]. Microglial TREM2 deficiency impairs cholesterol efflux pathways and induces cholesterol ester (CE) accumulation during myelin clearance [75].

Microglia also support OPC development by releasing IGF-1, IGF-2, tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and neurotrophin-1 (NP1) [65]. Among these, IGF-1 is particularly important: IGF-1 knockout mice show reduced OPC and mature OL populations, along with markedly decreased myelin content [76].

Colony-stimulating factor 1 receptor (CSF1R), a cell-surface receptor, regulates the survival of microglia and monocyte-derived macrophages (MDMs) in the CNS [77]. A landmark clinical case of a patient with homozygous CSF1R mutation showed complete absence of microglia, accompanied by hypoplasia of the corpus callosum and progressive white matter atrophy, which provides direct evidence of the indispensable role of microglia in myelin development and white matter homeostasis [78]. Methodologically, CSF1R knockout animal models are used to investigate microglial functions in the CNS [79]. However, traditional CSF1R knockout models deplete both microglia and MDMs, confusing cell-specific analyses [80]. To overcome this, McNamara *et al*. [33] developed the FIRE-deleted mouse model, which selectively eliminates microglia by deleting the CSF1R Fms intronic regulatory element [81]. Interestingly, this model revealed that microglia particularly maintain adult myelin integrity through transforming growth factor β1 (TGFβ1)-mediated lipid metabolism rather than developmental myelination [33]. Microglia replacement models serve as a valuable tool for investigating the role of microglia in CNS disorders and for developing new replacement therapies, as detailed in Zhou *et al*.'s [82] review.

3.3 Astrocytes: Important Immunomodulators and Metabolic Supporters

Astrocytes contribute to myelination through both structural and metabolic interactions [83]. Their processes wrap around cerebral microvessels to support BBB formation and regulate cerebral blood flow [83]. White matter astrocytes exhibit distinct features with compact somata and elevated glial fibrillary acidic protein (GFAP) expression [83,84]. GFAP-deletion mice show delayed optic nerve and spinal cord myelination, cerebellar white matter disorganization, and BBB leakage [85].

Metabolically, astrocytes supply energy substrates to both neurons and oligodendrocytes [86]. They transport glucose from blood vessels via GLUT1 and provide lactate for neurons and OLs [87]. This metabolic coupling is mediated by gap junctions and hemichannels formed by connexin (Cx), which transfer glucose, lactate, and Ca^{2+} across glial networks [88]. Mice lacking Cx47 and Cx30 exhibit OLs degeneration characterized by white matter vacuolization and myelination defects [89]. Astrocytes are also essential for lipid homeostasis, particularly cholesterol metabolism [90]. The availability of cholesterol is a crucial limitation on myelination [91]. While OLs initiate cholesterol synthesis during initial myelination, astrocytes become the predominant cholesterol source during myelin maintenance through APOE-mediated transport [92,93]. To mention, the APOE4 genotype is the strongest genetic risk factor for Alzheimer's disease. Carriers of APOE4 exhibit abnormal cholesterol accumulation, oligodendrocyte dysfunction, and reduced myelin content, which links astrocytic lipid metabolism to both myelin biology and neurodegenerative vulnerability [94].

4. Remyelination: Different Mode From Myelination

Remyelination is the regeneration of myelin sheaths around intact axons following demyelination, a process crucial for restoring axonal conduction and metabolic support [5]. Although it recapitulates key stages of developmental myelination, including OPCs migration, proliferation, and differentiation into myelinating OLs, remyelination exhibits distinct morphological and cellular features [20]. Regenerated myelins show thinner and shorter sheaths with an elevated g-ratio compared to developmental myelin, which may compromise conduction velocity [95]. Lineage-tracing studies using radiocarbon (14C) birth-dating demonstrated that mature OLs surviving from demyelination can contribute to myelin regeneration in adult MS lesions through proliferation-independent mechanisms [96]. However, zebrafish models indicate that while residual OLs exhibit remyelination capacity, their regenerative efficiency and structural precision are markedly lower than that of newly generated OLs derived from OPCs [97]. Moreover, Schwann cells, normally peripheral myelinating glia, can also participate in CNS remyelination via OPCs transdifferentiation, particularly in astrocyte-deficient lesions [98–100].

A critical distinction between myelination and remyelination is that controlled acute inflammation is indispensable for initiating remyelination [6]. In the early phase of inflammation, chemokines and semaphorins released by microglia and astrocytes recruit OPCs to lesion sites [101]. Optimal OPCs recruitment density activates mechanosensitive Piezo1 channels and elevates Netrin-1 levels, promoting their differentiation [102,103]. However, a recent study have shown that the mechanotransduction channel TMEM63A, rather than Piezo1, is expressed in OLs and promotes their differentiation. Additionally, activated microglia clear inhibitory myelin debris and release trophic signals necessary for OPCs proliferation and differentiation [104]. The limited period in which OPCs migrate and interact with pro-remyelination signals in the microenvironment is called the "remyelination-permissive

window" [104,105]. If exceeding this period, chronic inflammation establishes a hostile microenvironment characterized by inhibitory axonal molecules (e.g., PSA-NCAM), astrogliotic scarring, and inhibitory ECM deposition (e.g., CSPG), all of which hinder OPCs migration and differentiation [106,107]. Collectively, remyelination requires collaboration among diverse cellular populations. Transcriptomic studies highlight dynamic functional states of microglia, MDMs, astrocytes, and neurons across distinct phases of regeneration, and have linked these states to regenerative outcomes [108,109]. MS lesions with robust remyelination are characterized by reduced accumulation of foamy microglia and enrichment for epithelial–mesenchymal transition (EMT) pathways, along with pro-regenerative factors such as CXCL12, EGF, and HGF [108]. In the cuprizone (CPZ) model, during remyelination, astrocytes upregulate genes associated with detoxifying metabolic pathways and exhibit distinct transcriptional subpopulations, suggesting functional diversity [109]. Neurons, however, exhibit relatively limited transcriptional changes during remyelination, which needs further validation [109].

4.1 Microglia: The Key Regulator of Remyelination

In demyelinating conditions, circulating MDMs infiltrate through the compromised BBB and collaborate with resident microglia to mediate antigen presentation and myelin debris clearance [110,111]. Despite overlapping functions, MDMs and microglia diverge in their roles across disease stages. Comparative studies reveal that MDMs exhibit higher expression of MHC II molecules and co-stimulatory markers compared to microglia, positioning them as primary drivers in demyelination pathogenesis [110]. In lysolecithin (LPC)-induced lesions, both cell types initially display comparable densities and phagocytic capacities for myelin debris [112]. As demyelination progresses, however, microglia undergo robust activation and proliferation, becoming the dominant population, whereas MDMs are largely restricted to the acute demyelinating phase [113]. Microglia also restrain excessive macrophage infiltration by remodeling the extracellular matrix, modulating secretory profiles, and facilitating BBB repair [113]. Experimental microglial depletion exacerbates axonal loss and disrupts OPCs recruitment and differentiation, underscoring their indispensable neuroprotective and pro-regenerative roles [112,113].

During remyelination, microglia shift from a pro-inflammatory to a pro-regenerative phenotype through necroptosis-mediated elimination of pro-inflammatory subsets. This transition is tightly coupled to the stage of OPC differentiation [114,115]. Additionally, microglia P2X4R activation can also promote pro-regenerative polarization and remyelination [116]. Pro-regenerative microglia enhance remyelination by secreting a diverse repertoire of trophic and immunomodulatory factors, including activin A, IL-4, IGF1, TNF-α, NP-1, galectin-3, E-selectin, and semaphorin 3F [6,114].

