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REVIEW

# T Helper Cells and Cytokine Networks in the Immunopathogenesis of Multiple Sclerosis

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**Abstract:** Multiple sclerosis (MS) is a chronic autoimmune disorder of CNS with demyelination, neurodegeneration and compartmentalized inflammatory disorder. Excessive T-helper cell ($CD4^+$) activation and unregulated cytokine signaling play a key role in its onset and progression. These changes impair communication between peripheral immune cells and CNS resident microglia, astrocytes and oligodendrocytes. This review provides an overview on the contribution of specific subsets of T-helper cells to MS pathology/immunity. Th1 cells release interferon-γ and lymphotoxin, that stimulate activation of myeloid cells/antigen presentation. Activated by IL-23, the Th17 cells produce IL-17A/F that lowers the blood–brain barrier (BBB) integrity, recruit neutrophils and monocytes, and enhance microglial killing. Activation of $CD4^+$ T cells leads to activation of B cells via T follicular helper cells which couple these processes through the production of IL-21 and CXCR5. This leads to the development of tissue-like aggregates and intrathecal antibody production. T-cell plasticity adds to epitope spreading as well as chronic inflammation, IL-22, IL-9, IL-1β, IL-6, and TGF-β (these are additional mediators involved in the regulation of effector phenotypes). In MS, the regulation of dendritic cell co-stimulation and of glial activation often does not work. This is due to the lack of control of dendritic-cells co-stimulation and the lack of regulation of glial activation by regulatory pathways such as $FOXP3^+$ regulatory T cells and Tr1 cells that secrete IL-10 and TGF-Beta. The review also explores the cytokine network biomarkers, CSF and serum signatures and single-cell immune states, as well as existing and new drugs. These include migration blockade, targeting of S1P-receptors, anti-CD20 therapy, targeting of Th17/GM-CSF and JAK–STAT pathways, low-dose IL-2, approaches of targeting antigens and engineered Tregs. Investigating the areas of stage and compartment-specific $CD4^+$ T-cell circuits can help to advance targeted immunomodulation in progressive MS and neuro-repair.

**Keywords:** multiple sclerosis, central nervous system, T-Lymphocytes, helper-inducer, cytokines, neuroinflammatory diseases, autoimmunity

## Introduction

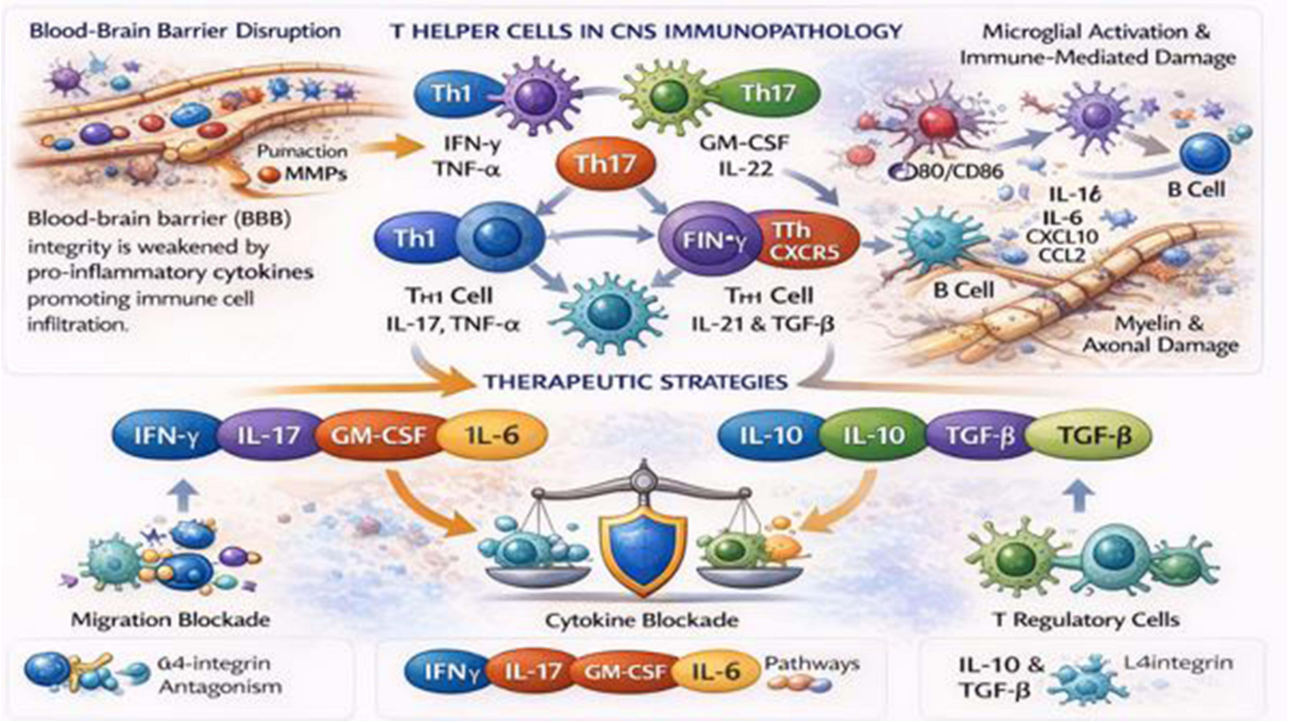
Multiple sclerosis (MS) is a neurological condition that has been reported to impact about 2.8 million individuals across the globe. It is one of the most frequent causes of non-traumatic neurological impairment in young adults.[1] The intersection of etiology, exposure to Epstein–Barr virus, low vitamin D, smoking and obesity converge on immune-based dysregulation that undermines tolerance in the central nervous system (CNS).[2,3] MS is clinically divided into relapsing-remitting, secondary progressive and primary progressive forms and is characterized by focal lesions, diffuse neurodegeneration and compartmentalized meningeal inflammation.[4] In all its manifestations, $CD4^+$ T-helper (Th) cells occupy a central position in pathogenesis and repair. They direct blood–brain barrier trafficking, license myeloid cells, provide B-cell help and regulate microglia and astrocytes through cytokines.[5] Among the pathogenic programs are Th1 (IFN-γ, TNF) and Th17 (IL-17A/F, GM-CSF) responses which increase chemotaxis, microglial activation, and oligodendrocyte injury, and Tfh-driven IL-21 that maintains intrathecal antibody production.[6] $CD4^+$ cells also create a check, notably $FOXP3^+$ regulatory T cells (Treg) and Tr1 cells (IL-10, TGF-β) suppress antigen presentation and glial activation.[7,8] Epitope spreading and chronicity result from plasticity between these states and depend on IL-1β, IL-6, IL-23, and tissue signals.

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**Graphical Abstract**




This review discusses the roles of $CD4^+$ T-helper cell subsets and cytokine networks in the immunopathogenesis of multiple sclerosis. It further examines their contribution to CNS inflammation, demyelination, disease progression, biomarker development, and some emerging targeted immunotherapeutic strategies.

## T Helper Cells in Immune Responses

T helper (Th) cells or $CD4^+$ T helper cells play a key role in the regulation of adaptive immunity. They mediate immune responses through cytokine production, regulation of other immune cells, and maintenance of the balance between host defense and immune tolerance.[9] T helper cells also play a crucial role in the pathology of the CNS in multiple sclerosis (MS); their effector activities can produce both disease-enhancing and disease-restricting effects.[5,10] Activation of naïve $CD4^+$ T cells by antigen-presenting cells (APCs) leads to differentiation into specialized subsets. This distinction is based on three major signals: antigen recognition by the T-cell receptor (TCR), costimulatory interactions, and the local cytokine environment.[11] Lineage commitment is critically determined by cytokines that activate subset-specific transcription factors which ultimately define the functional characteristics and cytokine production patterns.[12] The T helper subsets most relevant to MS include Th1, Th17, Th2, regulatory T cells (Treg), and T follicular helper (Tfh) cells.[7] These subsets perform distinct functions in promoting inflammation or maintaining immune tolerance.

