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Research Article

Unraveling MS Pathogenesis: The Critical Roles of B and T Cells in Disease Development

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Abstract

Introduction

Multiple sclerosis is a complex inflammatory disease characterized by the immune system's aberrant attack on the central nervous system , leading to localized inflammation and demyelination of nerve cell sheaths. This autoimmune response is primarily mediated by lymphocytes, the body's defensive cells, which mistakenly target healthy central nervous system nerve cells, ultimately causing neurological impairments and a range of debilitating symptoms.

LiteratureReview

In recent years, extensive studies have explored the underlying mechanisms of Multiple sclerosis pathophysiology. Traditionally, T cells have been understood as central to MS progression, mediating immune-driven central nerve system damage. However, emerging research has uncovered an equally critical role for B cells, challenging the established paradigm and broadening the understanding of immune involvement in Multiple sclerosis. This review reevaluates past research and recent findings on the dual contributions of T and B cells to MS pathology, highlighting how B cells may drive disease progression through mechanisms distinct from those of T cells.

Conclusion

Current insights into Multiple sclerosis pathogenesis reveal a more complex immune network than previously thought, with both T and B cells contributing to central nerve system inflammation and demyelination. The recognition of B cells' significant role, alongside T cells, offers new perspectives on therapeutic targets and suggests that effective MS treatments may require a multifaceted approach to immune modulation.

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1. Introduction

The exact cause of multiple sclerosis (MS) remains elusive, even as the disease exerts profound and debilitating effects on those affected. For clinicians and researchers dedicated to understanding MS pathophysiology and developing effective treatments, the disease presents considerable challenges. Despite ongoing efforts, a definitive cure remains out of reach, underscoring the complexity of MS and the need for continued research to unravel its underlying mechanisms [1].

Multiple sclerosis (MS) is a complex autoimmune disorder in which the body's immune system mistakenly targets healthy cells within the central nervous system (CNS). In MS, lymphocytes—key immune cells—become activated against the nerve cells of the CNS, leading to localized inflammation and progressive demyelination of the protective sheaths surrounding these nerve cells. This damage disrupts neural communication, resulting in a range of neurological symptoms and disease progression [2], the patient experiences a range of symptoms that vary in intensity, such as:

Symptoms of multiple sclerosis (MS) are diverse and may include fatigue, blurred vision, tingling or numbness, muscle spasms, stiffness, and weakness. Patients often experience mobility challenges, pain, cognitive difficulties impacting memory, learning, and planning, as well as emotional symptoms like depression and anxiety. Additionally, MS can lead to complications with bladder and bowel control, and difficulties with speech and swallowing [3]. atients with multiple sclerosis (MS) may experience a varying spectrum of symptoms, with some individuals affected more mildly than others. Additionally, MS is characterized by periods of remission and relapse. While there is currently no cure for MS, several therapies have been developed to slow or halt disease progression. Advancing our understanding of MS pathogenesis is crucial for developing more effective treatments, as many underlying mechanisms and mediators remain unclear. [2,4].

Multiple sclerosis (MS) is primarily caused by autoreactive effector T cells that enter the central nervous system and activate after crossing the blood-brain barrier.

Because these autoreactive T cells can drive immune-mediated damage, regulatory mechanisms are in place to prevent their presence in the bloodstream of both healthy individuals and MS patients. The suppression of these self-reactive T cells and the maintenance of peripheral tolerance are strongly influenced by regulatory T (Treg) cells, which play a critical role in controlling immune responses to prevent autoimmune conditions like MS [5].

A wide array of inflammatory mediators and proposed mechanisms contribute to our understanding of factors—particularly CNS nerve cell demyelination—that significantly impact the pathophysiology of multiple sclerosis (MS)[6].

The role of T cells in the pathogenesis of multiple sclerosis (MS) has long been established. However, the limited effectiveness of regulatory T cells (Tregs) in controlling MS, alongside the success of B cell-targeted therapies, has prompted increased interest in the involvement of specific B cell subsets in disease progression. This review will focus on the proposed mechanisms underlying B and T cell interactions to provide a deeper understanding of their roles in MS pathogenesis [5,7].

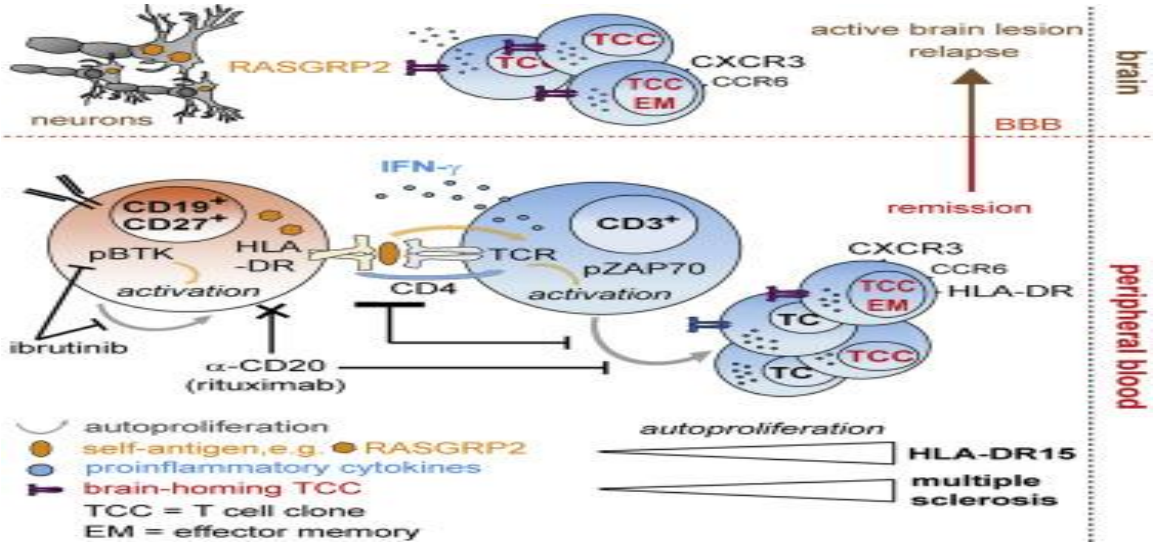

Figure 1: A diagram illustrating the suggested mechanisms.

