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REVIEW

Emerging Insights into the Role of Macrophages in Multiple Sclerosis: Pathogenesis and Potential Therapeutic Strategies

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Abstract: Multiple sclerosis (MS) is a chronic, autoimmune, demyelinating disease of the central nervous system (CNS) in which macrophages play a pivotal and multifaceted role. These highly plastic immune cells are key effectors in the immunopathology of MS, contributing to both inflammatory-driven demyelination and subsequent tissue repair. Historically, macrophage function was viewed through the binary lens of pro-inflammatory M1 and anti-inflammatory M2 polarization. However, recent research reveals a far more complex spectrum of activation states within the dynamic microenvironment of MS lesions. Understanding the intricate signals and molecular pathways that govern macrophage polarization in the CNS represents a critical frontier for therapeutic innovation. Interventions aimed at rebalancing macrophage phenotypes have yielded encouraging results in preclinical models, and some therapeutic agents are now advancing into clinical trials. Future investigations are focused on the diverse functions of macrophages in MS pathogenesis, including their involvement in oxidative stress, antigen presentation, and myelin debris clearance. A particularly innovative approach involves harnessing macrophages as cellular vehicles for targeted drug delivery across the blood-brain barrier, offering a potential solution to one of the most significant challenges in CNS therapeutics. The primary challenge now lies in the safe and effective clinical translation of these macrophage-centered therapies. Successfully navigating this transition from bench to bedside holds the potential to deliver transformative treatments that can halt disease progression and restore neurological function for individuals living with this debilitating disease.

Keywords: multiple sclerosis, macrophage, central nervous system, therapy

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Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system (CNS) characterized by inflammatory demyelination, neurodegeneration, and gliosis.[1,2] Affecting approximately 2.8 million people globally with rising prevalence,[3,4] MS primarily targets CNS white matter. The pathological hallmark of MS is demyelination, which refers to the destruction of the myelin sheath that insulates nerve axons.[5] This process, driven by inflammation, disrupts neural signal transmission and leads to progressive neurological disability. While the precise etiology remains elusive, established risk factors include genetic predisposition, Epstein–Barr virus infection, smoking, childhood obesity, and low serum vitamin D levels,[6–9] reflecting a complex interplay of genetic, environmental, and immunological influences on disease susceptibility.

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MS pathology extends beyond acute demyelination. Chronic inflammation, persistent neurodegeneration, and reactive gliosis collectively drive disease progression and irreversible accumulation of disability.[3,10] Early disease stages feature transient inflammation and immune activation, often followed by attempts at repair.[11,12] Emerging evidence suggests that newly differentiated oligodendrocytes exhibit enhanced remyelinating capacity compared to surviving cells,[13] potentially underpinning transient symptom remission. However, this endogenous repair is frequently incomplete or fails over time, leading to sustained deficits. As the disease progresses, widespread microglial activation and unremitting neurodegeneration dominate the pathological landscape.[14] A critical event in active lesions is blood-brain barrier (BBB) disruption, facilitating CNS infiltration by peripheral immune cell, Among these infiltrates, macrophages present as primary effector cells, playing a pivotal and multifaceted role in both driving demyelination and modulating the inflammatory milieu.[15]

Four distinct patterns of tissue damage have been proposed to elucidate the pathophysiological mechanisms underlying MS, characterized by variations in plaque location and extent, immunoglobulin and complement deposition, myelin proteins loss, and oligodendrocyte destruction.[11,16] Despite these differences, macrophage infiltration remains a consistent and defining feature across subtypes.[17] This universal presence underscores their fundamental contribution to MS pathogenesis. Consequently, macrophages represent not only key drivers of disease but also compelling therapeutic targets. This review synthesizes current understanding of the diverse roles macrophages play across the MS spectrum and critically evaluates emerging therapeutic strategies aimed at modulating macrophage function to ameliorate disease.

CNS Macrophages: Orchestrating the Immune Response Within the Brain

Macrophages are highly plastic immune cells that exhibit diverse phenotypes and functions, shaped by distinct developmental origins and tissue-specific niches. While traditionally considered to originate solely from hematopoietic stem cells,[18,19] recent research reveals that CNS macrophages arise from multiple sources,[20] including primitive yolk sac progenitors during embryogenesis and, under pathological conditions, circulating monocytes.[21–23] As shown in Figure 1, embryonic precursors migrate to the developing brain, progressing through A1 immature progenitor and A2 pre-macrophage stages before differentiating into either parenchymal microglia or CNS border-associated macrophages (BAMs).[24] These tissue-resident populations play essential roles in CNS homeostasis, yet their equilibrium can be disrupted in disease states such as MS, where peripheral monocyte-derived macrophages (MDMs) infiltrate the brain and contribute to neuroinflammation. The coexistence of these ontogenetically distinct subsets, each with unique functional properties, complicates their discrimination but also presents opportunities for targeted therapeutic intervention.

Functional Properties of CNS Macrophages

CNS macrophages harbor diverse macrophage populations, including BAMs and microglia, which play distinct yet interconnected roles in health and disease. BAMs, encompassing perivascular, meningeal, and choroidal macrophages, are strategically positioned at interfaces between the blood and the CNS,[25] serving as gatekeepers at the perivascular space, choroid plexus, and meninges (Figure 1). In contrast, microglia are parenchyma-resident immune cells that dynamically survey the neural environment. Both populations are crucial for CNS homeostasis, regulating neurogenesis, synaptic pruning, and debris clearance, while also contributing to neuroinflammatory and neurodegenerative processes.[26,27] CNS lesions trigger microglial activation and the recruitment of peripheral monocytes, which differentiate into macrophages upon infiltrating the brain.[28,29] However, distinguishing between microglia and infiltrating macrophages remains challenging due to overlapping phenotypic and functional properties. Current strategies rely on differential surface marker expression, anatomical localization, morphological features, and genetic markers.[23,30,31] Notably, studies in experimental autoimmune encephalomyelitis (EAE), a widely used experimental model for MS,[32] have revealed that infiltrating macrophages exhibit stronger pro-inflammatory responses compared to microglia,[33] highlighting their differential contributions to neuroinflammation.

