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The Immune Response in Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory, and neurodegenerative disease that affects the central nervous system (CNS). MS is characterized by immune dysregulation, which results in the infiltration of the CNS by immune cells, triggering demyelination, axonal damage, and neurodegeneration. Although the exact causes of MS are not fully understood, genetic and environmental factors are thought to control MS onset and progression. In this article, we review the main immunological mechanisms involved in MS pathogenesis.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system (CNS) that affects more than 2.5 million people worldwide. MS onset usually occurs between 20 and 40 years of age and is the most common cause of neurologic disability in young adults, affecting women about twice as often as men (1, 2). MS is characterized by focal lymphocytic CNS infiltration leading to myelin destruction and axonal damage, which result in neurologic syndromes and physical disability (3). MS clinical manifestations depend on the location of lesions in the CNS. Symptoms may include sensory and visual disturbances; motor and coordination impairment; and spasticity, fatigue, pain, and cognitive deficits (4). About 85–90% of MS patients develop a relapsing-remitting form of the disease, which is characterized by periods of symptom exacerbation followed by remission. As the disease evolves, the recovery from symptoms is incomplete, and around 50% of patients eventually develop a form of the disease known as secondary progressive MS, which is characterized by the progressive, irreversible accumulation of neurologic disability. A smaller number of MS patients (10–15%) follow a progressive clinical course from the onset of the disease that is termed primary progressive MS (1).

WHAT CAUSES MS?

MS is thought to arise from a combination of genetic and environmental factors. Epidemiological studies have shown that the risk of MS is higher among relatives of MS patients, suggesting some degree of genetic susceptibility (5). As such, first-degree family members carry a 2–4% risk of developing MS compared with an estimated 0.1% of the general population (3). In fact, genome-wide association studies have identified more than 200 gene variants linked to MS predisposition (6). The strongest linkage was found with major histocompatibility complex alleles, with HLA-DRB1 being the greatest risk allele in MS (7). The fact that the major risk allele and the vast majority of the risk alleles identified so far are related to the immune response supports a major role for the immune response in MS pathology.

Nevertheless, genetics account for only 30% of the explainable risk of MS (4). Indeed, studies conducted in twins, who carry a nearly identical genetic load, show that if one monozygotic twin has MS, the other has only a 25% risk of developing MS; moreover, in dizygotic twins, this risk decreases to 5% (8). In combination with additional epidemiological studies, these observations suggest that environmental factors are important contributors to disease development. Indeed, environmental risk factors such as latitude, low vitamin D levels (9), obesity, smoking (10), and infection—in particular Epstein-Barr virus (EBV)—have all been shown to influence disease incidence and/or prevalence (4). Hence, MS is thought to result from the combination of a genetic predisposition with certain environmental exposures (e.g., teenage obesity, smoking, and night-shift work).

Regardless of the specific triggering cause, a dysregulated immune response promotes CNS damage in MS. In this article, we briefly introduce the most important immune mechanisms relevant to MS pathology and their potential as therapeutic targets.

ADAPTIVE IMMUNITY IN MS

CD4$^+$ T Cells

The role of CD4$^+$ T cells in MS is supported by the identification of the HLA class II haplotype HLA-DRB1*15:01 as a major genetic risk factor for MS (11). Indeed, proinflammatory T helper type 1 (Th1) and Th17 cells have been linked to MS pathology (12). Following activation in the

presence of interleukin 12 (IL-12), naive CD4$^+$ T cells differentiate in Th1 cells, which express the transcription factor Tbet and produce interferon gamma (IFN-γ); activation in the presence of TGF-β1, IL-23, and IL-6 or IL-21 results in the differentiation of Th17 cells characterized by RORγt expression and the production of IL-17 (13, 14).

Conversely, CD4$^+$ regulatory T cells (Tregs) expressing FoxP3 transcription factor (15) and IL-10-producing CD4$^+$ type 1 regulatory T cells (Tr1) (16) limit pathogenic T cell responses through multiple mechanisms such as the production of inhibitory cytokines, cell contact-dependent cytolysis, and metabolic disruption. It has been postulated that a combination of diminished Treg numbers, decreased Treg suppressive activity, and resistance of pathogenic T cells to Treg control contributes to the dysregulated autoimmune T cell response associated with MS pathology (17, 18).