### Th1 and Th17 Cells: Drivers of Inflammatory CNS Immunity

The effector cells of inflammatory immunity, Th1 and Th17, play critical roles in the central nervous system (CNS) disease; multiple sclerosis. The Th1 differentiation is promoted by the signaling of IL-12 and IFN-γ through STAT4 and STAT1 and expression of T-bet. T-bet promotes the transcription of IFN-γ while it inhibits GATA-3 and RORγt independent of the activation of the alternative Th2 and Th17 programs, respectively.[13] Mature cells of the Th1 type release interferon γ (IFN-γ), tumour necrosis factor α (TNF-α), and lymphotoxin α. These cytokines promote antigen presentation, activate macrophages and microglia, stimulate the production of chemokines, and act to promote microbicidal responses.[14] CXCR3 and CCR5

expression allows their sequestration in the CNS compartments of inflammation, where they can enhance the resistance to intracellular microorganisms and damage tissue in response to persistent IFN-γ signals.[15] IL-17 expression, inflammatory plasticity and tissue residency are regulated by IL-6, IL-1β, IL-23 and TGF-β leading to Th17 differentiation from peripheral T cells.[16] Th17 cells produce IL-17A, IL-17F, IL-21, and GM-CSF. In addition, IL-17 opens tight junctions between endothelial cells, thereby affecting the blood brain barrier (BBB). Similarly GM-CSF attracts and activates myeloid cells in the CNS, amplifying the cytokine and chemokine cascades.[17] Equally hepatocellular carcinomas (HCCs) enter into the CNS and build inflammatory niches through CCR6 and integrin α4β1. These promote CNS entry and inflammatory niche formation by HCCs. Th17 cells including Th17-1 (IFN-γ- and/or GM-CSF-producing) subsets are very neuroinflammatory in both MS and experimental autoimmune encephalomyelitis (EAE).[18] Therapeutics to target Th1/Th17 polarization or trafficking or cytokines may dampen inflammatory pathogenic feedback loops but efficacy will vary with disease stage and immune phenotype[19] (Figure 1).

## Th2 Cells and Tregs: Regulators of Immune Balance and Tolerance

Th2 cells and regulatory T cells play important roles in counterbalancing inflammatory immune responses in multiple sclerosis although their effects are context dependent. IL-4 signaling via STAT6-mediated GATA-3 activation and the inhibition of Th1 programs via repression of T-bet is responsible for Th2 differentiation. Mature Th2 cells release cytokines that promote humoral immunity (IL-4, 13), eosinophil recruitment (IL-5), mast cell maintenance (IL-5 and 13), and B-cell help in class switch (IL-4, 9).[20] Classical macrophage and microglial activation may be inhibited, and M2-like repair, debris clearance and neuroprotection promoted. This can dampen damaging Th1 and Th17 immune responses, whilst treatments like glatiramer acetate can help induce more Th2 biased and regulatory immunity linked to less relapses

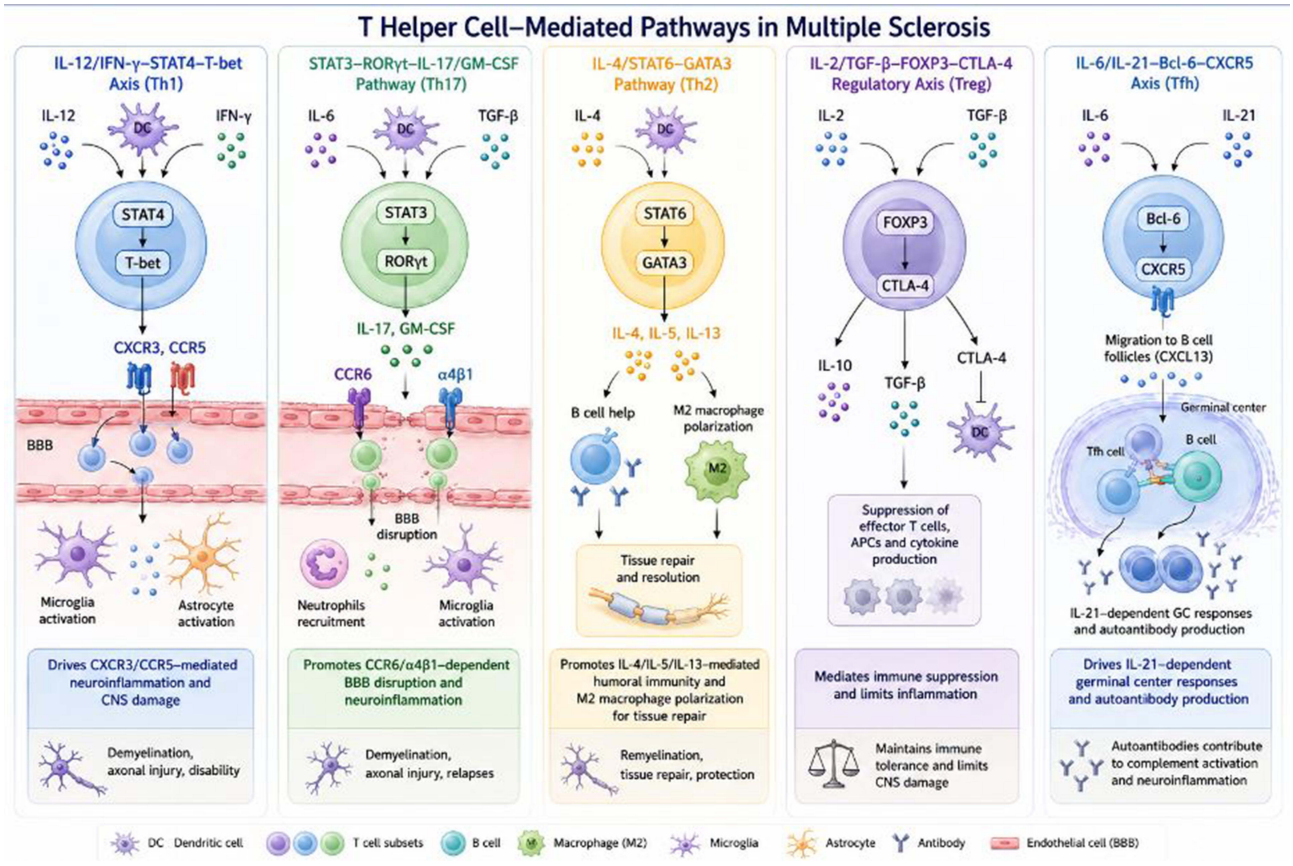



**Figure 1** Summarizes key T helper cell–mediated immune pathways implicated in multiple sclerosis, including Th1, Th17, Th2, Treg, and Tfh axes. Pro-inflammatory Th1 and Th17 responses promote blood–brain barrier disruption, immune-cell recruitment, microglial and astrocyte activation, demyelination, axonal injury, and relapse-associated neuroinflammation, whereas Th2 and Treg pathways support immune regulation, tissue repair, remyelination, and limitation of CNS damage. The Tfh pathway contributes to IL-21–dependent germinal center activity, B-cell help, autoantibody production, and complement-mediated neuroinflammatory injury.


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and stabilisation of the disease in some patients.[21,22] Th2 responses, however, do not always lead to protection, as boosting B-cell help can result in the production of autoantibodies, immune-complex formation, activation of complement and antibody-mediated demyelination in susceptible individuals.[23,24] IL-2 and TGF-β are necessary for the development, stability and survival of Tregs that are defined by FOXP3 expression.[25] Inflammation does not cause the loss of epigenetic imprinting of FOXP3 and does not down-modulate CD25 expression.[26] Tregs inhibit immune activation by secreting IL-10, TGF-β, IL-35, by decreasing the expression of CD80 and CD86 on antigen-presenting cells through CD80/CD86 interaction. It does this by consuming IL-2 and by inducing adenosine release and cytolysis of immune cells through CD39/CD73 pathways. In MS, Treg number can be normal, but their ability to suppress Th1 and Th17 activity is impaired, thus permitting the development of persisting MS-associated Th1 and Th17 activity.[27] Restoring Treg functions could be a therapeutic approach to restore tolerance without broad impairment in host immunity[28] (Figure 1).