Beyond M1 and M2: The Diverse Macrophage Polarization States

The concept of macrophage polarization provides a foundational, albeit increasingly simplistic, framework for understanding their functional plasticity.[34,35] Historically, macrophages were categorized into two distinct subsets: the pro-

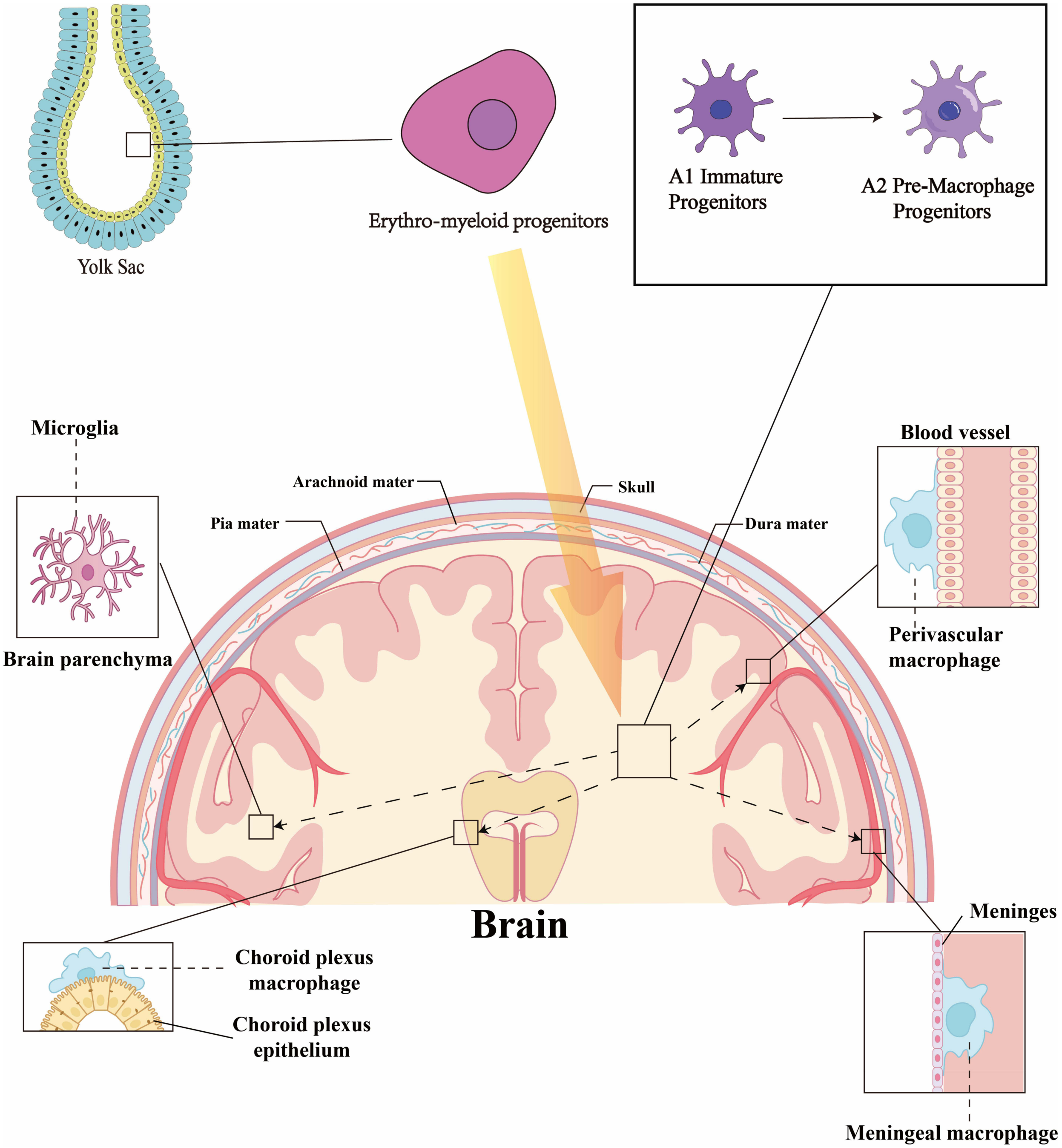

Figure 1 Developmental Origin and Anatomical Segregation of Myeloid Cells in the Central Nervous System (CNS). The CNS contains two main myeloid populations derived from yolk sac progenitors. As shown in the schematic, microglia are located within the brain parenchyma, while CNS-associated macrophages are restricted to the CNS border regions, including the meninges, perivascular spaces, and choroid plexus. Black boxes highlight the respective locations of each cell type. The differentiation from a common progenitor involves A1 and A2 intermediate stages.

inflammatory M1 phenotype and the anti-inflammatory M2 phenotype.[36–38] This limitation is especially pronounced when considering the distinct populations of resident microglia and infiltrating monocyte-derived macrophages in MS. Furthermore, compelling evidence from recent studies reveals that macrophages can co-express both M1 and M2 markers, often exhibiting intermediate or mixed phenotypes that underscore the continuous nature of their activation.[37–40] Despite its limitations, the M1/M2 paradigm remains a useful heuristic for conceptualizing the opposing functional poles of macrophage activity (Figure 2).