CD8$^+$ T Cells

CD8$^+$ T cells are central players in MS pathology, but their roles are sometimes underappreciated because most preclinical models of MS are driven by CD4$^+$ T cells and not CD8$^+$ T cells. The relevance of CD8$^+$ T cells in MS pathology is supported by two observations: (*a*) Large numbers of CD8$^+$ T cells are detected in the injured white and gray matter of MS patients—in fact, CD8$^+$ T cell frequency is higher than that of CD4$^+$ T cells (19), and (*b*) the HLA class I region has been associated with protective (HLA-A*02:01) and risk-increasing (HLA-A*03:01) genetic alleles (20, 21). CD8$^+$ T cells contribute to CNS damage via the production of granzymes and perforins, as well as Fas/FasL-mediated cytotoxicity (22, 23). In addition, CD8$^+$ T cells secrete proinflammatory cytokines, essentially IL-17 and lymphotoxin (13), and chemoattractants for CD4$^+$ T cells such as IL-16 and IP-10 (24).

B Cells and Antibodies

The intrathecal production of antibodies and the detection of oligoclonal bands in the cerebrospinal fluid (CSF) of MS patients have been known for more than 70 years. Following activation, B cells differentiate into memory or plasma cells, which secrete autoantibodies that participate in antibody-dependent cytotoxicity (ADCC) and complement injury (25). Antibody oligoclonal bands are detected in more than 90% of MS patients and can be used to confirm or fulfill diagnostic criteria (26). However, although altered antibody responses have been described in MS, their contribution to MS pathology is still debated. In addition to their antibody-production function, B cells can release proinflammatory cytokines, such as lymphotoxin and TNF-α, and have important functions as antigen-presenting cells (APCs) involved in T cell activation (27). Indeed, the APC function of B cells is thought to be at the core of the remarkable beneficial effects of B cell–depleting therapies in MS.

γδ T Cells

γδ T cells are a subset of T cells thought to bridge innate and adaptive immunity contributing to early tissue damage in MS (28). Indeed, a fraction of γδ T cells that express Vγ2 are found in the CSF of MS patients (29). γδ T cells promote demyelination as a result of their cytotoxic activity against oligodendrocytes mediated by the Fas ligand and also via the activation of ADCC, perforin, and granzyme B. Moreover, oligodendrocytes express hsp60, which is reported to induce γδ T cell expansion, suggesting a cell–cell cross talk in which oligodendrocytes might be a γδ T cell target and also a trigger for γδ T cell expansion (13, 30).

Mucosal-Associated Invariant T Cells

Mucosal-associated invariant T (MAIT) cells are a subset of innate-like $CD8^+$ T cells enriched at mucosal sites that express a semi-invariant T cell receptor (31). MAIT cells are increased in the MS brain, where they produce IL-17 (32, 33). The beneficial clinical outcome that follows MAIT cell depletion suggests that this cell population plays an important role in the pathogenesis of the disease (34).

INNATE IMMUNITY IN MS

Mast Cells

Mast cells have been described in large numbers in MS plaques and are recruited in response to gradients of RANTES chemokines. Mast cells are responsible for the release of histamine and tryptase, which contribute to the opening of the blood–brain barrier (BBB) and the recruitment of inflammatory cells into the CNS. Furthermore, tryptase and chymase produced by mast cells activate a cascade of matrix metalloproteinase (MMP) precursors that promotes neurodegeneration (2, 35).

Microglia and Macrophages

CNS-resident microglia and recruited macrophages are important players in CNS inflammation and pathology. Two polarization profiles were initially described for macrophages and microglia: (*a*) a proinflammatory (M1) profile that is responsible for the production of cytokines (IL-12, IL-23), chemokines, and metabolites, which are involved in neurodegeneration and act as APCs (14, 25), and (*b*) an immunoregulatory (M2) profile that is involved in the debris clearance necessary for remyelination (36, 37). However, it is now clear that multiple activation states of microglia and macrophages can be identified in MS (38). Some of these subsets produce neurotoxic products such as TNF-α, reactive oxygen species, and reactive nitrogen species [e.g., nitric oxide (NO)], which can have direct neurotoxic effects in MS (39, 40).