1.1. T cell importance in the development and course of MS

T cell expression a distinct T-cell receptor (TCR) as it matures in the thymus. TCRs are produced by random recombination of gene segments, which allows for the expression of a wide range of distinct TCR specificities [1]. "Molecular mimicry" by bacterial or viral proteins may cause myelin-reactive T cells to trigger the autoimmune pathogenesis [2]. Peptide antigen flexibility is made possible by nonconventional TCR binding however, to preserve specificity, the MHC class II binding pocket's TCR affinity must be increased. Consequently, it stands to reason cloned auto-reactive T cells would exhibit high level of efficient immorality in antigen identification which was indeed the example. MBP-reactive T cell clones have been show to exhibit resistance to additional myelin antigens, including myelin oligodendrocyte protein (MOG), and it was demonstrated that modification of the peptide ligand enhances T cell clone reactivity [3]. Moreover, T cells with degenerate TCRs are more common in MS patients than in healthy controls, and some of these cells are capable of recognizing myelin antigen, according to recent studies describing TCR degeneracy [4]. These results lend credence to the theory that during an infection, non-self antigen activates cross-reactive T cells in the brain. Myelin-reactive T lymphocytes may trigger autoimmune pathogenesis through "molecular mimicry" caused by bacterial or viral proteins [3]. Lesions with significant immune cell infiltrates in the central nervous system (CNS) are indicative of multiple sclerosis (MS) and serve as disease markers. These cells exhibit a notable ability to penetrate the brain parenchyma, breach the blood–brain barrier (BBB), and start the loss of oligodendrocytes that protect neurons. This leads to the dissection of neuronal axons, which in turn causes the death of neurons [5]. The biology of astrocytes, endothelial tight junctions, which support the blood-brain barrier, and the low expression of MHC molecules on CNS APCs typically tightly

regulate and limit immune infiltration and activation in the central nervous system [6].
Disarray Pathogenic B Illness Controlled by T Cells In secondary lymphoid organs, MS B and T cells interact closely to produce the best possible immune response against invasive pathogens. B cells use the highly specific B-cell receptor (BCR) within follicles to recognize antigens, which leads to internalization, processing, and presentation to T cells. This mechanism is distinct and requires five sequential steps that are interdependent. It is also highly coordinated [7].

1.2. Pathogenic B Cells in Multiple Sclerosis Regulated by Dysfunctional T Cells

In secondary lymphoid organs, B and T cells interact closely to coordinate an optimal immune response against invasive pathogens. Within follicular regions, B cells utilize their highly specific B-cell receptors (BCRs) to recognize antigens, initiating a series of steps that culminate in the internalization, processing, and presentation of these antigens to T cells. This complex mechanism involves five sequential, interdependent steps: (1) actin remodeling, (2) B-cell receptor signaling, (3) synthesis and trafficking of HLA class II molecules to specialized late endosomes (MIICs), (4) antigen processing and loading onto HLA class II molecules for presentation to CD4+ T helper cells, and (5) the formation and transport of endosomal structures [7-8]. The strong point of the HLA/peptide signaling regulates the formation of both germinal center (GC)-dependent and GC-independent memory B cells through their interactions with T helper (Th) cells [9]. Within germinal centers, B cells differentiate into class-switched (IgG+) subsets or antibody-producing plasmablasts and plasma cells in response to follicular T helper (Tfh) cells that secrete interleukin-21 (IL-21) [10-11]. These memory B cells subsequently activate Th effector subsets, which, in turn, support CD8+ cytotoxic T lymphocytes (CTLs) in targeting and eliminating infected cells. [9 - 12]. In multiple sclerosis (MS), the typical crosstalk between B and T cells appears to be disrupted, resulting in pathogenic rather than protective immune responses. This may be initiated by the peripheral choosing auto-reactive B cells that are naïve. Generally, peripheral tolerance checkpoints control autoreactive B cells that persist after central tolerance in the bone marrow eliminates most B-cell clones expressing polyreactive antibodies. Unlike other autoimmune diseases, MS is uniquely characterized by a deficiency in peripheral, rather than central, B-cell tolerance checkpoints, which correlates with elevated frequencies of naive polyreactive B cells in the blood. The precise cause of this escape from peripheral control remains unclear but may stem from (1) prolonged T-cell motivation or (2) intrinsic T-cell defects [13].

1.3. Th cells as pathogenic memory B cell inducers

Naive B cells that evade peripheral tolerance checkpoints likely interact with T helper (Th) cells within germinal centers (GCs), potentially leading to the formation of memory B cell populations that could later infiltrate the CNS in multiple sclerosis (MS). The precise mechanism by which peripheral effector Th cells promote the expansion of these pathogenic B cells in MS remains poorly understood. In autoimmune mouse models, autoreactive B cells in GCs are stimulated by follicular T helper (Tfh) cells that secrete high levels of IFN-γ [14]. The presence of IFN-γ induces the expression of the T-box transcription factor T-bet, which then upregulates CXC chemokine receptor 3 (CXCR3), facilitates IgG class switching, and enhances antiviral responses in murine B cells [15].

Recent researchs has shown that B cells from MS patients develop into CXCR3+ populations that preferentially migrate into the CNS [16]. In mice, the formation of these autoreactive GCs is driven largely by the IFN-γ receptor (IFNGR) and the downstream molecule STAT1 in B cells. Upon IFNGR activation, STAT1 undergoes phosphorylation, dimerization, and nuclear translocation, subsequently initiating

the expression of genes critical for GC responses, including T-bet and B-cell lymphoma 6 (BCL-6) [17]. B cells stimulated by IFN-γ in multiple sclerosis (MS) patients demonstrate heightened pro-inflammatory potential [18]. However, the specific role of alterations in the IFN-γ signaling pathway in the development of T-bet+ B cells that infiltrate the central nervous system (CNS) remains unclear. Interestingly, a missense single nucleotide polymorphism (SNP) in the IFNGR2 gene has been identified in MS patients, potentially influencing disease progression [19]. Additionally, IFI30, a gene encoding the IFN-γ-inducible lysosomal thiol reductase (GILT), is considered a causal risk variant in MS and is another target within the IFN-γ pathway [20]. GILT is essential for antigen processing and presentation via HLA class II molecules. Collectively, these findings suggest that Th effector cells producing IFN-γ in MS may readily activate T-bet-expressing B cells, which serve as potent antigen-presenting cells in the autoimmune response [21]

1.4. In MS, naturally occurring regulatory T cells

In multiple sclerosis (MS), naturally occurring regulatory T cells (Tregs) play a critical role in maintaining immunologic self-tolerance. This tolerance cannot be fully explained by the removal of self-reactive T cells in the thymus by cloning or by T-cell energy only, for instance possibly caused of disease auto-reactive T cells are extant in the peripheral blood of well persons [22]. For inhibit these auto-reactive T cells from driving immune complaints, alternative controlling mechanisms are essential. The suppression of self-antigen- responsive T cells and establishment of exterior acceptance are strongly influenced by regulatory T cells. Pioneering research by Sakaguchi et al [23]. demonstrated that the depletion of CD4+CD25+ Tregs in mice leads to the onset of systemic autoimmune diseases. Furthermore, in vitro studies show that co-transferring CD4+CD25+ cells with CD4+CD25− cells can prevent the expansion of autoimmune diseases for example, colitis, gastritis, insulin-dependent diabetes, and thyroiditis, underscoring the suppressive role of Tregs in autoimmune [24].