Notably, the oversimplified *in vitro* classification of microglia into "resting", "M1" (pro-inflammatory), or "M2" (pro-regenerative) phenotypes fails to capture their functional complexity *in vivo*, and has been abandoned by current researchers [113]. Single-cell transcriptomic profiling now provides a new paradigm for precisely distinguishing the functional states of microglia [117]. RNA sequencing in mouse models across developmental, aged, and post-demyelination has identified at least nine transcriptionally distinct microglial phenotypes [117]. A subset characterized by chemokine ligand 4 (Ccl4) expression is specifically associated with demyelinating pathology [117]. In another research, microglial subsets expressing high levels of the transcription factor MAFB are crucial for remyelination [109]. These findings suggest that future therapies may need to target specific microglial subsets to maximize repair while minimizing adverse effects.

Efficient myelin debris clearance is a prerequisite for remyelination. Accumulated debris not only damages axons but also inhibits OPC recruitment and differentiation [118,119]. Microglia recognize debris through receptors such as TREM2, complement receptor 3 (CR3), and signal-regulatory protein-α (SIRP-α) [120]. Following recognition, debris is internalized into phagosomes and degraded in lysosomes via the autophagy-lysosomal pathway [121,122]. TREM2 deficiency impairs debris phagocytosis and the secretion of OPC pro-maturation factors, which compromises remyelination [123,124]. Beyond debris removal, TREM2 signaling protects against oxidative phosphatidylcholine (OxPC), a neurotoxic lipid accumulating in MS and experimental autoimmune encephalomyelitis (EAE) lesions [125].

Debris clearance imposes high lipid-processing demands on microglia, especially for cholesterol and sphingolipids [126]. Proper lipid metabolism is critical for cellular homeostasis and inflammation resolution [126]. While the autophagy-lysosomal pathway enables lipid degradation, its hyperactivation can cause lysosomal overload, perpetuate pro-inflammatory phenotypes, and impair remyelination [127]. In LPC models, suppressing excessive autophagy-lysosomal activity or supplementing conjugated linoleic acid (CLA) during acute demyelination mitigates inflammation and promotes remyelination [127].

Microglia also recycle cholesterol from degraded myelin and transfer it to OPCs to support remyelination [93]. Liver X receptors (LXRs) regulate cholesterol efflux and have anti-inflammatory effects in acute demyelination [128,129]. However, in chronic lesions, impaired LXRs activation leads to toxic intracellular cholesterol accumulation, which triggers endoplasmic reticulum stress and apoptosis in microglia [130]. To buffer lipid toxicity, microglia esterify excess cholesterol into lipid droplets, a protective response that promotes foam cell formation [130]. Notably,

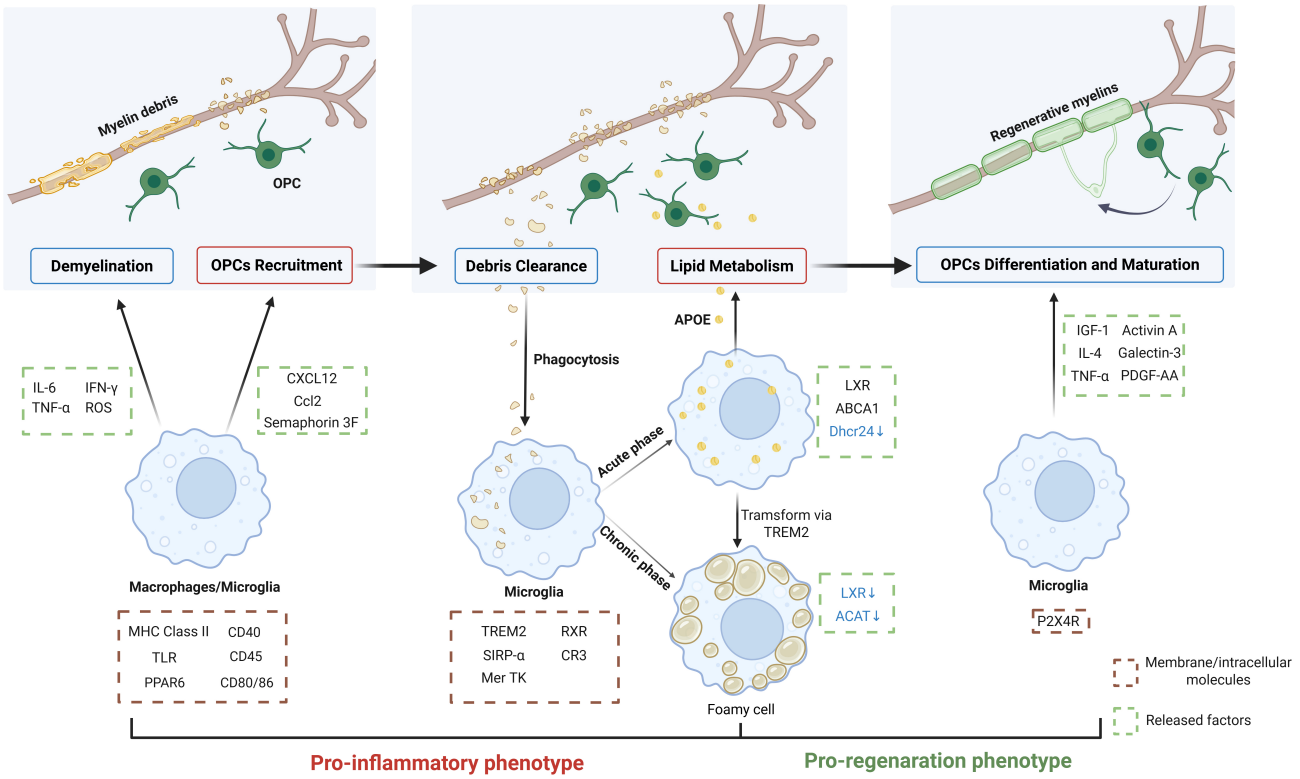

Fig. 2. Microglia in remyelination. Microglia and monocyte-derived macrophages serve as the primary immune mediators of demyelination, releasing cytotoxic factors to damage myelin sheaths. While amplifying inflammatory responses, they simultaneously secrete chemokines and semaphorins to recruit OPCs to lesion sites. During the acute inflammatory phase, microglia efficiently clear myelin debris, subsequently transferring processed lipids to OPC lineages to support remyelination. If inflammation resolution is impaired, chronic inflammation triggers microglia transformation into lipid-overloaded foam cells with compromised lipid-processing capacity. As inflammation subsides, microglia progressively transform to the pro-regenerative phenotype, releasing factors that promote OPC differentiation and maturation. Successful remyelination requires precisely coordinated regulation of these cellular functions across pathological stages. IL-6, interleukin-6; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-alpha; ROS, reactive oxygen species; CXCL12, C-X-C motif ligand 12; Ccl2, chemokine ligand 2; MHC, major histocompatibility complex; TLR, toll-like receptor; PPAR6, peroxisome proliferator-activated receptor 6; LXR, liver X receptor; ABCA1, ATP-binding cassette transporter A1; Dhcr24, delta24-dehydrocholesterol reductase; RXR, retinoid X receptor; SIRP-α, signal-regulatory protein-α; CR3, complement receptor 3; IGF-1, insulin-like growth factor-1; P2X4R, P2X purinoceptor 4. The figure was drawn using Biorender (https://www.biorender.com).