## T Follicular Helper Cells: Facilitators of B Cell–Mediated Pathology

B cell–mediated immune pathologies in multiple sclerosis are linked to T follicular helper (Tfh) cells. The mechanism that leads to their differentiation is regulated by IL-6 and IL-21 which bind to the receptor-associated protein (AM/HGDC) to phosphorylate Bcl-6, inhibit T-bet and Blimp-1 and stimulate expression of CXCR5 for B cell follicles migration.[29] Tfh cells at the mature stage are found to be positive for the expression of PD-1, ICOS and SAP-dependent SLAM receptors, which help them to get localized at the T–B border and the germinal centre. Tfh cells promote generations within germinal centers through IL-21 and ICOS and CD40L signaling, which induces somatic hypermutation, affinity maturation, immunoglobulin class switching, plasmablast survival,[30] and proliferation of B cells. Interthecal antibody production, formation of oligoclonal bands and meningeal lymphoid aggregates associated with cortical demyelination and disease progression[31] are driven by increased Tfh-like populations and chemokine signals in MS. The significance of such a Tfh–B cell axis is supported by successful immunotherapies which deplete B cells, such as anti-CD20 and more recently novel approaches focused on targeting IL-21, ICOS–ICOSL interactions or boosting Tfr cells.[32]

## Plasticity and Interconnectedness of T Helper Subsets

Cytokine conditions, persistence of antigens, costimulatory signals, environmental "cues" from tissues and cellular metabolism all form a composite, shifting landscape that impacts the differentiation committedness of T helper subsets.[33] Once the environment changes, $CD4^+$ T cells can be reprogrammed, as they have partially permissive epigenetic landscapes. For instance, Th17 cells can be induced to express T-bet when stimulated by IL-12 and IL-23, producing so-called Th17.1 or ex-Th17 cells co-expressing T-bet with IFN-γ, GMCSF and the other. These cells display greater migratory and neuroinflammatory potential, and have been implicated to have a strong role in CNS autoimmunity.[34,35] Regulatory compartments can also be plastic. A series of inflammatory cytokines, including IL-6, IL-1β and TNF, may destabilise the expression of Foxp3, especially in the absence of an IL-2 signal.[36] This may result in less suppressive ability of the ex-Treg and lower production of pro-inflammatory cytokines by the ex-Treg, contributing to increased immune activation and poor tolerance. Anmati et al, indicated that the peculiar expression of partial Bcl-6 and CXCR5 expression, even in inflamed tissue, reinforces the idea of B-cell help in this setting.[37] It's a mixed phenotype, indicating that T helper subsets exist along a continuum, and thus, targeting one lineage could affect multiple immune pathways.

## Integration and Therapeutic Implications of T Helper Responses in MS

In multiple sclerosis, the T helper cells, along with other T lymphocytes, collectively determining the inflammation, damage and therapeutic response of the central nervous system. Th1 and Th17 cells act together to induce inflammatory pathology, affect the blood–brain barrier, activate myeloid cells and maintain antigen presentation. Small amounts of pro-inflammatory cytokines, such as IFN-γ and GM-CSF, activate microglia and enhance chemokine production and neutrophil recruitment, thereby augmenting demyelination. Individuals low doses of pro-inflammatory cytokines, such as IFN-γ and GM-CSF can activate microglia, increase chemokine production, and recruit neutrophils, which can amplify

demyelination.[38] Th2 responses may break the inflammatory cycles by inhibiting the activation of classical pathways and induce repair associated phenotypes.[39] They may be able to also direct B-cell development, promote class switching of immunoglobulins and antibody-mediated demyelination. Tregs maintain self-tolerance and downregulate epitope spreading, yet loss of suppressiveness may allow for continue autoreactivity.[40] Tfh cells additionally sustain T–B cell autoimmunity through a supporting role in intrathecal antibody production and the presence of intrathecal ectopic lymphoid-like aggregates with a focus on the cortex that is associated with the pathophysiology.[41]

MS disease-modifying drugs are based on these immunological mechanisms. Interferon-β inhibits Th1 polarization, and glatiramer acetate exerts pro- and anti-inflammatory effects in promoting Th2- and Treg-biased immune responses, respectively.[42,43] Both natalizumab and fingolimod inhibit α4-integrin dependent lymphocyte trafficking into the CNS: natalizumab by blocking α4-integrin and fingolimod by modulating the sphingosine-1-phosphate receptor. We are developing new strategies to target IL-17, GM-CSF, for lessening the Th17-driven pathology and targeting low dose IL-2, restoring Treg function, and blocking ICOS–ICOSL or IL-21 signaling to disrupt the interactions of pathogenic Tfh and B cell. Antagonism of the TNFR1 receptor and penetration into the CNS by targeting glial activation strategies may also be considered ways of combating compartmentalized inflammation in progressive MS.[44]

## Insights from Experimental Autoimmune Encephalomyelitis (EAE) Models

Experimental autoimmune encephalomyelitis has played a central role in elucidating the contribution of T helper cells to MS pathogenesis. Immunization of rodents with myelin-derived antigens such as myelin oligodendrocyte glycoprotein (MOG) or proteolipid protein (PLP) in the presence of adjuvants is commonly used to induce EAE.[45] Early adoptive transfer studies showed that myelin-specific $CD4^+$ T cells alone were sufficient to induce paralysis in naïve animals, demonstrating the centrality of T helper responses.[46] Initially, the dominant paradigm was Th1-mediated pathology, but contradictory findings prompted reassessment.[47] The discovery of Th17 cells transformed this paradigm. IL-23-deficient mice were resistant to EAE, underscoring the importance of Th17 biology. IL-17 and GM-CSF produced by Th17 cells disrupt the blood–brain barrier and recruit myeloid cells, establishing a pathogenic inflammatory loop.[48,49] Notably, adoptive transfer of Th17 cells induces robust CNS infiltration.[50] Plasticity is also evident in EAE; Th17 cells often convert to Th17/1 hybrid phenotypes during chronic disease.[51] Conversely, transferred Tregs can suppress EAE, although their survival is limited in inflammatory environments.[52] Tfh-like cells also arise in EAE and promote B-cell activation and antibody production contributing to demyelination.[41]

## Evidence from Human Studies

Human studies confirm the relevance of T helper subsets identified in EAE while revealing disease-specific nuances. Cerebrospinal fluid analyses in relapsing MS demonstrate elevated IFN-γ, IL-17 and GM-CSF levels.[53] Flow cytometry of blood and CSF shows increased numbers of IL-17-secreting $CD4^+$ T cells, some of which also express IFN-γ.[54] Histopathological examination of MS lesions reveals infiltration by $CD4^+$ T cells including both Th1 and Th17 subsets.[55] Oligoclonal bands detected in CSF reflect sustained B-cell and Tfh interactions.[56] Functional impairment of Tregs is widely reported in patients.[57] Th2 responses appear insufficient to counterbalance inflammation although induction of Th2 responses by glatiramer acetate may provide therapeutic benefit.[58] Single-cell RNA sequencing studies further demonstrate pathogenic transcriptional signatures including IL-23 receptor and GM-CSF expression in active MS.[59]

## Stage-Specific Differences in T Helper Cell Responses

Multiple sclerosis is clinically heterogeneous and the contribution of T helper subsets changes across disease stages including relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS).[60] During RRMS relapses, Th1 and Th17 programs dominate with increased IL-17, IFN-γ and GM-CSF levels in blood and CSF.[61,62] Interferon-β dampens these pathways and reduces relapse frequency, whereas glatiramer acetate promotes a shift toward less inflammatory T-cell phenotypes.[63] As disease progresses to SPMS, inflammatory bursts give way to smoldering pathology characterized by neurodegeneration.[64] Tfh–B cell ectopic follicles within the meninges correlate with cortical demyelination and accelerated disability progression.[65] Tregs remain present but functionally impaired.[66] In PPMS, peripheral Th1 and Th17 activity is less pronounced, yet compartmentalized CNS inflammation persists.[67]

Histopathology reveals microglial activation and axonal degeneration.[68] The efficacy of B-cell depletion therapies suggests continued involvement of Tfh-mediated B-cell activation.[69] Collectively, RRMS is characterized by inflammatory T-cell bursts, SPMS by Tfh–B cell circuits with progressive neurodegeneration and PPMS by innate microglial pathology with residual humoral activity.[70]

### Bridging Bench and Bedside: Therapeutic Translation

Insights into T helper biology have directly influenced MS therapy. Interferon-β reduces Th1 responses and enhances IL-10 production[71] Glatiramer acetate promotes Th2 and Treg responses that counteract pathogenic Th1/Th17 activity.[58] Fingolimod limits CNS infiltration by retaining T cells within lymph nodes.[72] Low-dose IL-2 therapy aims to restore Treg competence and stabilize FOXP3 expression.[73,74] Therapies targeting Tfh pathways such as blockade of ICOS or IL-21 may complement B-cell depletion strategies and reduce autoantibody-mediated pathology.[32] B-cell-directed therapies including ocrelizumab and ofatumumab exemplify this translational progress.[75,76] T helper cells remain central to MS immunopathology. Th1 and Th17 subsets drive inflammatory damage, dysfunctional Tregs fail to maintain tolerance, Th2 cells exert context-dependent effects and Tfh cells connect cellular and humoral autoimmunity.[77] They are complex and interconnected, which makes them difficult but promising therapeutic targets. Combined experimental models and human studies represent a picture of dynamic immune networks which change between disease stages. Such insights are already translated into therapy and future improvements are expected to bring an even more accurate intervention. The final difficulty lies in suppressing autoimmunity without impairment of host defense a feat that will necessitate improved knowledge of T helper biology along the MS spectrum.