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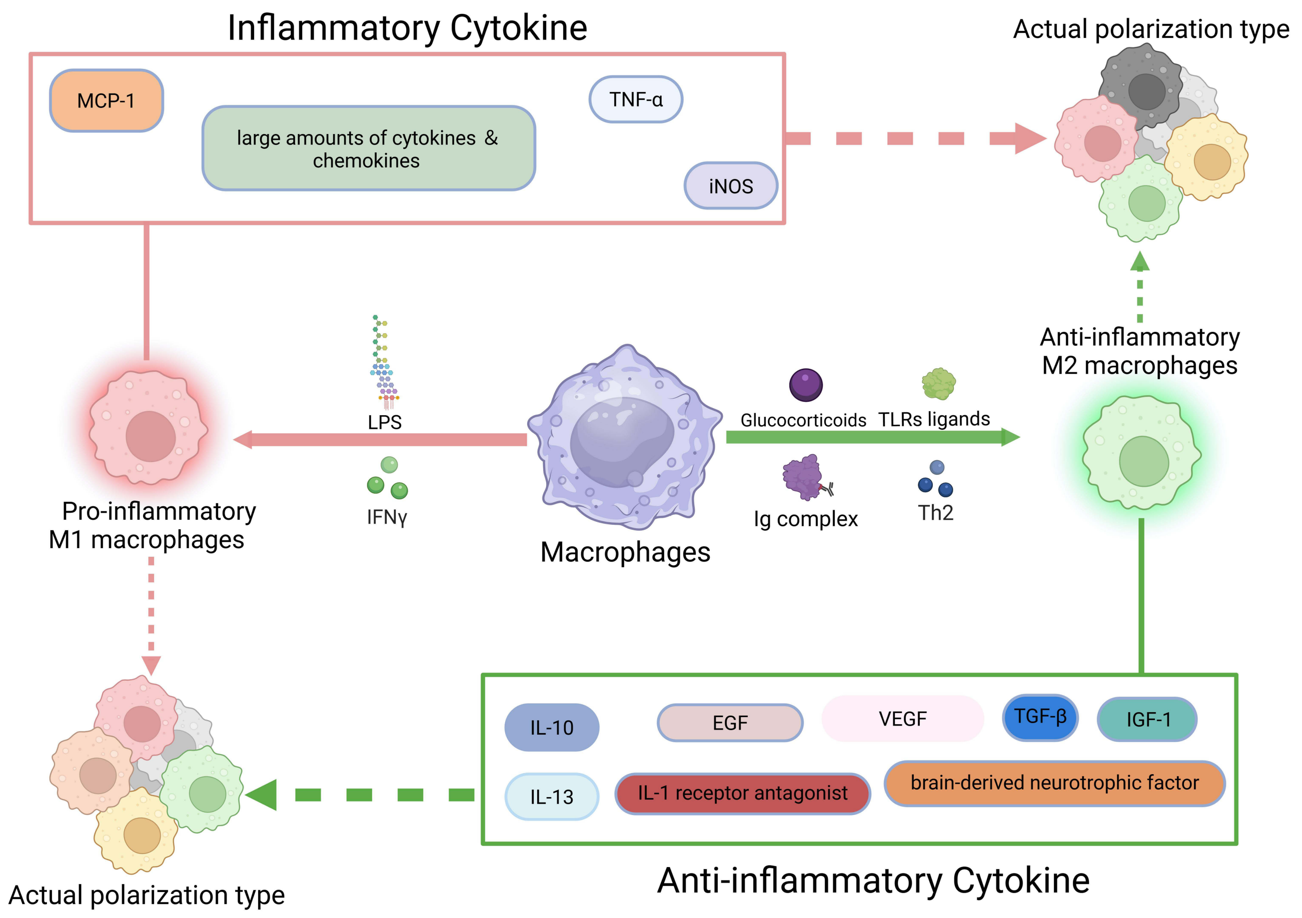

Figure 2 Macrophage Polarization: From a Dichotomous Model to a Functional Spectrum. Created in BioRender. Yang, j. (2025) https://BioRender.com/igx2k3g. This figure demonstrates the concept of macrophage polarization, contrasting the classic M1/M2 model with the reality of a functional spectrum. In the traditional model, pro-inflammatory M1 macrophages (pathway highlighted in red) are induced by LPS and IFN-γ They subsequently produce inflammatory mediators including iNOS, TNF-α, and MCP-1. Conversely, anti-inflammatory M2 macrophages (pathway highlighted in green) are activated by signals like Th2 cytokines, glucocorticoids, and immune complexes, leading to the secretion of tissue-reparative and immunoregulatory factors such as IL-10, TGF-β, IGF-1, and VEGF. However, this binary classification is an oversimplification. In vivo, macrophages exist along a continuum of activation states, represented here as the heterogeneous "Actual polarization type", which reflects the complex integration of multiple signals from the tissue microenvironment.

Abbreviations: EGF, epidermal growth factor; IFN-γ, interferon-γ; Ig, immunoglobulin; IGF-1, insulin-like growth factor-1; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; TGF-β, transforming growth factor; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

Typically induced by signals like interferon-γ (IFN-γ) and lipopolysaccharides, the pro-inflammatory (M1-like) macrophages are potent drivers of the inflammatory cascade.[41–43] They secrete an array of cytotoxic and pro-inflammatory mediators, such as tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1, and inducible nitric oxide synthase (iNOS), which are critical for pathogen defense but also contribute directly to tissue damage and chronic neuroinflammation when dysregulated.[44–46] In contrast, the Anti-inflammatory Pole (M2-like) macrophages are activated by cytokines such as IL-4 and IL-13 promotes a regulatory phenotype.[47–50] These macrophages are essential for resolving inflammation and orchestrating tissue repair, producing anti-inflammatory cytokines like IL-10 and growth factors such as transforming growth factor-β (TGF-β), insulin-like growth factor-1 (IGF-1), brain-derived neurotrophic factor, vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF).[51–55] A summary of the key markers, products, and functions associated with these polarized states in the CNS is provided in Table 1.

The simplistic M1/M2 dichotomy is now considered insufficient to capture the complexity of macrophage behavior in vivo. Driven by advances in high-resolution detection methods, the field is moving towards more sophisticated conceptual frameworks. This article discusses two leading models that have emerged to supersede the classic binary view.