TREM2 deficiency disrupts lipid droplet biogenesis, aggravates ER stress, and further impairs remyelination [131].

Collectively, microglia play crucial roles in different phases of demyelinating disease (Fig. 2).

4.2 The Multifaceted Roles of Astrocytes in Remyelination

Although not traditionally classified as immune cells, astrocytes play pivotal immunomodulatory roles in both demyelination and remyelination [6]. Interestingly, in EAE and MS lesions, astrocytes acquire epigenetic immune memory similar to classical immune cells. This process is mediated by ATP-citrate lyase (ACLY), which enhances transcription of NF-κB-dependent genes and primes them for amplified pro-inflammatory responses upon repeated stimulation [132].

During demyelination, astrocytes detect damage and become reactive. They release cytokines and chemokines that recruit immune cells and promote debris clearance [6]. Astrocyte-derived signals exert dual effects on remyelination: leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), and IGF-1 enhance OPCs proliferation; platelet-derived growth factor AA (PDGF-AA) and fibroblast growth factor 2 (FGF-2) drive OPCs differentiation; while endothelin-1 (ET-1) and FGF-9 inhibit remyelination [34]. Additionally, reactive astrocytes secrete ECM components that can limit lesion expansion but also hinder OPC migration and differentiation [34].

Astrocytes also regulate lipid metabolism during remyelination by supplying cholesterol through the ABCA1-mediated efflux pathway [133]. This process is linked to nuclear factor erythroid-2-related factor-2 (Nrf2) down-regulation in astrocytes [133]. Interestingly, chronic MS lesions exhibit sustained Nrf2 activation, which disrupts cholesterol metabolism and reduces OLs survival [133].

While constitutive Nrf2 activation impairs regeneration, it remains essential for antioxidant defense [134,135]. Nrf2 activation induces transcription of cytoprotective genes, including NAD(P)H quinone and oxidoreductase 1 (*Nqo1*), which mitigate oxidative stress via reactive oxygen species (ROS) scavenging, damage repair, and anti-inflammatory actions [136]. In EAE models, astrocytes display a distinct molecular profile marked by Nrf2 downregulation and MAFG upregulation. MAFG, a member of the sMAF (small musculoaponeurotic fibrosarcoma) transcription factor family, exerts gene expression control through combining with partner proteins. Accumulated MAFG represses Nrf2-driven transcriptional programs in astrocytes, consequently amplifying oxidative stress and neuroinflammation [137]. Consistently, Nrf2-knockout mice show cerebellar astrogliosis and myelin pathology, highlighting the need for balanced Nrf2 activity in maintaining myelin integrity [134].

Increasing evidences further highlight the indispensability of astrocytes for remyelination. In ethidium bromide (EB)-induced demyelination, OPCs fail to differentiate in astrocyte-depleted lesions [138]. However, the heterogeneous functional states of astrocytes remain poorly understood due to the lack of definitive surface markers. To address this, Clark *et al*. [139] developed nucleic acid detection and sequencing (FIND-seq) technology, a platform that tags astrocyte subsets using DNA/RNA signatures. Using this approach, they identified the role of nuclear receptor NR3C2 in suppressing transcriptional programs of pro-demyelinating astrocyte subsets [139]. However, conclusions regarding astroglial remyelination in MS drawn from rodent models require further validation, given the evolutionary divergence in genomic and transcriptomic profiles between mice and humans.

4.3 Neurons: Potential Mediators of Remyelination

Although less studied, neuronal activity may play a key role in regulating remyelination. The underlying mechanisms likely involve both direct neurotransmitter effects and indirect modulation of the microenvironment [140, 141]. Gautier *et al*. [140] reveal that in EB-induced focal demyelination, demyelinated axons in the corpus callosum form nascent synapses with OPCs, which promotes remyelination via AMPAR activation. Conversely, blocking neuronal activity impairs OPCs differentiation [140]. Moreover, neuronal activity induces axonal ATP release, which acts on astrocytes in a paracrine manner and stimulates their LIF secretion, enhancing myelin formation by mature OLs [141].

Repeated optogenetic neuronal stimulation enhances remyelination in callosal fibers and restores action potential conduction in demyelinated lesions [142]. However, outcomes vary depending on stimulation parameters, methods, and animal age [142]. While optogenetic tools enable precise neuronal control, their invasiveness limits clinical application [143]. Non-invasive brain stimulation (NIBS) broadly modulates the microenvironment, which activates microglia, astrocytes, and neural stem cells to promote anti-inflammatory microglial polarization and neurogenesis [144,145]. In rodent spinal cord demyelination models, NIBS increases remyelination, upregulates neurotrophic factors (BDNF, NGF), and suppresses pro-inflammatory cytokines (TNF-α, IL-6) [146].

4.4 The Aging Microenvironment Impairs Remyelination

Experimental, histopathological, and neuroimaging studies demonstrate a progressive aging-related decline in remyelination efficiency [147–149]. In MS, aging accelerates the accumulation of chronic lesions, with many patients transitioning to a progressive disease phase between 40 and 45 years. This shift markedly increases the risk of irreversible axonal degeneration and permanent disability [150–152]. Age-related remyelination failure is largely driven by OPCs dysfunctions, which involve two interconnected mechanisms: Intrinsic OPCs senescence and microenvironmental deterioration [153–156]. Transplantation experiments highlight the dominant influence of the microenvironment. Aged OPCs regain a youthful regenerative capacity and transcriptional profile when placed in a young CNS matrix, whereas young OPCs adopt impaired function in an aged environment [102]. This dysfunction may primarily arise from age-dependent increases in ECM stiffness, which excessively activates the mechanosensitive ion channel Piezo1 on OPCs, reducing their regenerative potential [102]. Furthermore, fibroblast growth factor 17 (FGF17), which supports OPC proliferation and differentiation, declines with age in both human cerebrospinal fluid (CSF) and mouse neurons [157]. Remarkably, infusing young CSF or FGF17 into aged mice enhances hippocampal myelination and rescues memory deficits, underscoring the potential of CSF-based therapies [157]. However, clinical translation remains limited by incomplete knowledge of FGF17 dynamics in human CSF and the unknown safety and efficacy of CSF infusion in patients.

The aged microenvironment is characterized by chronic, low-grade inflammation [6]. Interestingly, demyelinating injury promotes the accumulation of senescent microglia, which upregulate components of the senescence-associated secretory phenotype (SASP). These changes exacerbate inflammation and suppress remyelination [112]. Senescent microglia and macrophages exhibit diminished migration and phagocytic capacity, leading to myelin debris accumulation [130,158,159]. This dysfunction is associated with downregulation of the retinoid X receptor (RXR) pathway [160]. RXR is both a ligand-activated receptor and a transcription factor of genes related to macrophage immune regulation function and cholesterol transport, which is a positive regulator of remyelination [161]. Deletion of microglial RXRα in young mice delays debris clearance and remyelination, which mirrors aged microglial pheno-

types [160]. Notably, pharmacological activation of RXR, particularly with the RXR-γ agonist bexarotene, has shown promise in promoting remyelination and has progressed to a phase 2a clinical trial [162].