Man CD4+CD25hiFoxP3+ regulatory T cells (Tregs) exhibit like suppressive behavior to rat CD4+CD25+ oppressor cells, strongly inhibiting the proliferation of responder T cells in coculture while remaining anergic to in vitro antigenic stimulation. Both human and murine CD4+CD25hiFoxP3+ Tregs express the Treg-specific lineage factor FoxP3 and suppress CD4+CD25− (Tresps) in a cell contact-dependent mode. However, the human Treg population displays significantly greater heterogeneity than that of mice, both in cell surface phenotype and functional capacity. Among CD4+CD25+ cells in human peripheral blood, only 2-4% exhibit the highest level of CD25 expression, conferring their regulatory function, though up to 30% may express CD25 at lower levels in pathogenic environments [25]. CD62L (L-selectin) expression serves as a distinguishing marker for most human Tregs, setting them apart from recently activated effector cells, as over 95% of CD4+CD25high Tregs are CD62L+. Additionally, CD4+CD25high Tregs from adult tonsils or peripheral blood predominantly exhibit the CD45RO+, CD45RA−, and CD45RB low phenotypes [26]. The CD4+CD25 high Treg populace is too improved with various immunomodulatory external indicators, containing proteins not exclusive to Tregs, such as MHC class II, CD95 (Fas), glucocorticoid-induced tumor necrosis factor receptor family-related protein (GITR), and cytotoxic T lymphocyte-associated protein (CTLA-4). Among these, FoxP3, a nuclear transcription factor, remains the most specific and reliable marker of Tregs, with its expression correlating directly with suppressive function. While FoxP3 is expressed at low levels in activated CD4+ T cells [27], it is highly expressed in CD4+CD25high Tregs, and approximately one-third of this Treg population also expresses HLA-DR [25]. The contact-dependent

suppressive function of Tregs is not restricted by MHC, although CD4+ T cells presenting antigens through HLA-DR exhibit a notable level of anergy. HLA-DR appearance differentiates unique, functionally definite subset of what appear to be critically distinguished human Tregs, suggesting that antigen presentation by T cells does not primarily regulate this population [28]. HLA-DR+ Tregs display significantly higher levels of FoxP3 expression and demonstrate faster T cell response suppression kinetics than their HLA-DR− counterparts. These cells rely solely on contact-dependent mechanisms for suppression, without producing IL-10 [29], in contrast to HLA-DR− Tregs, which act later and less effectively. The latter subset suppresses T cell responses through both contact and IL-10 secretion, triggering an IL-10-mediated suppressive response from other T cells and thus enhancing their suppressive capacity. The HLA-DR− Treg subset exhibits a unique form of infectious tolerance, possibly due to the presence of adaptive Tregs within this population [28, 29]

Research by Venken et al. indicates that FoxP3 expression is lower in relapsing-remitting MS patients than in healthy controls, with secondary progressive MS patients showing little to no FoxP3 expression. However, it remains unclear whether the reduced FoxP3 appearance in MS cases results from a lower occurrence of FoxP3+ cells within the CD4+CD25hi T cell populace or a decrease in FoxP3 appearance within individual cells [30]

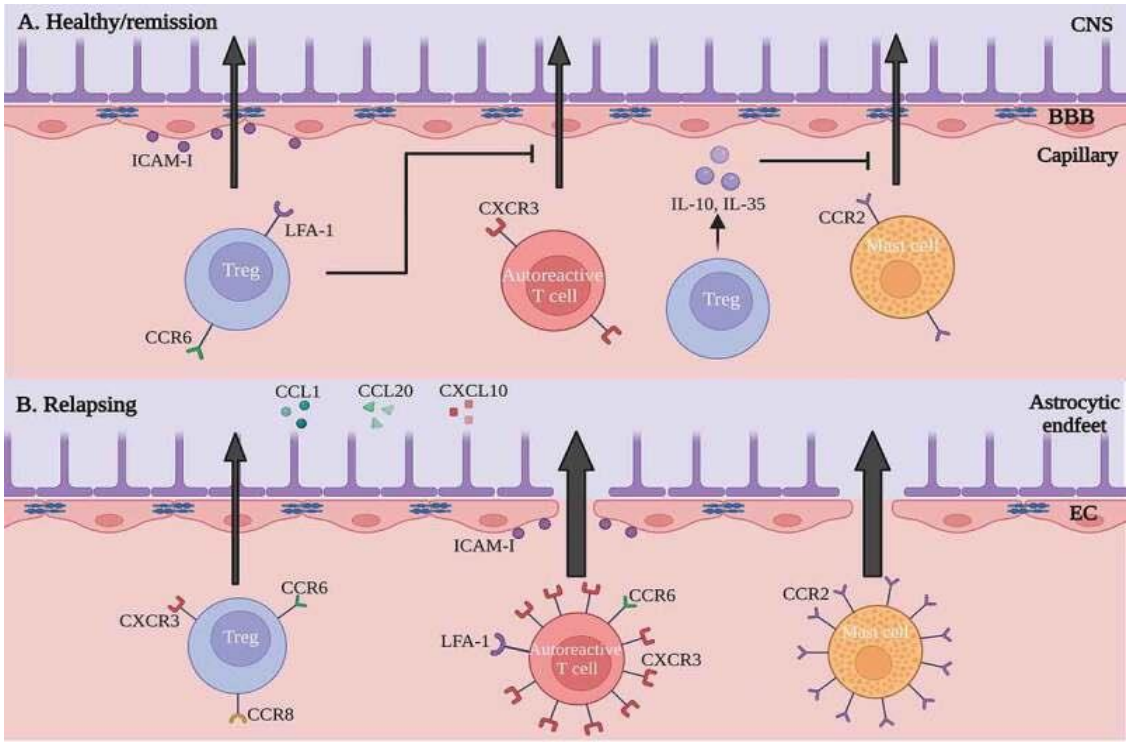

Figure (2) Summary of Treg migration in remission or healthy states versus progressive or recurrent MS. (a) By downregulating the CXCR3 receptor, Tregs reduce autoreactive T cell migration in healthy individuals or in MS patients who are remitting. Additionally, mast cell transendothelial migration is reduced as a result of Treg IL-10 and IL-35 downregulating the mast cells' CCR2 receptor. Tregs primarily migrate as a result of interactions between the CCR6 receptor and LFA-1. (b) Autoreactive T cells and mast cells migrate more when MS relapses. CCL1, CCL20, and CXCL10 are

chemokines produced from the inflammatory central nervous system that cause treg migration. MS, multiple sclerosis; Treg, CCR, C-C chemokine receptor; CNS, central nervous system; CXCL, C-X-C motif chemokine ligand; EAE, experimental autoimmune encephalomyelitis; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; LFA-1, leukocyte function associated antigen-1(80)