Table 1 Characteristics of Macrophage Phenotypes

Phenotypes	Activator	Markers	Products	Roles in MS	References
Pro-inflammatory	LPS, IFN-γ, and GM-CSF	CD80, CD86, MHC-II, iNOS	TNF-α, MCP-1, iNOS, IL-1α, IL-1β, IL-6, IL-12, IL-23, COX-2, CCL4, CCL5, CCL8, CXCL9, CXCL10, CXCL2, and CXCL4	Pro-inflammation, tissue damage, demyelination	[36,50,56–59]
Regulatory	IL-4, IL-10, IL-13, and TLR	CD206, IL-10, and VEGF	TGF-β, IL-10, CCL5, CCL13, CCL17, CCL22, CXCL10, and CXCL16	Anti-inflammatory, tissue repair, regeneration	[50,56–63]

Abbreviations: CCL, C-C motif chemokine ligand; COX, cyclooxygenase; CXCL, C-X-C motif chemokine ligand; GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, bacterial lipopolysaccharide; MCP, monocyte chemoattractant protein; MHC-II, major compatibility complex II; TGF, transforming growth factor; TLR Toll-like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

The first, the *Continuum Model*, posits that macrophage polarization is not a binary switch but rather a continuous spectrum of activation states.[64,65] In this model, the specific state of the cell is dynamically determined by the precise combination and intensity of micro-environmental signals (such as IFN-γ, IL-4, IL-10, lipopolysaccharide, etc).[66,67] This framework powerfully reflects the functional plasticity observed during the course of multiple sclerosis, especially during the transition between inflammatory flares and periods of remission and repair. The biological basis for this model is strongly substantiated by single-cell RNA sequencing (scRNA-seq) studies in MS models, which have revealed a continuous distribution of macrophage phenotypes rather than discrete populations.[68–70]

Complementing this view, the *Multidimensional Functional Model* proposes that a macrophage's state is best characterized by multiple, independently regulated functional modules.[71,72] These dimensions include inflammation, repair, antigen presentation, phagocytosis, and metabolic programming. Consequently, any given macrophage can be described by a unique functional signature—a vector defined by the intensity across these different axes. This model is exceptionally well-suited for integrating high-dimensional single-cell omics data (transcriptomics, proteomics, metabolomics), enabling a granular deconstruction of the cellular landscape within MS lesions.[73] By doing so, it provides highly refined insights into the specific functional roles of macrophage subsets, paving the way for targeted therapeutic interventions.

The Role of Macrophages in MS Pathogenesis

Macrophages as Antigen-Presenting Cells

MS is thought to be driven by an autoimmune response targeting self-antigens within the CNS, orchestrated in part by professional antigen-presenting cells (APCs), such as dendritic cells (DCs) and macrophages.[74] These cells play a dual role in disease pathogenesis, initiating T-cell activation in peripheral lymphoid organs and sustaining neuroinflammation within the CNS.[28] Studies by Inoue et al highlight the critical involvement of the NLRP3 inflammasome in APCs, which processes pro-IL-1β and pro-IL-18into active cytokines, thereby upregulating adhesion molecules such as Integrin α4β1 and chemokines like CCL7, CCL8, and CXCL16that facilitate immune cell infiltration.[75] Once in the CNS, both infiltrating macrophages (also referred to as MDMs) and resident BAMs contribute to local T-cell reactivation through elevated MHC class I and II molecules, as well as co-stimulatory molecules CD80/86 and CD40.[30,33,76,77] This sustained antigen presentation fuels chronic inflammation, driving demyelination and neuronal damage.[78] Targeting these APC functions, whether by modulating inflammasome activity, blocking co-stimulatory signals, or selectively inhibiting pathogenic macrophage subsets, holds promise for disrupting the autoimmune cascade in MS while preserving protective immune surveillance.[79]

Influence of Macrophages on Demyelination and Remyelination

Macrophage play a paradoxical yet central role in MS, driving both demyelination and, in certain contexts, potential repair.[80] While their phagocytic activity is essential for clearing inhibitory myelin debris, a prerequisite for remyelination, excessive or prolonged phagocytosis in chronic neuroinflammation contributes to disease progression. Studies highlight the particularly damaging role of MDMs, which infiltrate lesions and actively disrupt myelin integrity, particularly at vulnerable sites such as Ranvier nodes.[81] Here, MDMs exhibit invasive behavior, physically separating axons from their myelin sheaths and promoting axonal damage.

The temporal dynamics of macrophage function are critical; early in injury, phagocytic clearance of debris supports regeneration, but chronic activation leads to the accumulation of lipid-laden foam cells that perpetuate inflammation through cytotoxic cytokine release. This duality underscores the therapeutic challenge: strategies must either fine-tune macrophage phagocytic activity to prevent neurodegeneration while preserving repair mechanisms or selectively target pathogenic subsets like MDMs.[82]

Modulation of Inflammatory Response by Macrophages

Under normal physiological conditions, the CNS is protected by resident microglia and non-parenchymal macrophages, with minimal peripheral immune cell infiltration.[83] However, during MS and its experimental model, EAE, Ly6C^{hi} monocytes are recruited across the BBB in response to chemokine signaling.[84] These monocytes subsequently differentiate into macrophages within the CNS. Infiltrating macrophages, activated by factors such as T cell-derived IFN-γ, predominantly exhibit a pro-inflammatory phenotype.[85] Figure 3 provides a schematic overview of the recruitment and regulation of macrophages within the CNS during neuroinflammatory responses.