In addition, senescent microglia display impaired cholesterol processing, with insufficient activation of LXR-dependent efflux pathways. This defect leads to the accumulation of crystalline cholesterol within foam cells, triggering lysosomal rupture and NLRP3 inflammasome activation [130]. Moreover, astrocytes in the aged CNS also exhibit senescent features, including hypertrophic reactive morphology and autophagic vacuole accumulation [163]. These cells reduce cholesterol biosynthesis due to downregulation of key enzymes, limiting the lipid supply available for oligodendrocytes [164,165].

5. Autoimmune-Mediated Demyelination

5.1 How Autoimmune Disorders Invade the CNS

Autoimmune disorders of the CNS arise from failures in immune tolerance, leading to aberrant responses against self-antigens in neural tissues [166]. Major examples include demyelinating diseases such as multiple sclerosis (MS), acute disseminated encephalomyelitis, neuromyelitis optica spectrum disorder (NMOSD), glial fibrillary acidic protein astrocytopathy (GFAP-A), and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Other autoimmune encephalitides include anti-NMDAR encephalitis, anti-leucine glioma inactivated 1 (LGI-1) encephalitis, and anti-gamma aminobutyric acid-B (GABA-B) receptor encephalitis, etc. [166]. Among these, MS serves as the prototypical model and is widely studied using experimental autoimmune encephalomyelitis (EAE), lysolecithin (LPC)-induced, ethidium bromide (EB)-induced, cuprizone (CPZ)-induced, and viral infection models [167]. Of these, only EAE and viral models recapitulate autoimmune pathophysiology, with EAE remaining the most widely used platform to dissect mechanisms of autoimmune demyelination [168,169]. Insights from both EAE and MS patients indicate that disease progression occurs through three major phases [170].

Activation of the peripheral immune system. Central thymic tolerance eliminates most reactive T cells, though some escape to the periphery [170]. Under physiological conditions, peripheral tolerance mechanisms, including regulatory T cells and intrinsic lymphocyte inhibition, constrain their activation [170]. However, tolerance breach of peripheral tolerance via molecular mimicry or epitope spreading activates these escaped T cells. Once activated, they acquire the ability to disseminate in circulation and compromise BBB integrity [171–173].

Compromise of the blood-brain barrier. The CNS immune privilege relies on multiple protective barriers, including the BBB, blood-CSF barrier, and meningeal-lymphatic isolation [174]. Reactive T cells trigger the expression of adhesion molecules on endothelial cells, such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin, facilitating their migration across the BBB [173,175]. Recent studies reveal additional entry routes: meningeal lymphatic vessels that permit direct access of immune cells into the CNS [176]. Additionally, through the CSF, blood-derived innate immune cells located in the meningeal, perivascular, and ventricular spaces present antigen to T cells patrolling in CSF, which may also cause CNS inflammation [171].

Demyelination in brain parenchyma. Within the CNS, reactive T cells recognize antigen-presenting cells (APCs) such as microglia, macrophages, and astrocytes, which trigger their reactivation [170]. Reactivated T cells drive clonal expansion of $CD4^+$ T helper (Th) subsets, particularly Th1 and Th17 cells, which secrete pro-inflammatory cytokines and chemokines that amplify inflammation and recruit additional peripheral immune cells [170]. Myelin loss and axonal injury are then mediated by neurotoxic molecules, including ROS, nitrogen species (RNS), matrix metalloproteinases (MMPs), and TNF-α, secreted by activated macrophages, microglia, and astrocytes [177].

5.2 Multiple Sclerosis

Multiple sclerosis (MS) is characterized by focal inflammation, demyelination, and eventual neurodegeneration [169]. In addition to T cell-driven pathology, infiltrating peripheral immune cells such as monocyte-derived macrophages (MDMs) and neutrophils amplify neuroinflammation [169]. The mechanisms driving their generation remain incompletely understood. Recent work by Shi *et al.* [178] reveals that reactive T cells home to bone marrow in a CXCR4-dependent manner, where they stimulate hematopoietic expansion through CCL5 secretion. This finding not only deepens the understanding of reactive T cells as disease initiators but also highlights the therapeutic potential for hematopoietic stem cell transplantation (HSCT) in MS [178]. In a clinical trial, HSCT has shown superior efficacy to disease-modifying therapies (DMTs) in patients with relapsing-remitting MS, significantly delaying disease progression and improving neurological function [179]. Autologous HSCT has now emerged as a promising treatment option for patients with active RR-MS who show inadequate response to DMTs. However, several challenges remain, including precise patient selection, optimal timing of treatment, and integration into existing therapeutic sequences, which warrant further investigation to fully realize its clinical potential [180]. Dendritic cells (DCs) also shape disease course by suppressing reactive T cell activation and pro-inflammatory responses through lactate-mediated activation of the HIF-1α pathway, positioning them as a potential intervention target [181].

Beyond immune-mediated mechanisms, progressive MS is driven by neuronal and axonal injury. Oxidative stress, iron toxicity, and glutamate-induced calcium dysregulation contribute to cumulative neurodegeneration [177].

Neurodegeneration in MS remains an unresolved challenge [177]. Aberrant activation of the stimulator of interferon genes (STING) pathway in neurons may further accelerate neuronal damage [182]. In this process, IFN-γ released by immune cells and glutamate secreted by glia can activate STING signaling, which promotes glutathione peroxidase 4 (GPX4) autophagic degradation and ferroptosis, driving neuronal inflammatory stress responses [182].

Astrocytes also play critical roles in MS pathogenesis. They are recognized as mediators of environmental MS risk (e.g., herbicide exposure) and drivers of neurodegenerative processes in chronic MS [183,184]. In progressive MS stages, astrocytes exhibit disrupted sphingomyelin metabolism, which leads to elevated cytosolic phospholipase A2 (cPLA2) activity. This shift activates mitochondrial antiviral-signaling protein (MAVS) activation, which amplifies NF-κB-driven inflammation while reducing hexokinase 2 activity and lactate production. The loss of lactate weakens astrocytic metabolic support to neurons, leading to their injuries [184]. Emerging evidence suggests that astrocytic dysfunction may arise from inactivation of protective genes. Notably, C-type lectin domain-containing 16A gene (CLEC16A) dysfunction in astrocytes shows strong associations with neurodegeneration in MS patients. CLEC16A-driven mitophagy in astrocytes suppresses activation of NF-κB, NLRP3 inflammasomes, and gasdermin D, mitigating CNS pathology in EAE models [185].

Pathological and neuroimaging studies reveal that MS lesions evolve dynamically across disease stages, which is reviewed by Matthews *et al.* [186]. Remyelination capacity correlates with lesion chronology [187]. Acute lesions exhibit robust OPCs recruitment and increased density of cells, showing "shadow plaque" in pathological sections, whereas chronic lesions show OPC depletion and arrested pre-myelinating oligodendrocytes [187–189]. Mapping this lesion heterogeneity remains a challenge. Lin *et al.* [190] developed a multimodal pipeline integrating MRI images with spatial transcriptomics and tissue staining, identifying 28 lesion microenvironments in the course of the EAE marmoset model and identifying perivascular and periventricular aSERPINE1$^+$ astrocyte subsets as early lesion initiators. Notably, they suggest that the ratio of proton density-weighted signal to T1 relaxation time is an important MRI biomarker, which can predict lesion formation 30 days before conventional MRI examination, offering a potential breakthrough in early MS diagnosis [190].