## Cytokine Networks in Multiple Sclerosis

Cytokines are small secreted proteins that mediate immune communication and determine the rate and quality of inflammation.[78] They play important roles in the pathogenesis of neuroinflammation and immune tolerance in multiple sclerosis, as well as the dynamics of disease onset, relapse, and progression.[79] Cytokines are produced by T helper subsets together with antigen-presenting cells, B cells, and glia resident in the central nervous system, creating an interlocking network that determines the balance between pathogenic and protective immunity[80] The end result of MS pathology is a shift toward pro-inflammatory signaling in active lesions. Mediators such as interferon-γ, interleukin-17, tumor necrosis factor-α, and granulocyte-macrophage colony-stimulating factor dominate, whereas regulatory cytokines including interleukin-10 and transforming growth factor-β are reduced in quantity or functional activity.[81] The long-term consequences include central nervous system inflammation, disruption of the blood–brain barrier, peripheral leukocyte recruitment, and the characteristic sequence of demyelination and axonal injury.[81] Understanding how particular cytokine families respond and interact therefore provides insight into disease mechanisms and therapeutic intervention points (Figure 2).

### Interferons: Twofold-Edged Sword

Interferon-γ, the signature Th1 cytokine generated by activated $CD4^+$ and $CD8^+$ T cells and natural killer cells, increases antigen presentation by upregulating major histocompatibility complex molecules on antigen-presenting cells and enhances activation of microglial and macrophage effector programs.[82] Elevated interferon-γ levels in cerebrospinal fluid correlate with clinical relapses and neuroimaging activity in MS, and excessive signaling contributes to oligodendrocyte injury and disruption of the blood–brain barrier.[83] Conversely, type I interferons-particularly interferon-β produced by plasmacytoid dendritic cells during antiviral responses-exert largely anti-inflammatory effects.[84] They suppress Th1 differentiation, increase interleukin-10 production, and support regulatory T-cell function.[84] Recombinant interferon-β remains a major therapy in relapsing disease, reducing relapse rates and lesion accumulation by suppressing interferon-γ-driven responses, inhibiting leukocyte trafficking across the blood–brain barrier, and restoring a more regulatory immune balance.[85] Thus, the interferon family illustrates the duality of cytokine biology in MS, with interferon-γ representing a pathogenic component and interferon-β providing a therapeutic counterbalance.

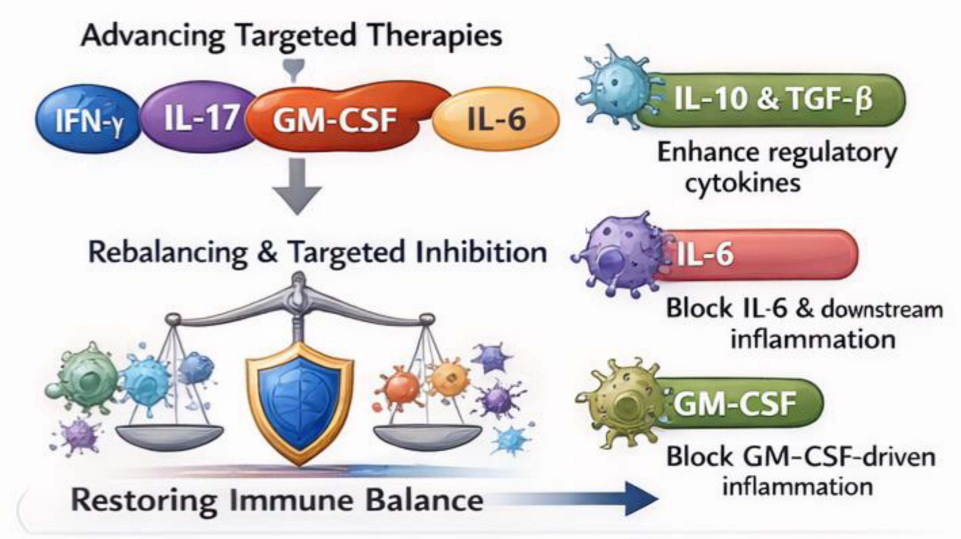



**Figure 2** Illustrates a therapeutic strategy for restoring immune balance in multiple sclerosis by targeting pro-inflammatory cytokines such as IFN-γ, IL-17, GM-CSF, and IL-6 while enhancing regulatory cytokines including IL-10 and TGF-β. The proposed approach emphasizes selective inhibition of IL-6– and GM-CSF–driven inflammatory pathways to reduce downstream neuroinflammation and promote immune homeostasis.

## Interleukin-17 and the IL-23/Th17 Axis

Recognition of Th17 cells redefined the importance of neutrophil mobilization and barrier disruption in MS pathogenesis.[86] Interleukin-17A and interleukin-17F act on endothelial and epithelial cells to induce chemokine production, promote granulocyte recruitment, and weaken tight junctions, thereby compromising the blood–brain barrier.[87] Elevated interleukin-17A levels in active lesions correlate with relapsing disease activity, and neutralization experiments in experimental autoimmune encephalomyelitis reduce disease severity.[87] Interleukin-23 produced by dendritic cells and macrophages stabilizes and expands the Th17 lineage and supports transcriptional programs that include granulocyte-macrophage colony-stimulating factor expression, a mediator essential for Th17-driven CNS autoimmunity.[88] Mice deficient in interleukin-23 are protected from experimental disease, highlighting its central role.[89] However, clinical translation has been complex; antibodies targeting interleukin-17 have shown inconsistent benefit in MS despite strong efficacy in psoriasis, suggesting redundancy within cytokine networks and heterogeneity among MS phenotypes.[89] These findings underscore the need for precision therapeutic strategies that target the dominant inflammatory axis in individual patients.

## Tumor Necrosis Factor-α: Pathogenic and Protective Roles

Tumor necrosis factor-α, produced by Th1 cells, macrophages, and microglia, exhibits marked biological pleiotropy.[90] On one hand, it promotes oligodendrocyte apoptosis, demyelination, and axonal degeneration and is highly expressed in active MS lesions. Genetic variation in TNF-related pathways may also influence disease susceptibility.[90] On the other hand, signaling through tumor necrosis factor receptor-2 supports oligodendrocyte survival and remyelination, demonstrating receptor-specific divergence in biological function.[91,92] This complexity has therapeutic implications. Non-selective blockade of tumor necrosis factor aggravated MS activity in clinical studies, increasing relapse frequency and disease progression.[93] Consequently, current research focuses on more selective approaches, such as preferential inhibition of tumor necrosis factor receptor-1 while sparing tumor necrosis factor receptor-2, with the aim of suppressing pathogenic inflammation while preserving reparative signaling.[94]

## GM-CSF: A Central Driver of CNS Inflammation

Granulocyte-macrophage colony-stimulating factor (GM-CSF) has emerged as a key cytokine in multiple sclerosis. It is produced by Th17 and Th1 cells as well as innate lymphoid cells and promotes recruitment and activation of inflammatory myeloid populations within the central nervous system.[95] Once activated, these cells produce additional

inflammatory mediators, amplify chemotactic signaling, and directly contribute to demyelination and axonal injury. Experimental evidence strongly supports this pathway: GM-CSF-deficient T cells fail to induce disease in experimental autoimmune encephalomyelitis models, demonstrating the non-redundant role of this cytokine in neuroinflammation.[96] Human studies similarly show elevated GM-CSF levels in the blood and cerebrospinal fluid of patients during active disease.[97] Therapeutically, antibodies targeting GM-CSF or its receptor are currently under investigation and have shown promising early results, positioning this axis as a potential strategy to suppress pathogenic myeloid activation without compromising host defense.[98]

## Interleukin-6: A Multifaceted Cytokine

Interleukin-6 is secreted by dendritic cells, macrophages, and astrocytes and exerts context-dependent immunological effects. In combination with transforming growth factor-β, IL-6 promotes differentiation of Th17 cells and sustains inflammatory signaling loops that destabilize the blood–brain barrier and recruit peripheral leukocytes.[99] Elevated serum and cerebrospinal fluid levels of IL-6 correlate with clinical and radiographic disease activity in multiple sclerosis.[100] Beyond T-cell programming, IL-6 supports B-cell survival, plasmablast differentiation, and antibody production, linking cellular and humoral components of autoimmunity.[101] Within the CNS, IL-6 activates astrocytes and microglia, contributing to gliosis and tissue injury.[102] Therapeutic blockade of IL-6 signaling, such as with tocilizumab, has demonstrated efficacy in neuromyelitis optica spectrum disorders and has inspired exploration of similar strategies in multiple sclerosis.[103]