These infiltrating macrophages amplify neuroinflammation by expressing high levels of MHC class II, iNOS, IL-6, IL-12p40, and inflammasome products IL-1α and IL-1β,[86] while also releasing reactive oxygen species (ROS) and

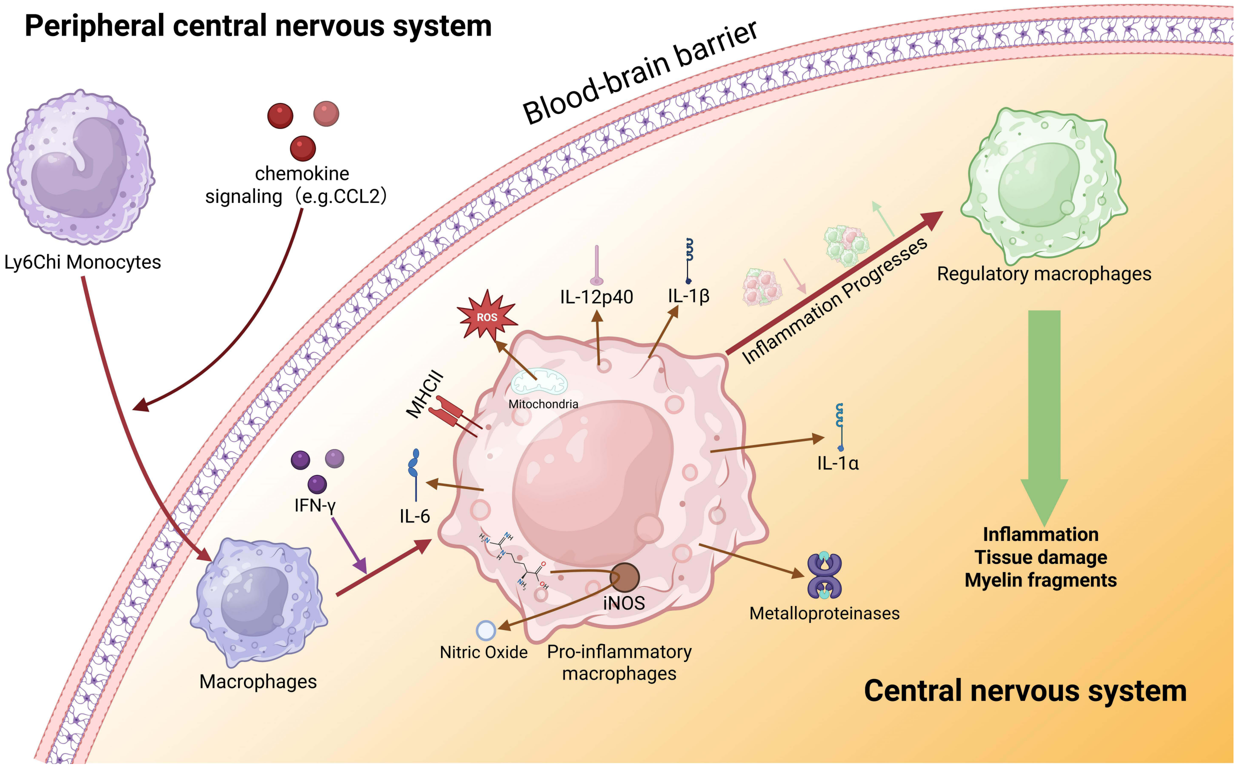

Figure 3 Dynamic Roles of Monocyte-Derived Macrophage in CNS Neuroinflammation. Created in BioRender. Yang, (J) (2025) https://BioRender.com/vcadyu2. This schematic illustrates the phased response of macrophages during inflammation in the CNS. Initially, peripheral Ly6Chi monocytes are recruited across the blood-brain barrier via chemokine signaling (eg, CCL2). Once inside the CNS, these monocytes differentiate into macrophages and, under the influence of cytokines like IFN-γ, polarize into a pro-inflammatory phenotype. This phase is characterized by the upregulation of MHCII and the production of cytotoxic mediators, including NO, ROS, metalloproteinases, and pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-12p40), which collectively drive inflammation and contribute to tissue damage. As the inflammatory process evolves, a phenotypic switch occurs, marked by a decrease in pro-inflammatory macrophages and a corresponding increase in regulatory macrophages. These regulatory cells are critical for resolving inflammation by clearing cellular and myelin debris, thereby promoting tissue repair.

Abbreviations: CCL2, chemokine (C-C motif) ligand 2; CNS, central nervous system; IFN-γ, interferon-γ; IL, interleukin; Ly6Chi, lymphocyte antigen 6C high-expressing; NO, nitric oxide; ROS, reactive oxygen species.

metalloproteinases (MMPs) that exacerbate tissue damage, including demyelination.[56] Interestingly, macrophages exhibit a dual role in MS progression and recovery. While pro-inflammatory macrophages dominate during disease induction and peak phases, regulatory macrophages become more prevalent during remission, secreting anti-inflammatory mediators that promote tissue repair, remyelination, and clearance of myelin debris.[87–89] Their ability to repair tissue and suppress inflammation makes regulatory macrophages crucial for disease resolution.[84]

Notably, both subsets contribute to remyelination, pro-inflammatory macrophages facilitate oligodendrocyte precursor cells (OPCs) recruitment by clearing inhibitory myelin debris, whereas regulatory macrophages support OPC maturation into myelin-producing into myelin-producing oligodendrocytes.[90,91] This dynamic interplay highlights the therapeutic potential of modulating macrophage polarization, either by suppressing pathogenic pro-inflammatory responses or enhancing reparative functions, to restore CNS homeostasis in MS.

Macrophages as Regulators of Oxidative Stress

Oxidative stress is a well-established contributor to the pathogenesis of MS,[92] driven primarily by ROS released from activated macrophages.[93] These cells generate harmful radicals, including hydroxyl radicals, superoxide, hydrogen peroxide, and nitric oxide via enzymes like myeloperoxidase, xanthine oxidase, and nicotinamide adenine dinucleotide phosphate oxidase.[94] The resulting oxidative stress exerts multiple detrimental effects on the CNS, contributing to disease progression. One critical consequence is the phosphorylation of axonal tau protein, linked to neuronal and axonal loss in EAE and MS.[95] ROS can also disrupt mitochondrial function, leading to impaired energy metabolism and the accumulation of mitochondrial DNA damage within MS lesions.[96] In axons, this mitochondrial dysfunction reduces ATP production, predisposing them to degeneration. Oligodendrocytes are particularly vulnerable, as oxidative stress triggers the release of apoptosis-inducing factors that translocate to the nucleus, inducing DNA damage. Subsequent activation of poly-ADP ribose polymerase in an attempt to facilitate DNA repair further depletes cellular energy reserves, ultimately driving apoptotic cell death.[97] Notably, oxidative stress and neuroinflammation engage in a self-amplifying cycle, wherein ROS production exacerbates inflammatory signaling, which in turn stimulates further oxidative damage.[98] This vicious cycle perpetuates demyelination, axonal injury, and progressive neurological decline in MS.