Current MS therapies mainly target peripheral inflammation, which provides symptom relief but fails to prevent progressive neurodegeneration [177,189]. Enhancing endogenous remyelination has emerged as a promising therapeutic paradigm to halt disease progression [9]. Early efforts focused on promoting OPC differentiation, yet efficacy depends on OPCs availability, which varies among patients [191–193]. Acute active lesions often contain adequate OPCs that fail to differentiate, whereas chronic progressive lesions are characterized by OPCs depletion and microenvironmental inhibition of remyelination [101,187,194]. These differences underscore the necessity for stage-specific therapeutic strategies tailored to the evolving lesion microenvironment.

5.3 Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune demyelinating disease marked by recurrent episodes of visual, motor, or sensory dysfunction, often leading to neurological disability [195]. The core pathogenic mechanism involves Aquaporin 4 (AQP4)-mediated inflammatory demyelination, accompanied by retinal ganglion cell (RGC) degeneration through microglial activation [196]. Notably, both demyelination and remyelination in NMOSD rely heavily on the regulation of astrocytes [197].

NMOSD is now recognized as a primary astrocytopathy [197]. Cerebrospinal fluid GFAP levels serve as biomarkers for astrocytic injury and clinical severity in NMOSD [198]. Acute phase NMOSD exhibits significantly higher GFAP concentrations compared to MS, with rapid normalization during chronic phases [198]. AQP4 water channels, expressed on astrocyte end-feet, are the principal targets of pathogenic AQP4-IgG autoantibodies [199]. The binding of these antibodies during acute relapses activates the classical complement cascade, driving infiltration of granulocytes and lymphocytes [200]. Then, escalating inflammation initially damages astrocytes, subsequently extending to OLs and neurons [201]. Astrocytic dysfunction also impairs remyelination [202]. Notably, AQP4-IgG-positive patients demonstrate reduced CXCL12 expression, a key astrocyte-derived chemokine required for OPCs activation and remyelination [202]. Although astrocytes occupy a central role in NMOSD pathogenesis, the disorder arises from broader dysregulation involving oligodendrocytes, microglia, neurons, and infiltrating immune cells, a complexity that requires further validation [203].

6. Demyelination-Associated Pathologies

Neurodegenerative and neurovascular disorders have long been described as neuronal loss and injury. However, growing evidence highlights myelin degeneration and OL dysfunction as shared features across these conditions [7,204]. Traditionally, myelin breakdown was regarded as secondary to neuronal pathology. However, recent work suggests that primary myelin defects in Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and ischemic stroke may actively drive disease onset and progression [8,205–207]. Here, we focus on AD and ischemic stroke, where demyelination-related mechanisms are increasingly recognized, and pro-remyelination strategies show therapeutic promise [208–210].

6.1 Alzheimer's Disease

The prevalence of AD is rising sharply with population aging, projected to exceed 139 million cases by 2050, imposing substantial individual and societal burdens [211]. Classically, AD is defined by extracellular amyloid-β (Aβ) plaques and intracellular tau tangles. However, limited correlation between these pathological hallmarks and clinical manifestations has prompted investigation into additional pathogenic mechanisms [212–214].

AD was long considered a gray matter disorder, but white matter pathology has gained increasing recognition [214,215]. White matter hyperintensities often appear in presymptomatic stages, predicting cognitive decline independently of Aβ or tau burden [216–218]. Postmortem studies report focal demyelination in 60% of AD patients, accompanied by OL loss and axonal degeneration [219, 220]. Given the essential role of OLs in preserving axonal conduction and structural integrity, their degeneration is likely a key contributor to cognitive decline in AD [221]. Recent transcriptomic analyses reinforce this view. Kenigsbuch *et al.* [222] identified a distinct population of disease-associated oligodendrocytes (DOLs) across multiple AD mouse models, independent of Aβ pathology. These OLs express markers such as SERPINA3N and SERPINA3, with levels correlating with cognitive impairment.

Importantly, myelin abnormalities may occur before Aβ and tau deposition, positioning myelin degeneration as one of the earliest detectable events in AD pathogenesis [205]. Using combined models of genetically induced myelin degradation and AD, Depp *et al.* [205] demonstrated that myelin damage promotes Aβ deposition by redirecting disease-associated microglia (DAMs) toward demyelinated regions, thereby diminishing their capacity for Aβ clearance. Aβ, in turn, worsens myelin degeneration, creating a self-reinforcing loop [223]. This interplay is reflected in human postmortem studies showing spatial overlap between Aβ plaques and OL loss [219].

Mitochondrial dysfunction, a shared pathological hallmark of aging and AD, triggers oxidative stress that creates a microenvironment detrimental to myelin maintenance [224,225]. Aβ, tau, APOE4 genotype, and metal ion imbalance all converge on impaired electron transport chain function, collectively exacerbating oxidative stress [226,227]. Notably, OLs exhibit greater susceptibility to oxidative stress compared to astrocytes and microglia, owing to low glutathione levels and high iron content [228]. This vulnerability may predispose OLs to oxidative damage [229].

APOE4 and TREM2 variants constitute major genetic risk factors for AD [230,231]. The APOE4 variant disrupts the lipid-binding region of APOE, impairing cholesterol transport [94]. Single-cell transcriptomic analyses of postmortem human brains further link APOE4 to myelin pathology, showing reduced expression of myelination-related genes and altered cholesterol homeostasis in oligodendrocytes of APOE4 carriers [94]. In co-culture experiments, APOE4 impairs intercellular lipid transport between astrocytes and OL [232]. Variants in *TREM2*, another AD risk gene, compromise microglial lipid sensing and myelin debris clearance [233]. Conversely, TREM2 overexpression restores phagocytic capacity, ameliorating both neuropathology and behavioral deficits in AD models [233].

Notably, remyelination-based interventions improve cognition in animal models, underscoring the therapeutic relevance of myelin protection and repair in AD [205].

6.2 Ischemia-Mediated Myelin Injury

Ischemic stroke (cerebral infarction) is caused by stenosis or occlusion of cerebral blood supply arteries, resulting in neurological dysfunction in affected brain regions [234]. White matter injury strongly correlates with post-stroke dementia risk [234]. In middle cerebral artery occlusion (MCAO) mouse models, acute OLs death causes myelin loss within two weeks of stroke, while insufficient remyelination in later weeks impairs neuronal survival and functional recovery [8]. These findings highlight myelin integrity as both a prognostic marker and a therapeutic target in ischemic stroke. Notably, Pro-remyelination approaches, including muscarinic receptor 1 deletion or treatment with the pro-OPC differentiation drug clemastine, maintain neuronal survival and enhance functional recovery in MCAO models [8].

Multiple mechanisms converge to damage myelin after ischemia, including metabolic failure, excitotoxicity, and inflammation [235]. Energy depletion impairs ion channel functions, such as Kir4.1 on OPCs, disrupting myelination [236,237]. Excitotoxicity is driven by extracellular glutamate accumulation, resulting from the reversed operation of the glutamate transporter GLT-1 under ischemic conditions, which triggers harmful calcium overload in neurons and OLs via AMPAR overactivation [238,239]. Furthermore, abnormal ATP signaling activates P2X7 receptors on glia, inducing oxidative stress and exacerbating OL injury [240,241].