## Interleukin-10 and TGF-β: Regulators of Immune Tolerance

Interleukin-10 and transforming growth factor-β are key regulators that counterbalance pro-inflammatory immune responses. Interleukin-10 produced by regulatory T cells, type-1 regulatory T cells, and regulatory B cells suppresses Th1 and Th17 responses, inhibits antigen presentation, and promotes a tolerogenic immune environment.[104] In multiple sclerosis, IL-10 signaling may be quantitatively or functionally impaired. Therapeutic agents that enhance IL-10 production, including interferon-β and glatiramer acetate, are associated with clinical improvement.[105] Transforming growth factor-β has a dual role: under steady-state conditions it promotes regulatory T-cell differentiation and maintains peripheral tolerance, whereas in inflammatory environments rich in IL-6 it may instead favor Th17 differentiation and pathogenic immune responses.[106] Reduced TGF-β signaling contributes to regulatory T-cell dysfunction in multiple sclerosis, demonstrating the importance of immunological context in determining cytokine effects.[107]

## IL-21 and the Tfh–B Cell Axis

T follicular helper cells produce interleukin-21, a cytokine central to germinal center biology.[108] IL-21 stimulates B-cell clonal expansion, immunoglobulin class switching, plasma-cell differentiation, and affinity maturation through activation of STAT3 signaling pathways.[109] While these processes are essential for protective humoral immunity, they may become pathogenic in autoimmune disease. Elevated IL-21 levels have been detected in cerebrospinal fluid and in ectopic lymphoid-like aggregates within the meninges of patients with progressive multiple sclerosis.[110] These aggregates resemble tertiary lymphoid follicles and are associated with sustained intrathecal antibody production and cortical demyelination. IL-21 also enhances Th17 differentiation and stabilizes Tfh phenotypes, creating functional crosstalk between Tfh and Th17 pathways.[111] Additionally, IL-21 can augment cytotoxic $CD8^+$ T-cell responses, potentially contributing to axonal injury.[109–111] These observations support therapeutic strategies targeting IL-21 signaling or Tfh–B cell costimulatory pathways such as ICOS–ICOSL interactions.

## Cytokine Networks and Disease Stages

The dominant cytokine pathways in MS vary across disease stages, reflecting evolving immunological architecture. During clinical relapses in relapsing-remitting MS, interferon-γ, interleukin-17, and GM-CSF levels rise, contributing to blood–brain barrier disruption, leukocyte recruitment, and acute inflammatory demyelination.[87] These cytokines activate microglia and infiltrating macrophages, amplifying tissue injury. In secondary progressive disease, interleukin-21 and tumor necrosis factor-α play greater roles in sustaining meningeal follicle-like structures and cortical demyelination.[112] In

primary progressive disease, peripheral inflammatory cytokines are less prominent, but low-grade parenchymal inflammation driven by microglia-derived interleukin-6 and tumor necrosis factor-α persists.[113]

## Therapeutic Implications of Cytokine Biology

Advances in cytokine immunobiology have reshaped therapeutic strategies in MS. Established treatments such as interferon-β and glatiramer acetate partially restore cytokine balance and reduce pathogenic immune trafficking.[114] Newer approaches aim for greater selectivity, including inhibition of GM-CSF to reduce inflammatory myeloid activation, blockade of IL-6 signaling to limit T- and B-cell-mediated pathology, enhancement of IL-10 or TGF-β pathways to restore regulatory tone, and targeting of IL-21 or Tfh pathways to disrupt antibody-mediated injury.[115,116] Cytokines represent a communication network linking T-helper programming, antigen-presenting cell function, and responses of CNS-resident glia.[80] In multiple sclerosis, a pro-inflammatory shift involving interferon-γ, interleukin-17, GM-CSF, tumor necrosis factor-α, and interleukin-6 drives lesion formation and disease progression, while regulatory cytokines such as interleukin-10 and transforming growth factor-β fail to adequately counterbalance this activity.[117] Continued mapping of cytokine networks is therefore critical for the development of targeted therapies capable of restoring immune homeostasis while preserving host defense (Figure 2).

# Interplay Between T Helper Cells, Cytokine Networks, and CNS Pathology

Multiple sclerosis can be summed up as an immune-CNS crosstalk disorder whereby peripheral stimulation prepares auto reactive lymphocytes that once they enter the central nervous system, cause and maintain destruction of tissue.[118] Coordinated but maladaptive interactions of T helper cells, their cytokines, innate immune infiltrates, and resident glial populations are the pathological hallmarks that result in the formation of focally inflammatory lesions of demyelination, axonal transection, and eventual progressive neurodegeneration.[119] The interactions are complex, a progression where blood-brain barrier is disrupted; immune cells are recruited and retained; antigens are presented locally and T cells are reactivated; microglia and astrocytes are changed to inflammatory amplifiers and finally, oligodendrocytes and axons are damaged.[87,119] Subsequent subsections follow this chain and place T helper biology in each of the stages (Figure 3).

## Blood–Brain Barrier Disruption and Immune Cell Entry

The blood-brain barrier (BBB) is a very complex and specialized endothelial interface, made up of poorly separated endothelial cells, pericytes, astrocytic end-feet, and an organized basement membrane.[120] Tight junction proteins-such as,

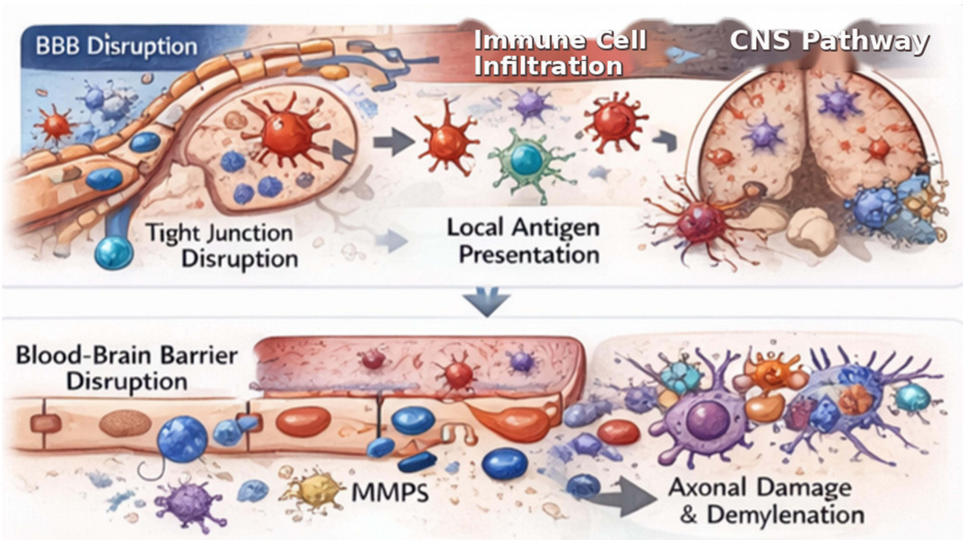



**Figure 3** Depicts the pathological sequence in multiple sclerosis, beginning with blood–brain barrier disruption and tight junction breakdown, followed by immune-cell infiltration and local antigen presentation within the CNS. The resulting inflammatory cascade contributes to matrix metalloproteinase activity, axonal damage, and demyelination.


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claudin-5, occludin and zonula occludens-1 (ZO-1)-limit paracellular diffusion under physiologic conditions and tightly control immune surveillance.[121] Pro-inflammatory cytokines sabotage this architecture of gatekeeping in multiple sclerosis (MS). Interferon gamma, tumor necrosis factor alpha (TNF-a) and interleukin-17 down regulate expression and disrupt organization of junctional proteins, promoting endothelial permeability and barrier weakness[117] (Figure 4).