1.4. Treg pathogenicity

Across all plate-bound αCD3 stimulation doses, Tregs isolated from both groups demonstrated anergic responses, indicating that CD4+CD25hi T cells insulated from MS individuals are not stimulated CD25+ T cells, as they failed to exhibit regulatory activity and instead promoted proliferation. Tregs from healthy controls consistently showed a 1:1 suppression of T cell proliferation, though this suppression decreased as the responder-to-suppressor cell ratio increased. In contrast, Tregs isolated from MS patients displayed a normal frequency in circulation but only marginally suppressed the proliferation of activated T cells. In these cultures, Tregs from healthy controls effectively inhibited T cell secretion of the Th1 cytokine IFN-γ, while Tregs from MS patients did not. The primary source of IL-10 in these cultures was the CD4+CD25− T cell response, although IL-10's role in mediating suppression by CD4+CD25hi Tregs could not be established. Notably, the suppressive function of these Tregs was preserved even when IL-10 or TGF-β was blocked, indicating that their regulatory effect operates independently of these cytokines (31). A potential explanation for the loss of regulatory T cell [31]. Treg cell functionality in MS patients may involve either an increased resistance to inhibition by activated responder T cells (Tresps) or a decline in the performance of CD4+CD25hi Tregs. Target responder T cells from both MS patients and healthy controls exhibited a proliferative response that Tregs from MS patients could only marginally suppress (23% suppression). By contrast, Tregs isolated from healthy controls achieved a 78% suppression of the proliferative response, indicating a notable regulatory defect in MS patient Tregs. Although the precise mechanism underlying this functional impairment remains unclear, additional regulatory T cell populations, particularly CD46-mediated Tr1 cells, may also be involved in MS pathogenesis. CD46, a recently identified costimulatory molecule, can induce the Tr1 phenotype and stimulate IL-10 released, an anti-inflammatory cytokine. In comparing MS patients to healthy subjects, significant abnormalities were observed in Tr1 cell induction with CD46 co-activation, as well as capacity to released IL-10, though not IFN-γ. These findings highlight potential regulatory pathway disruptions that may contribute to MS pathology [32, 33].

1.5. The role of regulatory T cells (Tregs) in autoimmune

Diseases is closely linked to the expression of FoxP3, a transcription factor essential for Treg function. Mutations in the FoxP3 gene can result in IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome), an immunodeficiency disorder characterized by autoimmunity affecting multiple endocrine organs. Impaired FoxP3 protein expression leads to widespread inflammatory caused disease in each humans and rats. Furthermost human autoimmune diseases, are multifaceted genetic complaints influenced by a combination of multiple common allelic variants and environmental factors, creating a pathological immune response [34].

Recent genome-wide association studies (GWAS) in patients with MS, type 1 diabetes (T1D), and rheumatoid arthritis (RA) have highlighted the role of several genetic factors, although a strong genetic association with FoxP3 itself was not found. However, MS and T1D have been directly associated with variations in the IL-2Rα chain, the main

receptor for Treg growth, as well as allelic variants in the IL-7Rα chain and CD58, which may affect Treg function to varying degrees in individuals with autoimmune diseases [34, 35] Within MS lesions, immune cells mediate myelin loss, oligodendrocyte damage, and axonal damage, all contributing to neurological abnormality in function. In activation to inflammation, immunomodulatory systems are activated, helping to suppress immune activity and initiate repair processes, which often lead to limited re-myelination and medical decrease. Nevertheless, in the relapsing form of MS, 80% or more of patients experience disease progression, and magnetic resonance imaging (MRI) may reveal signs of immune reactivation or relapse. The following discussion and summary (Fig. 3) reflect the current understanding of various effector T cells' roles in MS pathogenesis [35].