Post-ischemic myelin debris accumulation and local inflammatory cascades impede endogenous white matter repair [242]. HDAC3, a histone deacetylase implicated in various neurological disorders, is selectively upregulated in microglia after ischemic stroke [243,244]. The HDAC3/PU.1 axis drives pro-inflammatory microglia subset proliferation, exacerbating demyelination and neuronal injury [244]. Moreover, perivascular microglia respond to BBB breakdown by engulfing leaked low-density lipoprotein (LDL), but excessive lipid ingestion overwhelms their clearance capacity, impairing debris degradation and worsening white matter injury [245]. Interestingly, astrocytes also acquire phagocytic activity in chronic ischemic stages, mediated by LCN2-LRP1 signaling, but their debris uptake worsens demyelination [246]. Moreover, astrocyte-derived CXCL5 can inhibit microglial debris clearance, aggravat-

ing white matter damage and cognitive decline in carotid stenosis mouse models [247].

Extracellular vesicles (EVs), the nanoscale lipid bilayer particles containing proteins, lipids, and microRNAs, add another layer of regulation [248]. Astrocyte-derived EVs deliver pro-remyelinating factors such as FGF-2 and vascular endothelial growth factor (VEGF) to enhance OPCs migration and differentiation under ischemic conditions [249,250]. Interestingly, a recent study reveals that macrophage-derived foam cells within atherosclerotic plaques communicate with CNS microglia via EVs [251]. These EVs deliver miR-101-3p to microglia, which suppresses Nrf2 activity, triggering microglial metabolic dysfunction and exacerbating ischemic demyelination [251]. This pathway is independent of traditional hypoperfusion-mediated white matter injury, suggesting that atherosclerotic plaques may initiate myelin damage through early microenvironmental interference before overt clinical manifestations [251].

Pathological overlap between AD and stroke further supports a microenvironmental perspective. Approximately 80% of AD patients exhibit cerebral small vessel disease from vascular Aβ deposition, causing local white matter hypoperfusion and injury [252,253]. These shared mechanisms highlight myelin vulnerability as a common axis linking neurodegenerative and neurovascular disease.

7. Pro-Remyelination Therapy Targeting the Microenvironment

The development of high-throughput screening platforms has accelerated the discovery of compounds that promote OPCs differentiation, with several advancing to clinical trials [208,254,255]. Notable candidates include muscarinic receptor antagonist clemastine, histamine receptor antagonist GSK239512, and RXR-γ agonist bexarotene [10]. Unfortunately, none of these agents has shown improvement in core clinical outcomes of multiple sclerosis, such as relapse rate, disability scores, or brain atrophy. Clemastine reduced visual evoked potential (VEP) latency in relapsing MS, but the effect was limited by small sample size (n = 50) [256]. GSK239512 induced modest changes in magnetization transfer ratio (MTR), though these did not consistently align with MRI measures [257]. Bexarotene failed its primary outcome (mean lesion MTR) and showed poor tolerability [162]. Emerging strategies focus on microenvironmental modulation through synergistic approaches, including neutralizing OPC differentiation inhibitors, mitigating CNS inflammation, and enhancing myelin debris clearance (Table 1, Ref. [123,258–269]) [270]. In addition, anti-aging is also considered an effective auxiliary means to improve the response capacity of OPCs [258].

7.1 Targeting Extracellular Inhibitory Signals

Pathological deposition of ECM components and axonal surface molecules critically impair remyelination [25]. CSPGs restrict cell migration and repair in MS and traumatic injuries [271,272]. Inhibiting CSPG biosynthesis with the glucosamine derivative Ac-4,4-diF-GlcNAc reduces neuroinflammation and improves clinical outcomes in EAE models [259]. Hyaluronic acid, which accumulates in MS and EAE lesions, halts OPC differentiation at premyelinating stages [273]. The flavonoid derivative S3, by blocking hyaluronidase, restores OPC maturation in lysolecithin-induced demyelinating mice [260]. In addition, neurite outgrowth inhibitor receptor co-receptor (LINGO-1) inhibits OPCs differentiation and axonal regeneration [274]. Clinical trials of the LINGO-1 antibody opicinumab showed modest benefit in optic neuritis but no efficacy in relapsing MS [261,262].

7.2 Regulating CNS Inflammation

Bruton's tyrosine kinase (BTK), a regulator of B cell and myeloid cell activation [275]. It is an important target for the treatment of mantle cell lymphoma and chronic lymphocytic leukemia and has emerged as a therapeutic target in MS [275]. In EAE, the oral BTK inhibitor evobrutinib suppresses peripheral immune activation, shifts microglia away from a pro-inflammatory phenotype, and enhances phagocytosis, collectively promoting remyelination [276]. In clinical trials, evobrutinib lowered MRI-enhancing lesion counts in a dose-dependent manner in relapsing MS patients [263]. However, comparative studies revealed that its therapeutic efficacy did not surpass its active comparator, teriflunomide [277]. Broader immunomodulators are also under investigation, including ibudilast and masitinib. Ibudilast, a multi-target agent inhibiting cyclic nucleotide phosphodiesterases (PDEs) and TLR4, showed efficacy in slowing cerebral atrophy progression in phase 2 MS trials [265]. Masitinib, a selective tyrosine kinase inhibitor, significantly delayed disability progression in phase 3 MS studies [267]. Notably, these agents are also being tested in AD [267]. BTK upregulation observed in AD patient brains and 5$\times$FAD mouse models positions it as a potential therapeutic target [264]. BTK inhibition mitigates PLCγ2 activation (a key AD genetic risk factor) and prevents synaptic loss [264]. Moreover, chronic ibudilast administration reduces amyloid plaque burden, tau pathology, and spatial memory deficits in transgenic 344-AD rats [266]. Masitinib's phase 3 trials also demonstrated cognitive benefits in mild-to-moderate AD patients [268]. However, these findings remain preliminary, and the mechanisms underlying the efficacy of these drugs in AD require further validation. To note, there is currently no direct evidence linking their effects to enhanced remyelination in AD.

Table 1. Microenvironment-targeted potential remyelinating agents.

Drug	Mechanism	Result
Ac-4,4-diF-GlcNAc [259]	Inhibits astrocytic CSPG synthesis and reduces monocyte and lymphocyte infiltration.	Mitigated clinical severity in EAE mice and reduced immune cell infiltration.
S3 [260]	A modified flavonoid. Suppresses hyaluronidase activity, reduces high-MW HA degradation products, and reverses HA-mediated inhibition of OPC maturation.	Enhanced remyelination in LPC-induced demyelination models and improved conduction velocity in lesions.
Opicinumab [261,262]	A human monoclonal antibody against axonal inhibitor LINGO-1. Blocks LINGO-1-mediated OPC differentiation inhibition.	Improved optic nerve conduction in optic neuritis patients (phase 2 trials). No efficacy observed in relapsing MS (phase 2 trials).
Evobrutinib [263]	A highly selective BTK inhibitor. Suppresses CNS immune infiltration, enhances phagocytosis, and promotes remyelination.	Reduced MRI-enhancing lesions in relapsing MS patients (phase 2b trial).
CC-292 [264]	A BTK inhibitor. Inhibits PLCγ2 activation and reduces microglial phagocytosis.	Modulates phagocyte function in 5×FAD mice, potentially reducing synaptic loss.
Ibudilast [265,266]	A non-selective PDE inhibitor. Antagonizes TLR4, inhibits pro-inflammatory cytokines, and promotes neurotrophic factor release.	Slowed brain atrophy in MS patients (phase 2 trials). Reduced AD pathology in the hippocampal dentate gyrus of 344-AD rat models and enhanced spatial learning/memory.
Masitinib [267,268]	A selective tyrosine kinase inhibitor. Suppresses microglia, macrophages, and mast cell activity.	Slowed disability progression in MS patients (phase 3 trials). Improved cognition in mild-to-moderate AD patients (phase 3 trials).
AL002 [123,269]	A TREM2-agonistic monoclonal antibody. Enhances myelin debris clearance, OPC maturation, and modulates inflammation.	Enhanced remyelination and axonal integrity in CPZ-induced demyelination models. Reduced amyloid plaque formation and behavioral deficits in 5×FAD mice.
Metformin [258]	Activates AMPK pathway, improves cellular senescence and mitochondrial function, and restores OPC responsiveness to differentiation signals.	Enhanced remyelination in EB-induced demyelination models.