Interleukin-17 also prompts endothelial and perivascular cells to synthesize matrix metalloproteinases (MMPs) and in particular MMP-2 and MMP-9 which break down basement membrane and extracellular matrix components.[122] This remodelling through enzymes relaxes structural constraints and allows passage of immune cells. At the same time, the TNF-a increases adhesion molecules like VCAM-1 and ICAM-1 on endothelial surfaces that enhance leukocyte rolling, adhesion and diapedesis.[123] Granulocyte-macrophage colony-stimulating factor (GM-CSF) recruits and generates circulating myeloid cells that enhance oxidative stress and proteolytic damage at the vascular interface generating more portals of entry.[124] The net result is permissive vasculature, which permits the entry of autoreactive CD4+ and CD8+ T cells, B cells, and monocytes into the central nervous system (CNS). Acute inflammatory activity and relapse is radiographically detected by means of gadolinium-enhancing lesions on magnetic resonance imaging (MRI), which are episodes of BBB breakdown as clinically evident.[125]

## Reactivation of T Cells in the CNS

After the process of transmigration, T cells face a special antigen-presenting condition in the CNS. Microglia and invading macrophages are the main antigen-presenting cells, and astrocytes may also play this role in inflammatory states.[126] Myelin-derived peptides-myelin basic protein, proteolipid protein, and myelin oligodendrocyte glycoprotein-are processed and presented on MHC class II molecules by these cells, and they contain signals required to restimulate local T cells.[127] Th1 reactivation produces interferon gamma and TNF-a that increases microglial antigen presentation and strengthens a proinflammatory environment.[128] Th17 cells also release interleukin-17 and GM-CSF which attract neutrophils and inflammatory monocytes and enhance effector responses.[129] T follicular helper cells provide T cells with interleukin-21 and costimulatory signals to B cells, which induces plasmablast differentiation and antibody production in the meningeal and perivascular niches.[130] These bidirectional interactions create a feedback loop of inflammatory maintenance whereby the recruitment mediated by the cytokines leads to additional antigen presentation and subsequent activation of T cells, and is the origin of lesion growth and relapse patterns in MS (Figure 5).

## Microglia and Astrocyte Activation

The immunologic signals are transformed into structural injury by resident glia. Microglia is the macrophage of CNS, which reacts to interferon gamma and GM-CSF by increasing MHC class II and generating tumor necrosis factor alpha, interleukin-1 beta, reactive oxygen species, and proteases.[131] These effectors cause direct damage to myelin sheaths, interference with nodes of Ranvier, and damage to axons. Thought to be primarily supportive, astrocytes are activated by the effect of interleukin-17 and tumor necrosis factor alpha.[132] They release interleukin-6 and chemokines like CCL2 and CXCL10 that continue leukocytes recruitment and organization in the parenchyma.[133] Astrocytes with time also play a role in glial scar formation which limits cellular migration as well as inhibits remyelination and axonal proliferation.[134]

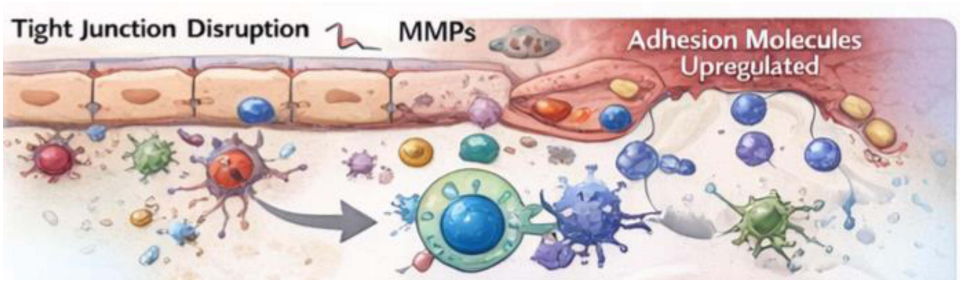



**Figure 4** Illustrates blood–brain barrier disruption characterized by tight junction breakdown, matrix metalloproteinase activity, and upregulation of adhesion molecules. These changes facilitate immune-cell trafficking across the endothelial barrier into the CNS, contributing to inflammatory infiltration and subsequent neuroinflammatory injury.

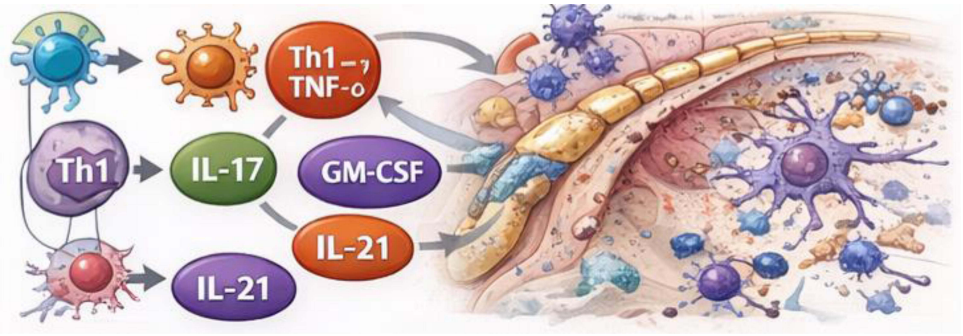



**Figure 5** Depicts Th1- and Th17-associated cytokine signaling in CNS inflammation, highlighting mediators such as TNF-α, IL-17, GM-CSF, and IL-21. These cytokines promote immune-cell activation and recruitment across the blood–brain barrier, contributing to neuroinflammation, demyelination, and tissue injury in multiple sclerosis.

Through this, cytokines released by infiltrating T cells reprogram glial cells of homeostatic sentinels into amplifiers and maintainers of neuroinflammation attaching the development of focal inflammation to chronic neurodegeneration.[135]

## Oligodendrocyte Injury and Demyelination

The oligodendrocytes or myelin forming cells of the central nervous system can be found at the cross road between the inflammatory attack and the conduction blockage in multiple sclerosis.[136] Their fate is determined by cytokines in receptor and context-specific manners. TNF alpha, which acts via TNFR1, activates apoptotic programs in adult oligodendrocytes, which causes the thinning of the myelin sheath and loss of the cellular reservoir required to repair myelin.[137] Interferon gamma reduces the synthesis of myelin proteins and also increases susceptibility to oxidative stress, worsening metabolic demands during active lesions.[138] Simultaneously, interleukin-17 and granulocyte-macrophage colony-stimulating factor bring together and mobilize the cytotoxic myeloid cells whose mediators further damage oligodendrocytes and their progenitors.[139] The resultant effect is the loss of saltatory conduction due to demyelination, which produces acute neurological deficits that are typical of relapse. Oligodendrocyte precursor cells can repair lesions and trigger remyelination, although persistent exposure to cytokines, scarring, and axonal loss often abate the response, which leads to partial recovery.[140]

## Axonal Injury and Neurodegeneration

Although demyelination can be partially reversible by remyelination, axonal transection is the long-term structural loss which is the main cause of long-term disability in multiple sclerosis.[141] The occurrence of axonal injury is caused by overlapping inflammatory and metabolic stresses in lesions and normal appearing tissue.[142] Stimulated microglia and infiltrating macrophages produce nitric oxide and reactive oxygen species that causes damage of mitochondrial DNA, inhibition of respiratory chain complexes of respiration and decrease of adenosine triphosphate production.[143] Long, demyelinated axons are especially vulnerable to energy failure, where they need more metabolic assistance to sustain saltatory conduction. Glutamate homeostasis is also disturbed by inflammation.[144] The microglia and astrocyte activation triggered by cytokines promotes glutamate in the extracellular space and decreases its internalization by excitatory amino acid transporters, triggering excitotoxic calcium release into neurons and axons.[145] High intracellular calcium triggers proteases and lipases, which destroy cytoskeleton components which eventually causes axonal swelling and transection.[146] Continuous stimulation of degenerative cascades by tumor necrosis factor alpha and interleukin-1 beta persists, despite the subsistence of active demyelination.[147] Progressive MS is characterized by compartmentalized parenchymal inflammation that promotes smoldering lesions or chronic active lesions.[148] The lesions are marked by rims of iron-laden and chronically activated microglia which sustain oxidative and inflammatory stress at lesion boundaries. Notably, the process can be induced without continuous peripheral immune infiltration, and this is one of the reasons to explain the unstopping progression even with decreased relapse rate. The progressive accumulation of mitochondrial dysfunction, oxidative damage and excitotoxicity leads to a progressive axonal loss and neurodegeneration.[149]


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## Meningeal Inflammation and Ectopic Follicles

Compartmentalized meningeal inflammation is becoming a highly valued core cause of pathology especially in secondary progressive MS.[150] Amongst the leptomeninges, B cells, T follicular helper cells and follicular dendritic cells form aggregates which form ectopic lymphoid-like follicles resembling germinal centers.[110] T follicular helper cells produce interleukin-21 that stimulates B cells to proliferate, switch classes of immunoglobulins, and differentiate into plasmablasts.[151] At the same time, B cells are recruited and retained in the stromal and glial-derived CXCL13 niches, which maintain local immune activation.[152] Myelin and neuron antigen antibodies, combined with complement deposition and the presence of Fc receptor-bearing effector cells enhance the process of demyelination in the surrounding cortex.[153] These follicles are spatially close to cortical tissue, which is associated with faster cortical thinning, heightened loss of neurons, and more adverse clinical progressions. These results outline the importance of the fact that adaptive immune interactions may be self-sustaining in the central nervous system, and do not need consistent peripheral support.