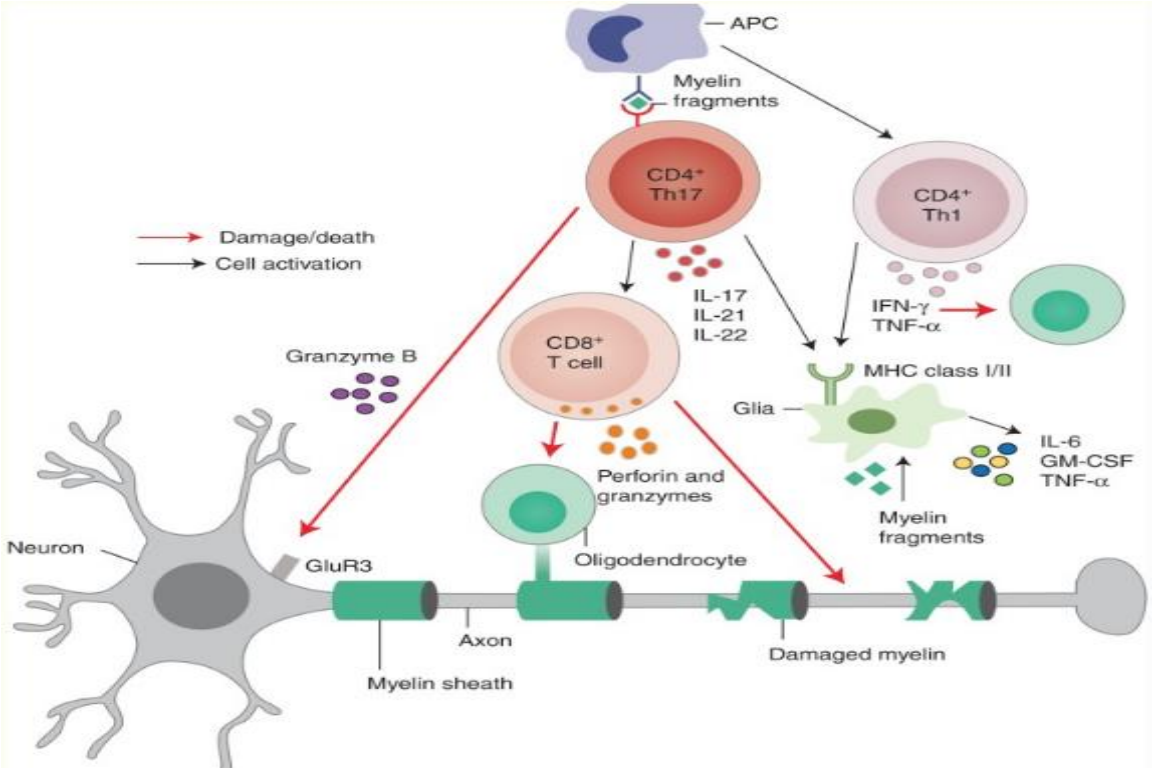

Figure 3: T cells infiltrating the (CNS), specifically the CD4 and CD8 subtypes, play a pivotal role in driving and sustaining inflammation, contributing to oligodendrocyte loss, demyelination, and, ultimately, neuronal degeneration. Upon entry into the CNS, these T cells secrete cytokines like interleukin-17 (IL-17) and interferon-gamma (IFN-γ), which upregulate Major Histocompatibility Complex (MHC) class I and II molecules on antigen-presenting cells (APCs). This activation prompts local glial cells and APCs to restimulate myelin-reactive T cells, further amplifying the immune response. IL-17, along with tumor necrosis factor-alpha (TNF-α), promotes the expression of proinflammatory cytokines such as IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF), intensifying CNS inflammation. IFN-γ, in particular, can directly harm oligodendrocytes, while granzyme B, released by IL-17-secreting CD4 and CD8 T cells, can induce neuronal death via binding to glutamate receptors (GluR3).

1.6. Role of CD T cell (Th1 – and Th17) in MS

CD8 T cells, equipped with cytolytic granules containing granzyme and perforin, target and kill neurons and oligodendrocytes, especially near demyelinated axons. The primary pro-inflammatory CD4 T cell populaces involved in MS are Th1 and Th17 cells. Th1 cells release IFN-γ and TNF-α, while Th17 cells produce IL-17, IL-21, and IL-22. In contrast, Th2 cells, which secrete IL-4, IL-5, and IL-13 upon IL-4 stimulation, are primarily associated with allergic responses and are not typically involved in the inflammatory mechanisms observed in MS.(36) Th1 and Th17 CD4 T cells rely on specific transcription factors—T-bet for Th1 cells and RORC2 for Th17 cells—while Th2 cells require the GATA3 transcription factor to become active. IFN-γ (produced by Th1 cells) and IL-17 (produced by Th17 cells) are both thought to increase immune activation within the central nervous system (CNS) by promoting the secretion of pro-inflammatory intermediaries, enhancing antigen presentation, or directly affecting the survival and function of CNS-resident cells. Though both IFN-γ and IL-17 have been closely linked to autoimmune pathology, studies using experimental autoimmune encephalomyelitis (EAE) models have shown that Th17 cells are particularly essential for the development of CNS autoimmunity. In vitro studies indicate that naïve T cells differentiate into Th1 cells in response to IL-12, while stimulation with IL-6 and transforming growth factor β (TGF-β) polarizes them toward a Th17 cell phenotype [37]. These in vitro findings are thought to reflect the polarization process that occurs in vivo, where activated accessory cells release cytokines, fostering an inflammatory environment that activates naïve T cells. Myeloid-lineage antigen-presenting cells (APCs), including microglia and infiltrating macrophages, are primary producers of IL-6 and IL-12, while astrocytes can also secrete proinflammatory cytokines that support immune cell activation within the central nervous system (CNS). In multiple sclerosis (MS), Th1 and Th17 cells are frequently detected in peripheral blood, cerebrospinal fluid (CSF), and spinal cord lesions, with Th1 cells typically present in peripheral blood and CSF at levels roughly ten times greater than Th17 cells. However, during clinical relapse, Th17 cell frequencies increase in the CSF of MS patients, distinguishing them from patients in remission or those with non-inflammatory neurological disorders. Interestingly, while some studies have linked relapse specifically to increased IFN-γ rather than IL-17, it is essential to recognize that not all cells producing IFN-γ or IL-17 are pathogenic in MS; rather, distinct subsets of these cells may serve as initiators, mediators, or aggravators of disease progression [38- 41] .

The roles of IFN-γ and IL-17 in multiple sclerosis (MS) versus experimental autoimmune encephalomyelitis (EAE) remain complex and somewhat contradictory. Prior to the identification of Th17 cells, it was thought that deleting the IL-12 p40 subunit could reduce disease severity, suggesting that IFN-γ-producing Th1 cells, stimulated by IL-12, were the primary mediators of EAE [42]. However, p40 is also a component of IL-23, a cytokine essential for stabilizing the Th17 phenotype and promoting IL-17 expression, indicating that the deletion of p40 could impact both Th1 and Th17 cells. This dual effect further complicated interpretations, especially as IFN-γ appeared to play a protective role in the EAE mouse model—since genetic deletion of IFN-γ actually worsened EAE severity, strengthening the idea that IL-17 might be the primary driver of EAE pathology, see figure 4.

In human MS, however, evidence suggests both IL-17 and IFN-γ contribute to pathology. Since the late 1980s, IFN-γ-expressing cells in MS have been recognized as inflammatory, and clinical trials have supported their pathogenic role. In a 1990s trial, IFN-γ administration in

MS patients significantly worsened their condition, directly contradicting findings from the EAE model and underscoring the complexity of human MS. More recently, clinical trials targeting IL-17 with neutralizing medications have shown promising preliminary results, indicating a reduction in relapse rates for patients with relapsing-remitting MS (RRMS). [43- 45]. In contrast, a clinical trial using a monoclonal antibody targeting the p40 subunit of IL-23, aimed at blocking IL-17 stabilization, proved effective for treating psoriasis and Crohn's disease but showed no therapeutic benefit for patients with relapsing-remitting MS (RRMS) [46]. One explanation for the seemingly paradoxical outcomes between blocking Th17-stabilizing IL-23 versus directly blocking IL-17 is that participants in the IL-23 trials may have been in more advanced stages of the disease [47]. Furthermore, certain cytokines may play different roles in the initial onset of a disease versus its progression or exacerbation. Consequently, IFN-γ and IL-17 might exert stage-specific effects in the course of MS in humans. Additionally, Th17 cells derived from both MS patients and healthy controls express lower levels of Fas ligand (FASL) compared to Th1 cells, resulting in a reduced susceptibility to cell death. This resistance to apoptosis may allow Th17 cells to persist longer, potentially enhancing their contribution to MS pathogenesis [48-49]