Therapeutic Potential of Macrophage-Targeted Approaches for MS

Translating the understanding of macrophage biology into effective MS therapies represents the next frontier in treatment, with strategies spanning from preclinical small molecules to clinically advanced inhibitors and futuristic gene-editing technologies. A summary of these approaches, their specific targets, and their translational status is detailed in Figure 4.

Regulated Polarization

A number of compounds have shown efficacy in preclinical EAE models by directly shifting the macrophage balance from a pro-inflammatory to a regulatory state.[99–101] For example, agents like the Akt inhibitor B9 promote regulatory polarization, exhibiting favorable pharmacokinetics and restructuring the inflammatory microenvironment by increasing regulatory macrophages and decreasing pro-inflammatory macrophages in both the CNS and periphery. B9 also attenuates proinflammatory Th1 and Th17 responses, ameliorating EAE symptoms and reducing demyelination.[102] Similarly, Circ_0000518 modulates macrophage polarization via the FUS/CaMKKβ/AMPK pathway, alleviating CNS injury in EAE mice.[103] While these compounds, along with others like neuropeptide Y and resveratrol, provide crucial proof-of-concept, their therapeutic potential in MS remains to be established, pending further investigation into their pharmacokinetics, safety, and efficacy in clinical settings.

Moving from preclinical concepts to the clinical arena, the most advanced strategy involves targeting Bruton's Tyrosine Kinase (BTK), a key signaling hub in both B cells and myeloid cells.[104–108] The clinical journey of BTK inhibitors offers a soberingly realistic view of the bench-to-bedside gap.[109,110] For example, while evobrutinib, showed promise in vitro[105] and in an mouse cerebellar model,[111] its Phase 2 trial failed to significantly reduce relapse rates, a common outcome when moving from cellular models to complex human disease.[112] Another BTK inhibitor, tolebrutinib, effectively decreases the severity of EAE and inhibits B-cell receptor (BCR) and Fc receptor-mediated activation of B cells and macrophages, respectively, in vitro.[105,113–115] In contrast, tolebrutinib has shown more encouraging phase 2b results,[116] but its path to