## Gray Matter Pathology and Cognitive Decline

MS does not only occur in the white matter, the pathology of gray matter is both wide and clinically significant. Meningeal inflammation cytokine-laden-characterized by interleukin-21 and TNF-α-relates to cortical ribbon loss as well as neuronal dropout.[154] In the parenchyma, interleukin-6 and granulocyte-macrophage colony-stimulating factor mediate microglia and complement pathway skewing towards an aberrant synaptic pruning.[155] Overtagging synapses enhances their removal, thus resulting in the loss of synapses and disconnection of networks.[156] These mechanisms result in cognitive impairment, slower information processing, fatigue and mood disturbances that can surpass expectations when considering lesion load of the white matter only.[155] These cellular processes are reflected in imaging correlates such as thalamic and cortical atrophy, which associate the milieu of inflammatory cytokines with advanced neurological dysfunction and progressive functional loss.

## Cytokine Imbalance and Clinical Phenotypes

The diversity of clinical manifestations of multiple sclerosis is a reflection of a dynamic change in the preeminence of cytokines in disease progression. Blood–brain barrier disruption, leukocyte influx and focal inflammatory lesions occur in relapsing-remitting MS due to episodic surges of Th1- and Th17-associated cytokines-especially interferon gamma, interleukin-17 and granulocyte-macrophage colony-stimulating factor.[157] These exudations are associated with clinical relapse and radiographic activity. During secondary progressive MS, the inflammation becomes even more compartmentalized in the central nervous system.[158] Continuous tumor necrosis factor alpha, interleukin-6, and interleukin-21 maintain meningeal follicle formation, cortical demyelination and progressive disability development even with obvious relapse death.[159] Characteristic of primary progressive MS is smoldering, microglia-focused inflammation that contains continued tumor necrosis factor alpha and interleukin-6 signaling and comparatively dull peripheral cytokine peaks.[160] This immunologic heterogeneity is the source of stage-dependent activity of therapies, and agents that are effective in relapse biology may have limited action once inflammation has become chronic, compartmentalized, and neurodegeneration-based.

## Therapeutic Implications of Immune-CNS Crosstalk

As designs of therapy map more and more onto the immune–CNS circuitry described above. Interferon beta corrects cytokine patterns by suppressing interferon gamma, increasing interleukin-10, and restricting the entrance of leukocytes into the blood-brain barrier.[161] Natalizumab inhibits the α4-integrin interaction with VCAM-1, inhibiting lymphocyte adhesion and transmigration at endothelial interfaces.[162] Anti-CD20 drugs like rituximab and ocrelizumab break down B cell–T follicular helper cooperation and are likely to minimize the development of meningeal aggregates.[163] Granulocyte-macrophage colony-stimulating factor inhibitors (experimental) and TNFR1 selective antagonists (experimental) are meant to suppress myeloid recruitment and glial activation respectively.[164] In the future, it is likely that rational combinations capable of toning down both peripheral activation and CNS-compartmentalized inflammation will be required, particularly when glial drivers dominate in progressive phenotypes.[5] Multiple sclerosis arises as a result of a dynamic interaction between autoreactive T helper cells and their cytokines with cells within the central nervous system.[165] The immune penetration through the blood–brain barrier facilitated by cytokines, the maintenance of local

antigen presentation and glial activation, and the resultant environment kill oligodendrocytes, strip myelin, and cut axons.[166] With disease progression into non-relapsing stages, pathology becomes confined to systemic glial and meningeal mechanisms of pathogenesis.[167] This biology should be translated into practice in a way that endorses specific, stage-sensitive interventions that suppress pathogenic pathways without impairing host defense. It should also permit repair, shifting the field away from blanket immunosuppression to specific immunomodulation of the immune–CNS interface.

## Conclusion and Future Directions

Multiple sclerosis is a prototypical disease of immune–CNS interactions with a chronic inflammatory, demyelinating and neurodegenerative response occurring as a result of an attack on myelin and neural tissue. Pathology is through cytokines (especially Th1 and Th17: interferon gamma; interleukin 17 and GM-CSF): these capillaries, which disrupt the blood-brain barrier, promote antigen presentation, and recruit damaging myeloid cells. The failure of regulatory T cells allows for sustaining autoimmunity, and T follicular helper cells facilitate B cell autoimmune function. In the CNS, activated microglia and astrocytes exacerbates injury and result in damage to oligodendrocytes, conduction block and axonal loss. Treatment for progressive disease is still a challenge. A comprehensive summary table brings these into proper perspective (Table 1).

**Table 1** Key Immunological Pathways and Therapeutic Implications in Multiple Sclerosis

| Pathway/Target | Key Mediators | Clinical Consequences | Therapeutic Strategies |
|---|---|---|---|
| **Th1 inflammation** | IFN-gamma, TNF-alpha, lymphotoxin-alpha; T-bet+ CD4+ T cells | Amplifies antigen presentation, BBB dysfunction, myeloid activation, and relapse-associated tissue injury. | Interferon-beta; strategies that reduce T-cell activation, antigen presentation, or CNS entry. |
| **Th17/IL-23 axis** | IL-17A/F, IL-21, GM-CSF; IL-6, IL-1beta, IL-23, TGF-beta; RORgammat+ cells | Weakens BBB tight junctions, recruits neutrophils/monocytes, and drives acute inflammatory demyelination. | Phenotype-directed IL-17, IL-23, or GM-CSF pathway targeting; broader cytokine-network modulation. |
| **Tfh-B cell pathway** | Tfh cells, IL-21, CXCR5, ICOS, CD40L; B cells and plasmablasts | Supports intrathecal antibodies, oligoclonal bands, meningeal follicles, cortical demyelination, and progression. | Anti-CD20 therapies; emerging IL-21 or ICOS-ICOSL blockade and other Tfh-B cell costimulation targets. |
| **Regulatory tolerance** | FOXP3+ Tregs, Tr1 cells, IL-10, TGF-beta, IL-35, CTLA-4, CD39/CD73 | Reduced suppressive function permits autoreactive T-cell persistence, epitope spreading, and chronic CNS inflammation. | Low-dose IL-2, expanded or engineered Tregs, and antigen-specific tolerization platforms. |
| **Th2 modulation** | IL-4, IL-5, IL-9, IL-13; GATA-3+ Th2 cells | Can restrain Th1/Th17 inflammation and support repair phenotypes, but may also enhance humoral autoimmunity. | Glatiramer acetate; context-specific immunomodulation rather than broad Th2 enhancement. |
| **Immune-cell trafficking** | alpha4beta1 integrin, VCAM-1, ICAM-1, CCR6, CXCR3, CCR5, S1P receptors | Enables leukocyte adhesion, transmigration, CNS infiltration, gadolinium-enhancing lesions, and relapses. | Natalizumab; S1P receptor modulators such as fingolimod and related agents. |
| **TNF signaling** | TNF-alpha, TNFR1, TNFR2 | TNFR1 promotes oligodendrocyte apoptosis and axonal injury; TNFR2 may support survival and remyelination. | Avoid non-selective TNF blockade; investigational TNFR1-selective antagonism while preserving TNFR2 repair signals. |
| **IL-6/JAK-STAT signaling** | IL-6, STAT3, JAK-STAT pathway; astrocytes, B cells, Th17 cells | Promotes Th17 differentiation, B-cell survival, plasmablasts, gliosis, and glial-mediated tissue injury. | Selective IL-6 pathway blockade and JAK-STAT-directed strategies under investigation. |

(*Continued*)


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**Table 1** (Continued).

| Pathway/Target | Key Mediators | Clinical Consequences | Therapeutic Strategies |
|---|---|---|---|
| **CNS-compartmentalized inflammation** | Activated microglia/astrocytes, IL-1beta, IL-6, TNF-alpha, oxidative stress, inflammasome pathways | Sustains smoldering lesions, mitochondrial dysfunction, excitotoxicity, axonal transection, and progressive disability. | CNS-penetrant approaches including BTK inhibitors, glia-directed agents, and oxidative/inflammasome modulators. |
| **Repair and precision monitoring** | Oligodendrocyte precursor cells; repair signals; CSF/serum cytokines; single-cell and imaging biomarkers | Determines remyelination failure, irreversible disability, disease-stage classification, and treatment-response prediction. | Remyelinating/neuroprotective therapies plus biomarker-guided patient stratification and pharmacodynamic monitoring. |

**Note**: Concise summary of major immune targets, clinical consequences, and therapeutic strategies discussed in the manuscript.
**Abbreviations**: BBB, blood-brain barrier; BTK, Bruton tyrosine kinase; CNS, central nervous system; CSF, cerebrospinal fluid; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; JAK-STAT, Janus kinase-signal transducer and activator of transcription; MS, multiple sclerosis; Tfh, T follicular helper; Treg, regulatory T cell; TNF, tumor necrosis factor.