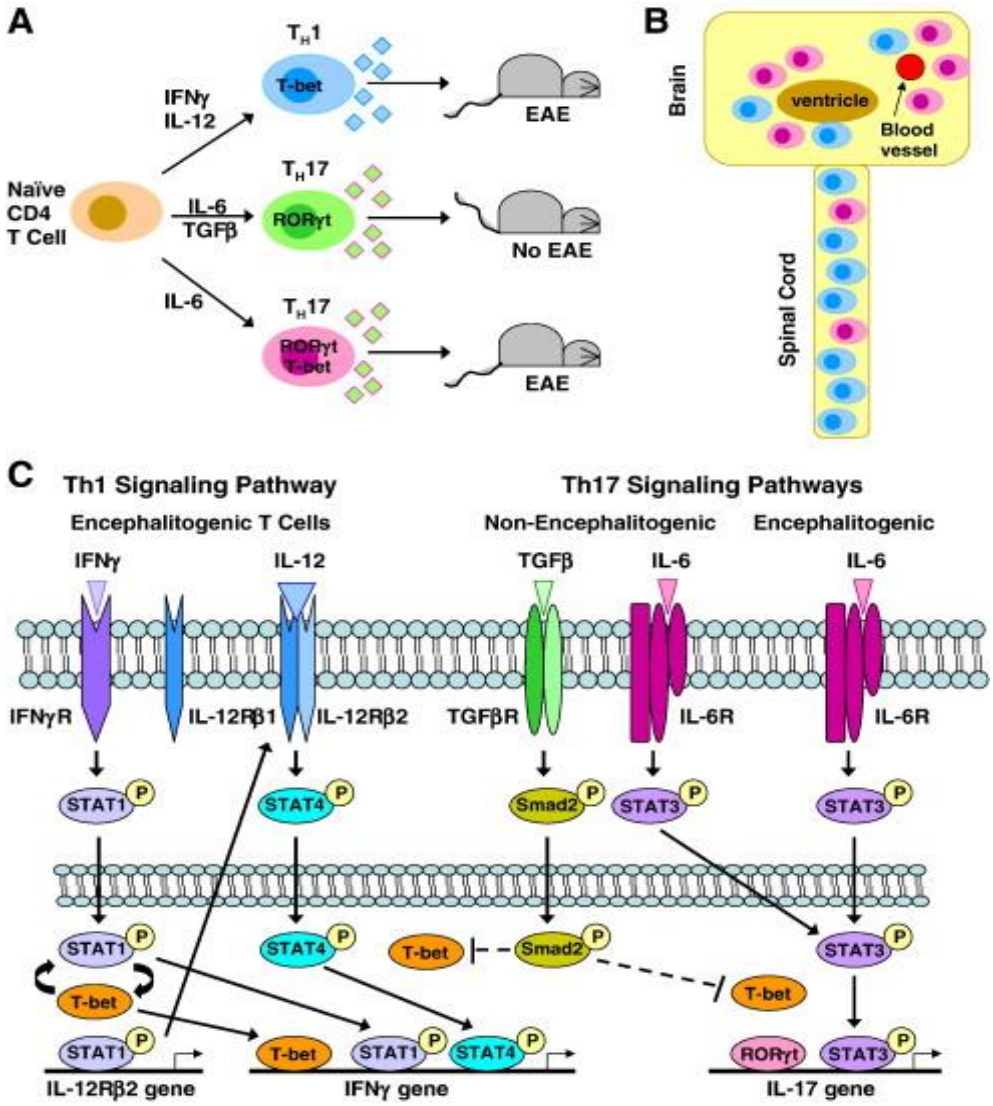

Figure (4) Trafficking to the central nervous system and differentiation of Th1 and Th17 cells. (A) Th1 or Th17 cells can develop from naïve CD4 T cells. TGFβ can increase IL-17 synthesis during Th17 cell differentiation, but this reduces the cells' ability to cause EAE. (B) Th1 and Th17 cell distribution in the central nervous system varies in EAE. Whereas Th17 cells seem to preferentially travel to the brain, Th1 cells preferentially home to the spinal cord. In myelin-immunized mice, Th1 cells in the central nervous system (CNS) greatly outnumber Th17 cells. (C) Th1 and Th17 differentiation transcriptional regulation provides information about signaling pathways that might be crucial for the growth of encephalitogenic T cells. T-bet is present in Th1 and Th17 encephalitogenic cells. The presence of TGFβ during Th17 cell differentiation contributes to the inhibition of T-bet, resulting in non-encephalitogenic Th17 cells if primed with IL-6 + TGFβ.

1.7. Pathophysiology of Th-17

IL-17 signals through a receptor that is widely expressed and plays a crucial role in defense against extracellular bacteria and fungi [50]. It has been suggested that IL-17 can specifically alter the behavior of activated astrocytes [51], enhancing their inflammatory potential [51]. The effects of IL-17 vary by target cell type but include increased secretion of proinflammatory cytokines (such as TNF-α, IL-6, and granulocyte-macrophage colony-stimulating factor [GM-CSF]), chemokines (CCL8, CXCL2, and CCL20), and complement proteins [52]. These responses aid in recruiting neutrophils, macrophages, lymphocytes, and microglia to the site of inflammation while also supporting the persistence of Th17 cells [53]. IL-17 and disease activity are closely correlated, according to data from MS patients. IL-17 messenger RNA (mRNA) has been found in MS brain lesions using microarray analysis. [54], with active lesions showing higher concentrations of IL-17-producing glial cells, as well as CD4 and CD8 T cells, compared to inactive regions [55]. Additionally, plaques in MS brains express elevated levels of the IL-17-associated RORC2 transcription factor relative to healthy brain tissue. Increased occurrences of IL-17-generating cells and higher levels of IL-17 mRNA have been observed in patients' peripheral blood, correlating positively with disease activity. Patients undergoing a relapse exhibit significantly elevated IL-17 mRNA and protein in both blood and cerebrospinal fluid (CSF). Furthermore, MRI studies have shown a relationship between increased IL-17 secretion by myelin basic protein (MBP)-stimulated cells and greater disease activity [54-57].