Note: This table summarizes the agents that have the potential to promote remyelination through targeted modulation of the microenvironment in recent years, as well as their mechanisms of action and results. CSPG, chondroitin sulfate proteoglycan; EAE, experimental autoimmune encephalomyelitis; LINGO-1, immunoglobulin domain-containing protein 1; BTK, Bruton's tyrosine kinase; PLCγ2, phospholipase C gamma 2; PDE, phosphodiesterases; MS, multiple sclerosis; 5×FAD, 5× Familial Alzheimer's Disease; AMPK, AMP-activated protein kinase.

7.3 Enhancing Phagocytosis and Debris Clearance

Several molecular targets have been identified to enhance phagocytosis, including TREM2, CD36, and Mer tyrosine kinase (MerTK) [120]. In CPZ-induced models, the TREM2 agonist AL002a enhances myelin clearance, increases OPC density, and boosts remyelination [123]. TREM2 activation also shows promise in AD, where the agonist AL002c reduces Aβ plaque burden and neuritic damage in mouse models [269]. Phase 1 trials of AL002 demonstrated enhanced TREM2 signaling in patient CSF with good safety profiles [278]. These findings suggest that enhancing phagocytosis could serve as a strategy for both demyelinating and neurodegenerative diseases.

7.4 Anti-Aging Treatment

Heterochronic parabiosis study shows that a youthful systemic environment can restore remyelination in aged mice [279]. Pharmacological advances have identified promising anti-aging agents, including RXR agonists, nicotinamide, and metformin [161,258,280]. Combining agents may be particularly effective: pairing the pro-differentiation agent clemastine with metformin, for example, can both stimulate OPCs differentiation and overcome age-related resistance [281]. In aged demyelination models, metformin reduces SASP markers, reverses regenerative deficits in OPCs, and restores OPCs responsiveness to pro-regenerative agents [258].

8. Cell Transplantation Therapies for Microenvironment Remodeling

8.1 Mesenchymal Stem Cell Therapy

Mesenchymal stem cell (MSC) therapy has shown potential in treating MS through its immunomodulatory and neurorestorative properties [282]. MSCs secrete anti-inflammatory cytokines, including indoleamine 2,3-dioxygenase (IDO) and prostaglandin E2 (PGE2), which effectively suppress T-cell proliferation, rebalance T-cell subsets, and attenuate autoimmune responses [283]. They also regulate B-cell and dendritic cell activity through direct contact and paracrine signaling, lowering autoantibody

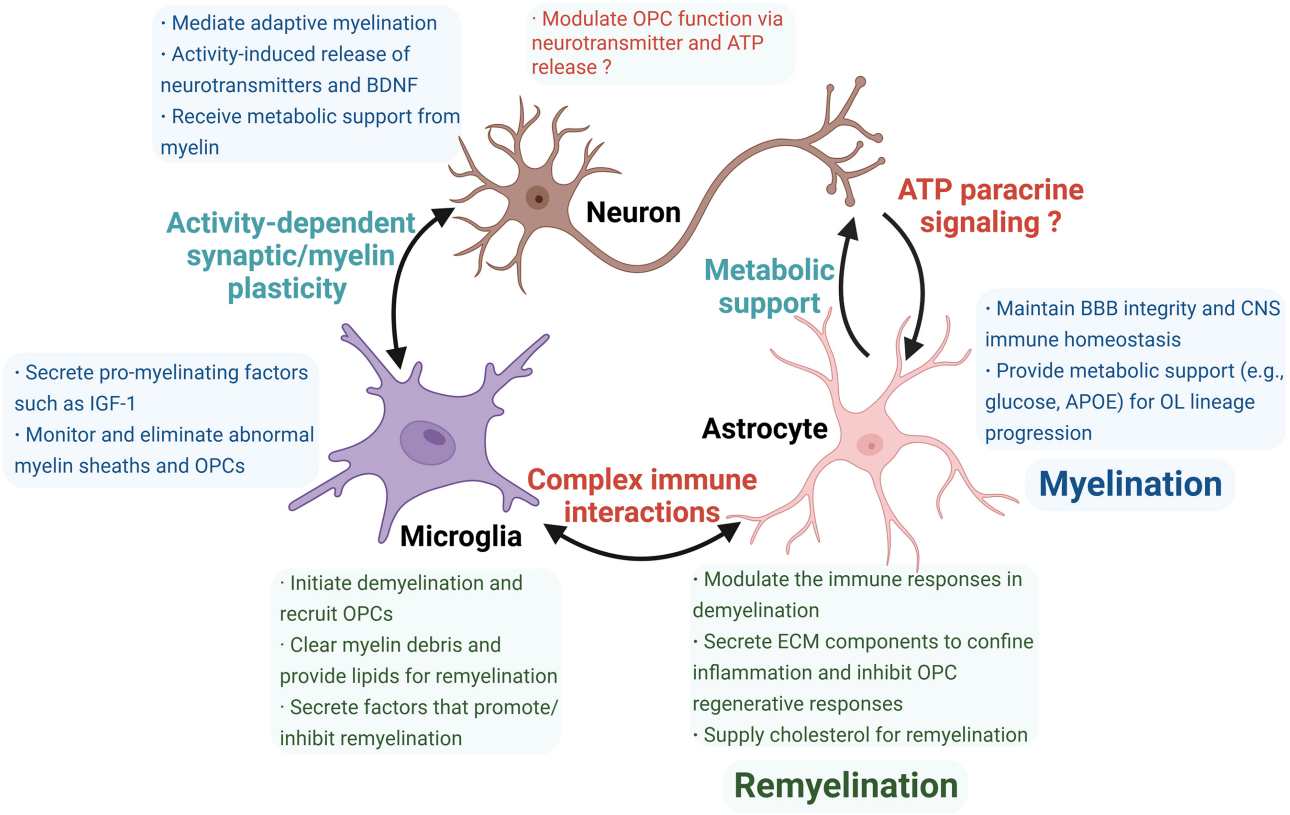

Fig. 3. Summary of roles and interactions of neurons, microglia, and astrocytes in myelination (blue box) and remyelination (green box). Neurons, microglia, and astrocytes perform distinct functions during myelination and remyelination, contributing to microenvironmental differences between these two processes. Cellular crosstalk represents an emerging research area with unresolved questions (red highlights), including the incompletely understood role of neurons in remyelination and their interactions with astrocytes, which require further validation. Additionally, complex immune communication between microglia and astrocytes remains unclear. ATP, adenosine triphosphate; ECM, extracellular matrix. The figure was drawn using Biorender (https://www.biorender.com).

production and weakening antigen presentation [284]. Beyond immunomodulation, MSCs release neurotrophic factors, including BDNF and NGF, that support OPCs survival and differentiation [285]. In EAE models, MSC administration decreases demyelinated lesions and ameliorates neurological deficits [282]. Preclinical studies and early-phase clinical trials indicate favorable safety profiles and tolerability of MSC therapy, with some trials reporting symptom improvement and reduced disease activity [286]. However, challenges, including optimal dosing, delivery routes, and treatment timing, require further investigation to advance clinical translation [287].