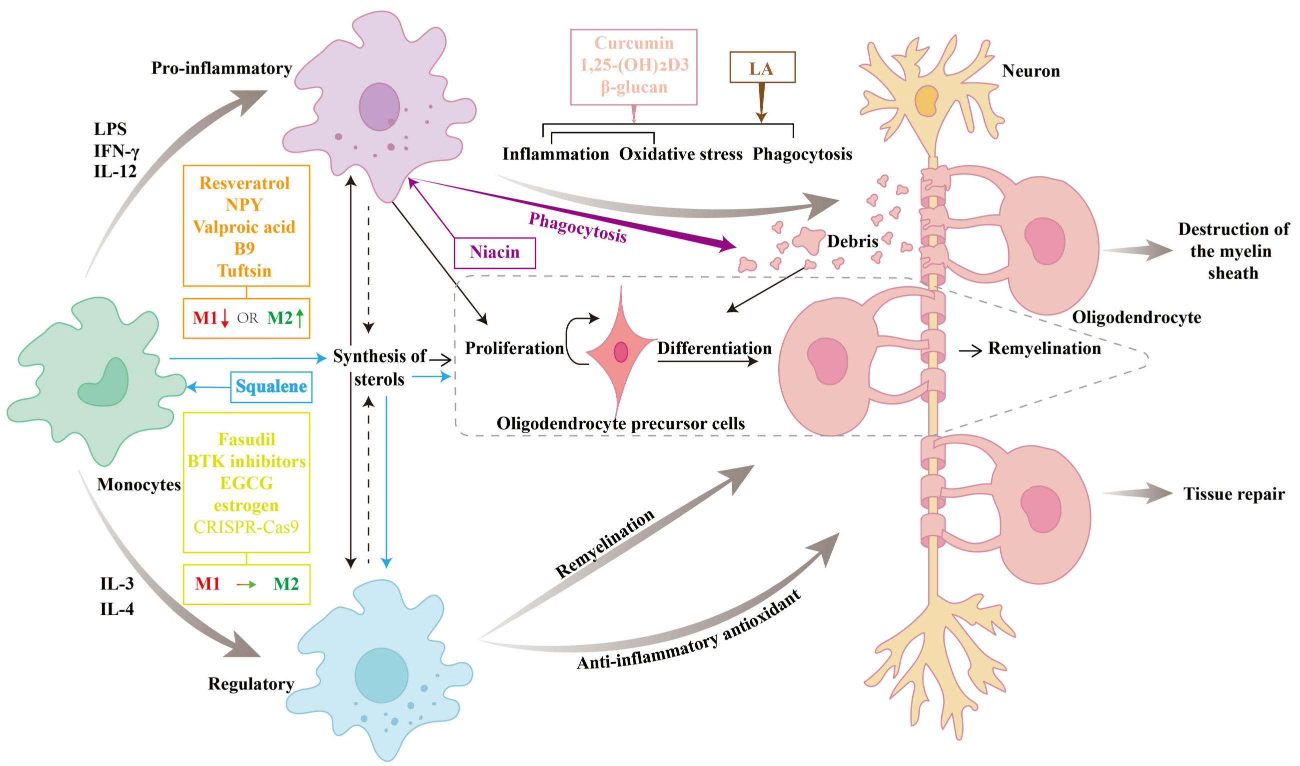

Figure 4 Mechanisms of Therapeutic Agents Modulating Macrophage Activity in Multiple Sclerosis (MS). This figure illustrates the multiple mechanisms by which therapeutic agents modulate macrophage activity and polarization in MS. Several agents (Orange font in the figure), including resveratrol, NPY, valproic acid, and tuftsin, directly inhibit pro-inflammatory macrophage activation or enhance the activity of regulatory macrophages (red arrows pointing downwards indicate suppression of the pro-inflammatory phenotype, and green arrows pointing upwards indicate increases in the regulatory phenotype). In parallel, compounds like curcumin, 1,25-(OH)$_2$D3, and β-glucan mitigate tissue damage by reducing macrophage-mediated inflammation and oxidative stress (pink font and pink arrows in the figure, where arrows transition from thick to thin to indicate reduction and alleviation). A complementary and crucial approach is to promote a regulatory phenotype by repolarizing existing pro-inflammatory cells using agents like fasudil, BTK inhibitors, and estrogen, thereby creating an environment conducive to tissue repair (arrow in the bright yellow box in the figure changes from red to green, indicating a change in phenotype). Beyond polarization, specific effector functions are targeted to support remyelination; for example, niacin enhances the clearance of myelin debris, a necessary step for repair by oligodendrocyte precursor cells (purple text and arrows in the figure, where arrows transition from thin to thick indicate enhancement). Finally, the pro-reparative functions of macrophages can be metabolically supported by agents like squalene, which provides essential precursors for sterol synthesis (blue text and arrows in the figure).

Abbreviations: BTK, Bruton's tyrosine kinase; EGCG, epigallocatechin gallate; IFN-γ, interferon-γ; IL, interleukin; LA, lipoic acid; LPS, lipopolysaccharide; NPY, neuropeptide Y.

approval is still contingent on larger, long-term Phase 3 data.[117] Crucially, the success of these agents hinges on their ability to effectively modulate myeloid cell function in the CNS, not just B cells, a mechanism that is still being fully elucidated.

Looking forward, gene editing technologies like CRISPR/Cas9 offer a paradigm-shifting but currently distant strategy for precision medicine.[118] By using macrophage-specific promoters to drive Cas9 expression and employing cationic lipid-assisted nanoparticles for delivery, researchers can achieve targeted gene editing in macrophages, minimizing off-target effects and enhancing in vivo safety and efficacy.[119] The ability to selectively silence pro-inflammatory genes (eg, LPA1 receptor) in macrophages holds immense therapeutic potential.[120] Yet, this approach is constrained by major logistical and safety challenges, primarily the need to develop safe and efficient in vivo delivery systems that can specifically target CNS macrophages without off-target effects.

In short, modulating macrophage polarization is no longer a theoretical concept but an active area of clinical drug development. However, the path forward requires moving beyond broad M1/M2 modulation toward highly specific interventions that can account for the heterogeneity of macrophage function and the complexities of human neuroinflammation.

Remyelination

Inhibiting cytokine production, promoting phagocytosis of myelin debris, and stimulating remyelination are crucial therapeutic strategies in MS.[121–123] Among clinically translatable candidates, niacin demonstrates efficacy in preclinical models by augmenting macrophage phagocytosis of inhibitory myelin debris, a critical step for OPC recruitment and subsequent remyelination, particularly in the aging CNS.[124] However, while doses below 1000 mg/d exhibit a favorable safety profile in MS patients, higher doses may induce gastrointestinal disturbances, hepatotoxicity, and hyperuricemia,[125] necessitating careful dose optimization.

Lipoic acid (LA), a endogenous antioxidant with pleiotropic anti-inflammatory effects,[126] presents another clinically viable option. Beyond suppressing MS-related cytokines like TNF-α, IL-6, and IL-1, LA modulates macrophage phagocytic activities via cyclic adenosine monophosphate signaling, correlating with reduced lesion activity in MS.[127] LA has a safety profile in MS clinical trials,[128] with minimal reported side effects, including rash and gastrointestinal intolerance.[129] Notably, a two-year randomized, double-blind pilot study in secondary progressive MS reported preserved ambulatory function with LA treatment,[130] suggesting potential neuroprotective benefits.

For acute lesion repair, squalene, a natural cholesterol precursor, exerts dual benefits by polarizing macrophages toward an anti-inflammatory phenotype via desmosterol synthesis while concurrently supplying oligodendrocytes with cholesterol for myelination.[131] Its established safety in murine and human studies underscores its therapeutic potential.

Autophagy

Autophagy is a fundamental cellular process responsible for the degradation and recycling of proteins and organelles, playing critical roles in both physiological and pathological conditions.[132] In EAE and MS, autophagy has shown to influence disease progression through multiple mechanisms. It helps suppress inflammatory responses, clear ROS and toxic aggregates, maintains BBB integrity, protect myelin sheaths and axons from damage, and support remyelination in MS patients.[133]

Trehalose, a natural disaccharide autophagy inducer, demonstrates promise by simultaneously addressing multiple pathological features. Preclinical studies show it reduces lipid accumulation in macrophages, promotes an anti-inflammatory phenotype, and enhances remyelination capacity in demyelination models.[134,135] These effects may be further optimized through targeted delivery approaches, as demonstrated by nanoparticle-encapsulated autophagy inducers that specifically modulate macrophage function while minimizing off-target effects.[136]

However, the role of autophagy in MS in MS is complex and context-dependent. While its protective functions are well-documented, excessive or dysregulated autophagy may also contribute to disease pathology. For instance, heightened autophagy can enhance antigen presentation, activate lymphocytes, promote pro-inflammatory cytokine release, and interfere with the clearance of the myelin oligodendrocyte glycoprotein.[133,136] Conversely, studies have revealed that pharmacological inhibition of autophagy, through various compounds with distinct mechanisms of action, can improve myelin production and restore axonal myelination.[137] Given these opposing effects, whether autophagy should be enhanced or suppressed for therapeutic benefit in MS remains an open question requiring further investigation.