# Future Directions

## Precision Cytokine Targeting

The clinical experience of single-cytokine blockade, eg, interleukin-17A blockade, highlights the issue of redundancy and plasticity in T helper networks.[168] The mechanisms to withstand pathogenic circuits provide compensation by parallel pathways so that inflammation tends to persist despite specific treatment. Future strategies are thus moving toward combination approaches which moderate convergent nodes in the inflammatory cascade. Both recalibration of pathogenic programs by targeting common downstream mediators, for example through signaling hubs such as the JAK–STAT pathways, and targeted perturbation of lineage-defining transcription factors such as T-bet and RORγt could be beneficial. The main dilemma lies in suppressing disease-promoting immunity while preserving antimicrobial immunity and vaccine responsiveness without falling into generalized immunosuppression.

## Restoring Immune Tolerance

The restoration of regulatory balance is one of the cornerstone therapeutic goals. Interleukin-2 therapy at low doses is designed to selectively increase and stabilize active regulatory T cells (Tregs), thereby enhancing suppressive immune tone without prominently stimulating effector populations.[169] Complementary strategies include adoptive transfer of ex vivo-expanded polyclonal Tregs or antigen-specific Tregs genetically engineered to target inflamed central nervous system tissue. Antigen-specific therapies-including peptide-based, nanoparticle, and tolerogenic dendritic cell platforms-are aimed at selectively silencing autoreactive clones, restoring self-tolerance while preserving global immune competence.[170]

## Targeting CNS-Compartmentalized Inflammation

Later in the progression of multiple sclerosis, inflammation becomes increasingly compartmentalized behind a preserved or partially repaired blood–brain barrier. It is therefore critical that therapies capable of penetrating the CNS and influencing resident immune cells are available. Bruton tyrosine kinase inhibitors, which affect both B-cell and microglial signaling, show promise particularly for progressive phenotypes.[171] Other small molecules that inhibit innate immune activation, inflammasome signaling, or oxidative stress may reduce the activity of smoldering lesions and delay neurodegeneration.[160]

## Neuroprotection and Remyelination

Recovery requires not only immunologic control but also preservation and restoration of axons and myelin in order to improve long-term outcomes. Remyelinating agents that facilitate differentiation of oligodendrocyte precursor cells, growth factor-based strategies, and stem-cell-derived repair therapies are currently advancing through clinical development.[172] Understanding how the inflammatory cytokine milieu influences oligodendrocyte lineage development will be essential for aligning immunomodulation with regenerative therapies.

### Systems Biology and Biomarker Discovery

Recognition of T helper cell heterogeneity in multiple sclerosis is being refined by high-dimensional technologies such as single-cell transcriptomics, proteomics, and metabolomics. Biomarkers reflecting cytokine activity, immune cell phenotypes, and compartmentalized inflammation will enable patient stratification, real-time pharmacodynamic monitoring, and more precise therapeutic selection.[173] Ultimately, a strategy combining suppression of pathogenic effector circuits with restoration of regulatory pathways and stimulation of CNS repair is likely to provide the most rational approach to altering disease progression without compromising host defense.

### Limitations and Gaps in Mechanisms for Further Investigation

Although great strides have been made towards defining the functions of the different subsets of $CD4^+$ T-helper cells and cytokine networks in multiple sclerosis, a number of significant gaps exist. Most of the mechanism was provided by experimental autoimmune encephalomyelitis (EAE) models, which mimic important inflammatory aspects of MS but not the heterogeneity, chronicity, cortical involvement and progressive neurodegeneration found in the disease. Further, the proportion of the different Th subsets is challenging to define because any given Th can adapt to various tissue environments and disease states, and they enjoy a significant degree of plasticity in their relative proportions that could shift depending on the occurrence of antigenic stimulation, therapeutic intervention, and the specific tissue compartment. Important unanswered questions are: How peripheral autoreactive cells are reactivated in specific sites in the CNS, what defines the blood–brain barrier and its different compartments of the meninges, perivascular space and parenchyma with respect to their cytokine gradients and how immune-mediated lesions or damage becomes dissociated from overt relapse activity during progressive disease. The relationship between formation of Tfh–B cell aggregates, activation of microglia, and failure of oligodendrocyte precursor cells, mitochondrial dysfunction, and irreversible axonal loss, is also poorly understood. In addition, more effective markers that can distinguish pathogenic from reparative immune responses, that can predict response to treatment and that will identify patients with compartmentalized CNS inflammation have yet to be developed. Future long-term clinical and preclinical analysis of these gaps will include human single-cell profiling in parallel with spatial transcriptomics, proteomics, advanced imaging techniques, and functional studies performed in blood, CSF, and CNS tissues in order to optimize drug development and targeting for individualized therapy.

## Unique Contribution of the Review

The unique contributions of this review are the circuit-based synthesis, from a few isolated mechanisms, of the biology and functions of the $CD4^+$ T-helper cell, cytokine signaling, and immune pathology in the CNS of MS. The review did not just focus on individual concepts of Th1, Th17, Treg cells, cytokines, glial activation, blood brain barrier disruption and therapies. It tried to establish a linkage between these factors, theoretically integrating peripheral immune activation into a single entity that eventually triggers the compartmentalized inflammation of the CNS and progressive tissue damage. It also focuses on the novel aspects of cell types and liver anatomy involved in the immune response to MS disease activity in each of the MS focal disease states (relapsing-remitting MS, secondary progressive MS, and primary progressive MS). Clearly, this points to the fact that therapy successful in relapsing-remitting MS may not be effective in progressive phenotypes. The review offers a translational view that can help form strategies for precision immunomodulation and future neurorepair-based therapies by connecting cellular mechanisms, cytokine networks, biomarkers and emerging targets for medications to treat this devastating condition.

## Conclusion

MS is best thought of as a stage-dependent disorder in which pathogenic programs and functions of CD4+ T cells, humoral immune responses, and cytokinesis and the activation of glia are all involved in driving demyelination and neurodegeneration. The findings presented suggest that disease progression is not just an escalation of relapse biology, but rather a transition to compartmentalized inflammation in the CNS, dysregulated immune activation and unachieved repair. But there are many gaps in our understanding; the failure to fully translate the EAE studies to human MS and whether and how peripheral immune activation is maintained in discrete compartments of the CNS. The dominant

immune circuits will then need to be identified at the individual patient's level. A combination of targeted immunomodulation and strategies for promoting neuroprotection and remyelination will be needed in the future to achieve therapeutic progress. To develop effective, stage specific, and patient-tailored interventions these mechanistic gaps need to be addressed in longitudinal human studies, and through single-cell profiling, spatial immune mapping, and the development of better biomarkers. This integrated approach represents a more rational approach to attempting to decrease relapse activity, to reduce any rate of progressive disability, and to maintain neurological function.

## Abbreviations

JAK-STAT, Janus Kinase-Signal Transducer and Activator of Transcription; CSF, Cerebrospinal Fluid; CD, cluster of differentiation; MS, Multiple sclerosis; TNF, Tumour necrosis factor; PD-1, Programmed Cell Death Protein 1; ICOS, Inducible T-Cell Co-Stimulator; SLAM, Signaling Lymphocytic Activation Molecule; ICOSL, Inducible T-Cell Co-Stimulator Ligand; GATA-3, GATA Binding Protein 3; RORγt, Retinoic Acid Receptor-Related Orphan Receptor Gamma t; CCR6, C-C Chemokine Receptor Type 6; TGF-β, Transforming Growth Factor Beta.

## Data Sharing Statement

Data sharing is not applicable as no datasets were generated being a review article.

## Disclosure

The authors declare no competing interests in this work.

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