Th17 cell activity may contribute to disease manifestation and neurological dysfunction in MS [58]. Human Th17 cells demonstrate neurotoxic effects and cross blood-brain barrier (BBB) models more efficiently than Th1 cells in vitro [59]. Elevated levels of IL-17A in the cerebrospinal fluid (CSF) of MS patients are associated with neutrophil expansion and BBB disruption. IL-17 may also play a role in glutamate excitotoxicity, as suggested by the correlation between increased IL-17A and CSF glutamate levels in MS patients [60]. Th17 cells secrete additional cytokines, such as IL-21 and IL-22, which may further impact disease progression [55]. IL-21 controls immune cell stimulation and persistence, influencing lymphocyte infiltration in active white matter MS lesions. High levels of IL-22, which promotes BBB disorder, have also been found in the peripheral blood and CSF of MS patients. Notably, Th17 cells expressing both IL-17A and IL-22 can also produce granzyme B, a cytolytic enzyme that, unlike inactive T cells, exhibits neurotoxic effects on human fetal neurons in culture [58-59]. Granzyme B, when released extracellularly, can target the glutamate receptor GluR3 [60-61], leading to neuronal cell death. This cytotoxic activity underscores the potential neurotoxic effects of Th17 cells in MS. Additionally, the excretion of GM-CSF by Th17 cells appears essential for stimulating CNS myeloid cells, such as microglia, macrophages, and dendritic cells, as GM-CSF-deficient Th17 cells are unable to induce experimental autoimmune encephalomyelitis (EAE) [61].

Clinical studies have shown that positive therapeutic outcomes in MS are often associated with a reduction in Th17 activity. For instance, IFN-β treatment has been shown to inhibit Th17 differentiation in vitro [62]. Patients who respond poorly to IFN-β therapy tend to exhibit higher serum levels of IL-17F compared to those who benefit from the treatment. Similarly, a decrease in Th17 responses has been linked to therapeutic success with drugs such as fingolimod and dimethyl fumarate [60- 63].

1.8.Pathology of The Th-1

While T cells and natural killer (NK) cells are the primary producers of the Th1 cytokine IFN-γ, it can also be secreted by B cells, antigen-presenting cells (APCs), and natural killer T

(NKT) cells. Th1 cells release substantial amounts of both TNF-α and IFN-γ, with IFN-γ serving as their defining cytokine. IFN-γ plays a importante role in influencing the activation and survival of CNS-resident cells [64], prompting these cells to increase the expression of MHC molecules. Due to the widespread expression of IFN-γ receptors across various CNS cell types, nearly all CNS cells can respond to IFN-γ [65]

Elevated IFN-γ levels have been related with an increased incidence of active MS lesions [66], and T cells derived from MS patients have been shown to produce higher levels of IFN-γ prior to disease flare-ups [67]. Genetic polymorphisms linked to IFN-γ have also been associated with a heightened risk of MS [68]. Importantly, research has demonstrated that IFN-γ not only activates microglia to adopt phagocytic and antigen-presenting roles but can also directly harm oligodendrocytes [69], resulting in a loss of neuronal myelination in the CNS [70]. Additionally, IFN-γ has been observed to inhibit synapse formation and cause dendritic retraction, further contributing to neural damage [71]

IFN-γ is thought to develop the antigen-presenting capacity of myeloid cells within meningeal and perivascular sites by upregulating MHC molecule expression, which, in turn, allows these cells to restimulate myelin-antigen-specific CD4 and CD8 T cells. Studies suggest that antigen-presenting cells (APCs) in MS patients can activate myelin-reactive CD8 T cells through a process called antigen cross-presentation, where exogenous myelin is displayed on MHC class I molecules [72]. This activation permits CD4 and CD8 T cells to infiltrate CNS tissue, perpetuating immune-mediated damage [73]

In both MS and experimental autoimmune encephalomyelitis (EAE), T cells have been observed to concurrently or sequentially produce IL-17 and IFN-γ. Fate-mapping studies indicate that cells initially producing IL-17 in EAE can transition into ex-Th17 cells, characterized by high IFN-γ production without IL-17 expression [74]. Interestingly, Th17 cells were found to be the primary source of the Th1 cells infiltrating the CNS in this study [58]. The detection of T cells co-expressing IL-17 and IFN-γ in MS brain tissue further suggests that these dual-expressing effector cells may contribute significantly to disease progression [69,71]

Additionally, some studies suggest that Th1 cells might have a protective role in MS. Blocking TNF-α—a Th1 cytokine—has been shown to induce myelin autoimmunity in rheumatoid arthritis patients and to exacerbate MS symptoms in clinical trials [75]. This finding implies that TNF-α may have a protective effect against MS in certain contexts. While IFN-γ has been shown to stabilize tight-junction protein expression in brain endothelial cells at the blood-brain barrier, enhancing barrier integrity, IL-17, in contrast, weakens these tight junctions, promoting barrier disruption and inflammation [76].

2. The Essential Role of B Cells in Multiple Sclerosis Pathophysiology

Recent evidence supports that multiple sclerosis (MS) is not solely driven by T cells but also involves critical roles for B cells. This is highlighted by the success of anti-CD20 therapies, which specifically target B cells, underscoring their involvement in MS pathogenesis. Additionally, the activation of B cells in MS appears to contribute more through antigen presentation and cytokine production rather than direct antibody generation. However, the precise interactions between B and T cells that lead to CNS infiltration and subsequent demyelination in MS remain incompletely understood (70).

It is hypothesized that B and T cell interactions may amplify pathogenic effects and initiate triggers contributing to MS progression. Both genetic and environmental factors appear to play integral roles in MS pathogenesis. Advances in genetic mapping have identified variants in the human leukocyte antigen (HLA) gene within the major histocompatibility

complex (MHC) as significant genetic risk factors. However, these genetic predispositions are estimated to account for only about 30% of total MS susceptibility, suggesting a substantial role for environmental triggers. Key environmental factors include smoking, vitamin D deficiency, and Epstein-Barr virus (EBV) infection, all of which may prime the immune system to foster an MS-prone environment [77].

Normally, immune responses involve coordinated communication between B cells, T cells, and cytotoxic T cells. In MS, however, this coordination is disrupted, leading to B cell infiltration into the CNS, activation of cytotoxic T cells, and the demyelination of neuronal sheaths . Persistent antigen presentation by B cells, potentially due to chronic infections like EBV, may drive this breakdown in immune regulation. Furthermore, diminished regulatory T cell (Treg) function and control over effector T cells (CD4+ T cells) are also implicated in MS pathophysiology(67).

While peripheral T-B cell interactions in MS remain poorly understood, it is known that autoreactive B cells that escape immune checkpoints reach germinal centers (GCs) in lymphoid tissues. Within these GCs, B cells may form complexes, influenced by various mediators, that enable their migration from lymph nodes into the CNS. Once in the CNS, these B and T cells form myelin-reactive complexes, with weakened blood-brain barrier (BBB) integrity allowing their entry and accumulation, ultimately escalating the MS disease cascade [58].