Antioxidant Therapy

Antioxidant therapies have shown promise in mitigating or even preventing the progression of MS.[94,138,139] Curcumin has demonstrated significant immunomodulatory effects, including inhibition of NF-κB activation and suppression of inflammatory cytokine secretion in monocytes and macrophages.[138,140] Clinical data from a randomized controlled trial showed that curcumin supplementation significantly improved Expanded Disability Status Scale scores in MS patients compared to placebo[141] and did not increase adverse effects.[141–144] Similarly, 1,25-$(OH)_2D_3$ (active vitamin D) has shown neuroprotective potential in preventing EAE, reducing CNS macrophage infiltration while promoting inflammatory cell apoptosis and enhancing neuronal survival.[138,145,146] Clinical observations further suggest that vitamin D repletion following MS onset may preserve cognitive function and CNS integrity.[147]

The therapeutic landscape extends to other antioxidants, including β-glucan, which enhances innate immune function by augmenting macrophages, neutrophils, and natural killer cells.[138] However, its effects appear context-dependent: while microbial β-glucan (curdlan) attenuated axonal degeneration in viral-induced demyelination, it exacerbated pathology in autoimmune-mediated EAE.[148] This dichotomy underscores the need for personalized therapeutic approaches that account for disease heterogeneity and potential microbial triggers. The dual role of glutathione in MS pathophysiology further illustrates the complexity of antioxidant therapies. While it may prevent EAE by inhibiting macrophage-derived glutamate production, excessive extracellular glutamate, mediated by xCT upregulation, can impair oligodendrocyte survival and exacerbate demyelination.[149,150] These findings highlight the importance of carefully balanced redox modulation in therapeutic development.

Beyond antioxidants, direct macrophage modulation offers promising avenues for intervention. IL-9, for instance, attenuates macrophage activation while promoting their anti-inflammatory phenotype,[151] suggesting its potential as a therapeutic target. Nanosystems and exosomes also hold promise. Innovative delivery systems, such as macrophage-derived exosomes loaded with resveratrol, have shown efficacy in reducing neuroinflammation and improving clinical outcomes in EAE.[152] Furthermore, the phagocytic capacity of macrophages, makes them ideal targets for nanoparticle (NP) and microparticle (MP) delivery. Future studies should prioritize optimizing particle design to account for macrophage polarization states and uptake efficiency.[84] For example, phosphatidylserine-coated liposomes have demonstrated an ability to skew macrophages toward an anti-inflammatory phenotype.[153] Collectively, these findings underscore the potential of combining antioxidant strategies with macrophage-targeted therapies to address the multifaceted pathophysiology of MS.

Delivery Vehicle

Beyond being therapeutic targets, macrophages emerge as promising intelligent delivery vehicles for precision interventions in MS. This potential originates from their innate biological capacity to detect inflammatory signals within demyelinating lesions, enabling active migration across the BBB and targeted accumulation at disease sites. Exploiting this natural tropism, engineered macrophages function as sophisticated “living carriers” capable of dual therapeutic action. When equipped with molecular payloads—such as anti-inflammatory cytokines, antioxidant enzymes, or pro-remyelination factors—these cells simultaneously deliver therapeutics directly to lesions while performing their endogenous functions: phagocytosing myelin debris and modulating local immune responses. This convergence of targeted drug delivery and intrinsic repair mechanisms creates a potent synergistic therapeutic effect. Conceptual validation for this cellular *Trojan horse* approach comes from oncology research, where inflammatory chemotaxis was leveraged in neutrophils to deliver enzyme-loaded nanorobots to glioblastomas.[154]

Macrophages possess analogous homing capabilities for inflammatory CNS environments,[155] positioning them as ideal candidates for MS-targeted delivery with potentially greater biological relevance to neurological pathology. Compared to synthetic nanocarriers, macrophage-based systems offer distinct advantages: enhanced biocompatibility and innate immune evasion due to their endogenous origin; superior BBB penetration through natural migratory pathways; and intrinsic therapeutic synergy where carrier functionality complements delivered therapeutics. However, translating this promising strategy faces significant barriers. Current limitations include suboptimal lesion-specific migration efficiency, challenges in controlling spatiotemporal payload release, unpredictable in vivo phenotypic stability, potential off-target immune activation risks, and unresolved scalability of clinical-grade production. Addressing these through advanced bioengineering remains essential to realize macrophages’ full potential as next-generation therapeutic vectors for MS.

Conclusion

In summary, macrophages play complex yet central roles in MS pathogenesis, making them compelling therapeutic targets. While preclinical studies and early clinical trials demonstrate the potential of macrophage-targeted therapies, significant translational hurdles remain. Key challenges include overcoming macrophage heterogeneity, improving CNS-specific delivery systems, ensuring long-term biosafety, and establishing standardized protocols for clinical-grade cell therapies. Additionally, deeper mechanistic insights into macrophage interactions with other CNS cell types and their dynamic roles across disease stages are needed to refine therapeutic strategies. Bridging the gap between preclinical models and human MS pathology will be critical for developing effective, precision-targeted macrophage therapies. Future research must integrate advanced technologies, personalized approaches, and rigorous regulatory frameworks to fully realize the therapeutic potential of macrophage modulation in MS.

Abbreviations

APC, antigen-presenting cell; BAM, border-associated macrophage; BBB, blood-brain barrier; BTK inhibitors, Bruton's Tyrosine Kinase Inhibitors; CCL, C-C motif chemokine ligand; CNS, central nervous system; COX, cyclooxygenase; CXCL, C-X-C motif chemokine ligand; DCs, dendritic cells; EAE, experimental autoimmune encephalomyelitis; EGCG, epigallocatechin-3 gallate; EGF, epidermal growth factor; GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; IGF-1, insulin-like growth factor-1; IL, interleukin; iNOS, inducible nitric oxide synthase; LA, lipoic acid; LPS, lipopolysaccharide; MCP, monocyte chemoattractant protein; MDMs, monocyte-derived macrophages; MHC-II, major compatibility complex II; MMP, metalloproteinase; MS, multiple sclerosis; NPY, neuropeptide Y; OPCs, oligodendrocyte precursor cells; ROS, reactive oxygen species; TGF, transforming growth factor; TLR, Toll-like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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