8.2 Replacement Therapies for Microglia

Another strategy aims to restore CNS homeostasis by replacing dysfunctional microglia. This can be achieved through bone marrow transplantation (BMT), hematopoietic stem cell transplantation (HSCT), or direct transplantation of microglia [288]. BMT and HSCT have been used for adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), X-ALD, MLD, and lysosomal storage disorders (LSDs), where therapeutic benefits partially stem from bone marrow-derived monocyte-macrophages compensating for impaired microglial functions [289–293]. Strikingly, a recent study reveals that BMT effectively replaces genetically defective microglia in patients with ALSP, leading to halted disease progression [294]. Cell replacement therapy also shows promise in globoid cell leukodystrophy (GLD/Krabbe disease), a severe leukodystrophy caused by galactocerebrosidase (GALC) mutations, where macrophages transform into neurotoxic globoid cells [295]. Transplantation of GALC-expressing monocytes into GLD mouse models reduces pathological hallmarks and extends survival [295].

Despite these advances, conventional transplantation approaches have limitations. Chemotherapy and radiotherapy have the side effects of exacerbating CNS injury, and bone marrow-derived cells are unable to completely replicate microglial and BAM functions [293,296]. To overcome these barriers, emerging strategies combine resident macrophage depletion with targeted microglial transplantation [293]. In LSD and AD mouse models, the CSF1R inhibitor PLX3397 enables efficient microglial replacement, leading to improved neurological outcomes [296].

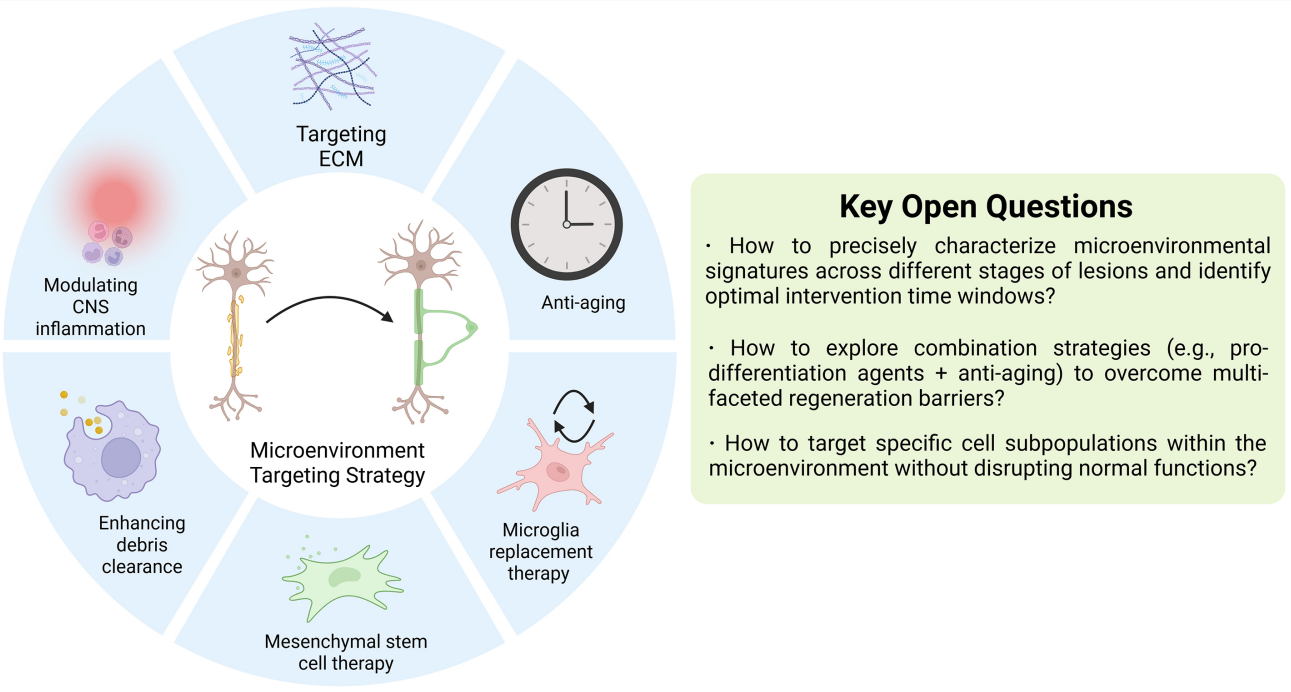

Fig. 4. Summary and outlook for microenvironment-targeting therapeutic strategies. To date, most strategies remain at the pre-clinical stage. A notable exception is microglia replacement therapy, which has achieved clinical success in ALSP patients by halting disease progression. However, the complexity and high heterogeneity of microenvironmental alterations in autoimmune demyelinating diseases and neurodegenerative disorders pose significant challenges for therapeutic development. Future research should prioritize addressing these core issues to facilitate translation. ALSP, adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; CNS, central nervous system. The figure was drawn using Biorender (https://www.biorender.com).

Moreover, another study reveals that PLX3397 pretreatment enhances monocyte-derived macrophage replacement of BAMs in mice [293]. Given that PLX3397 is already FDA-approved for tenosynovial giant cell tumors and under investigation for glioblastoma, its use in transplantation strategies underscores translational potential [297]. These synergistic approaches suggest that integrating microglial depletion with cell transplantation could provide a viable therapeutic avenue for neurodegenerative and demyelinating diseases.

9. Conclusions

The microenvironment regulates dynamic myelin remodeling by coordinating OPCs proliferation, recruitment, differentiation, and myelin formation. Microenvironmental homeostasis is essential for protecting myelin against immunological, degenerative, and ischemic challenges, as well as for regeneration after injury. This review synthesizes current knowledge on microenvironmental regulation in demyelination and remyelination, especially the roles and interactions between neurons, microglia, and astrocytes (Fig. 3). These interactions form a highly complex network, and disentangling the dominant regulatory roles remains a central research challenge. Future progress will depend on the development of biomarkers and analytical platforms capable of resolving microenvironmental composition with spatiotemporal precision. Such tools would allow the identification of critical cellular and molecular determinants of myelin injury and repair. Recent breakthroughs, such as the discovery of injury-initiating aSERPINE1^{+} astrocyte subsets through integrated neuroimaging-transcriptomic approaches, exemplify this paradigm [190]. Microenvironmental targeting medicines and cell transplantation strategies hold significant promise for developing interventions tailored to lesion-specific pathological states (Fig. 4). Successful clinical translation of remyelination strategies could transform the treatment of diverse CNS disorders and bring the field closer to personalized medicine.

Author Contributions

YW, LT, LL, XH, SZ, HS contributed to the study conception and design. YW, LL, and LT collected and sorted the references and designed and prepared the figures and tables. The first draft of the manuscript was written by YW, LL and LT. The content editing was performed by SZ, HS and YW. The format editing was in the charge of XH. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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