Pathology in MS is further exacerbated by reactivation of myelin-reactive CD4+ and CD8+ T cells in the brain. IFN-γ plays a role here, facilitating interactions with B cells that stimulate further T cell production, sustaining the inflammatory cycle. Notably, the brain in MS is targeted by more than just myelin antigens; EBV antigens are also cross-presented, which may enhance the immune response and further activate MS pathways within the CNS. This cross-presentation between EBV and myelin antigens highlights a complex interplay that amplifies MS activation in the brain [67].

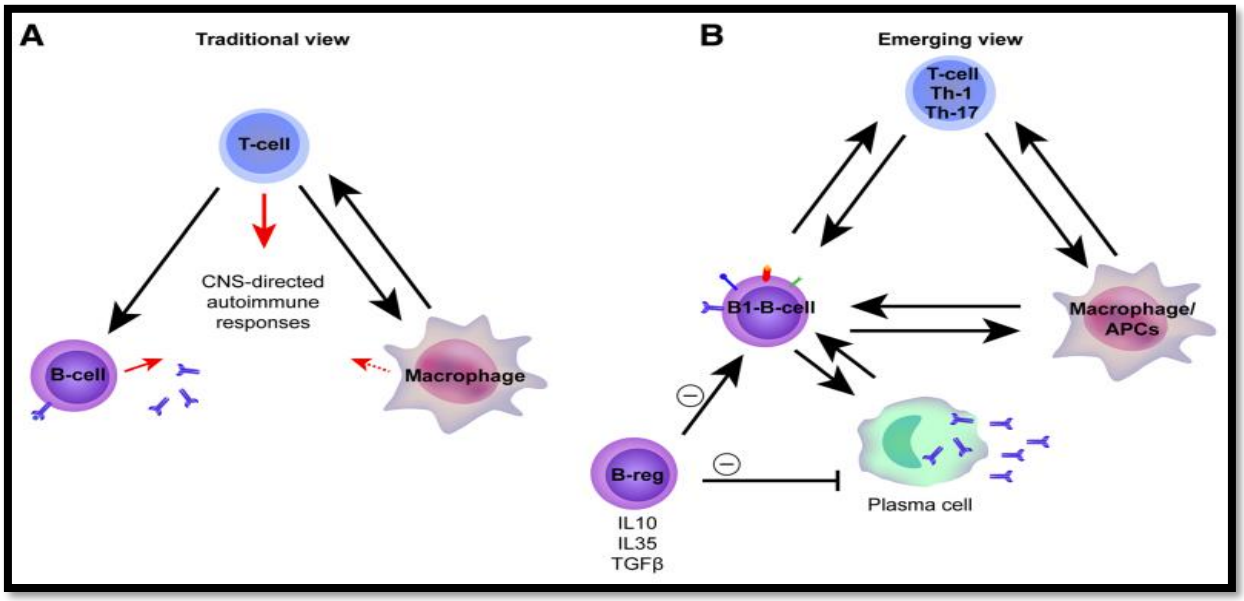

Figure 5: Impact of B cells on the pathophysiology of multiple sclerosis. [79] The changing understanding of how cell subsets contribute to the pathogenesis of multiple sclerosis. **A**. The conventional view of a B cell. T cells have a key role in the immunological pathogenesis of multiple sclerosis as well as the control of CNS-directed autoimmunity. New

MS attacks are triggered by an imbalance between proinflammatory type-1 helper T cells (TH1) and TH17 effector T cells (Teff) and Treg cells. The primary antigen-presenting cells (APCs) that influence T cell responses are myeloid cells. Myeloid cell responses can then be influenced by differentiated T cells. The population of B cells is passive and comparatively homogeneous. They wait for T cells to assist them in differentiating into plasma cells and plasmablasts that secrete antibodies. **B**. The view of the updated B cell. According to the revised perspective, the B cell is an active member of a complex network. T cells, regulatory B cells, and macrophages are all part of this network. This intricate network somehow became dysregulated in MS. Additionally, B cells can be divided into two well-known subtypes: B1B cells and B2B cells. The B1B cells become uncontrollable in MS patients' autoimmune reactions. Additionally, the outcomes of anti-CD20 (aCD20) therapy for multiple sclerosis point to a greater involvement for B cells in newly diagnosed MS attacks, which frequently seem to be antibody independent. B cells' antibody-independent function, which is partially regulated by the production of certain cytokines, can take the form of either anti-inflammatory regulatory cells or proinflammatory effector B1B cells (B-1-B).

Conclusion

The etiology of multiple sclerosis (MS) is increasingly recognized as a complex interplay of immune dysregulation, genetic susceptibility, and environmental factors, each contributing uniquely to disease progression. MS pathogenesis is not the result of a single immune malfunction but rather a culmination of predisposing genetic "readiness," environmental triggers such as Epstein-Barr virus (EBV) infection, smoking, obesity, and vitamin D deficiency, as well as the maladaptive responses of both T and B lymphocytes.

Historically, the role of T cells, particularly autoreactive CD4+ and CD8+ subsets, has been the focal point in MS research. These T cells penetrate the blood-brain barrier (BBB), initiate local CNS inflammation, and contribute to demyelination and neuronal damage. However, the growing body of evidence supporting the involvement of B cells has shifted the paradigm. Contemporary studies show that B cells contribute to MS pathogenesis through antigen presentation, cytokine production, and sustained inflammation rather than through antibody production alone. The success of B cell-targeted therapies, such as anti-CD20 agents, underscores the importance of B cells in the disease mechanism and has led to intensified research into their specific contributions to MS.

This shift toward investigating B cells has been made possible by advances in immunological research and technology, including genomic and proteomic analyses, which allow researchers to explore the genetic markers and molecular pathways associated with MS more precisely than ever before. These advancements have revealed that MS is not merely a T cell-driven autoimmune disorder but a multifaceted immune-mediated condition. B cells, once considered secondary players, are now acknowledged as critical in sustaining the autoimmune response, opening new avenues for targeted therapies that could alter the disease course more effectively than traditional approaches.

Moreover, this understanding has brought to light the broader implications of immune interactions in MS. The interaction between T and B cells suggests a feedback loop within the CNS that promotes chronic inflammation, allowing for sustained neuronal damage. This interaction may explain why MS is a progressive disease, with periods of relapse and remission punctuated by long-term neurodegeneration.

In summary, the evolving insights into MS underscore the need for a dual-focused therapeutic strategy targeting both T and B cells, as well as personalized treatments that consider genetic predispositions and

environmental exposures. Future research must continue to refine our understanding of these interactions to develop treatments that not only slow MS progression but potentially prevent its onset by addressing its root causes.

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