Astrocytes

Astrocytes are the most abundant glial cells in the CNS. Astrocytes modulate CNS inflammation via the expression of cytokines, chemokines, and surface molecules that participate in cell interactions with other cells in the CNS. Although not derived from any immune progenitor and not strictly an innate immune cell, astrocytes can promote innate inflammation and neurodegeneration in MS through the expression of cytokines (e.g., IL-6 and TNF), chemokines (e.g., CCL2), and neurotoxic metabolites (e.g., NO) (41–45). Conversely, specific astrocyte subsets can limit T cell autoimmunity in the CNS via the secretion of cytokines (e.g., IL-27) or the induction of tumor necrosis factor–related apoptosis-inducing ligand (TRAIL)-dependent apoptosis (46, 47). Of note, astrocytes, microglia, and monocytes do not operate in isolation. Indeed, they establish poorly characterized cell interactions that can amplify CNS pathology and may offer novel targets for therapeutic intervention (48, 49).

Natural Killer Cells

Natural killer (NK) cells are innate immune cells that participate in the immune response against several types of tumors and microbial infections. NK cells can be classified according to their homing characteristics. The $CD56^{dim}$ $CD16^+$ subset of NK cells contains perforin-expressing cells that are found in peripheral blood and spleen and show cytotoxic activity against tumor cells.

In contrast, CD56^{bright} CD16^{-} NK cells locate in lymph nodes and tonsils and do not secrete perforin (50).

CD56 NK cells are decreased in MS patients (51) and seem to play an immunoregulatory role in the disease by secreting immunomodulatory cytokines such as IL-5, IL-13, and TGF-β and by inducing target cell lysis through perforin- and TRAIL-dependent mechanisms (52, 53). Moreover, NK cells recently have been shown to induce TRAIL expression in astrocytes, which can then promote TRAIL-driven T cell apoptosis. Important insights on the role of CD56 NK cells in MS were obtained during a study of the therapeutic effects in MS of monoclonal antibodies directed against IL-2 (daclizumab), which triggered the expansion of CD56 NK cells concomitant with significant disease improvement (54). However, additional studies are needed to understand the effects of multiple NK subsets in MS.

IMMUNE MECHANISMS INVOLVED IN MS DEVELOPMENT AND RELAPSES

Predisposing Factors

Although specific triggers still remain unclear, epidemiologic studies suggest that MS develops in genetically predisposed individuals influenced by certain environmental factors (**Figure 1**).

There are about 200 independent gene risk associations with MS, most of which are highly linked with the adaptive immune system (55). Interestingly, some MS-linked gene variants are

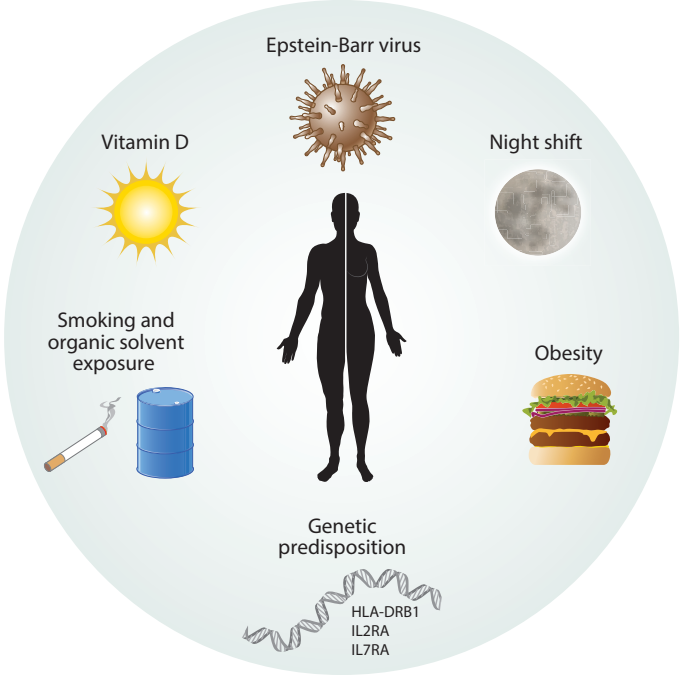

Figure 1

Genetic and environmental factors contribute to multiple sclerosis (MS) pathology. The mechanisms of action of MS risk factors are not well understood, but it is thought that environmental factors such as vitamin D levels, viral infections, night-shift work, obesity, organic solvent exposure, and smoking can influence and promote MS in genetically susceptible individuals such as HLA-DRB1*15:01 carriers.

shared between MS and other autoimmune diseases, being protective for one disease but conferring risk to the other. MS genetic susceptibility is strongly represented by HLA-DR and HLA-DQ variants, with HLA-DRB1*15:01 being the highest risk genotype (56). The DR15 haplotype is associated with immune-related genes such as TGFB1, CTLA-4, TNF, IL1, IL1RA, and estrogen receptor encoding gene (2). Aside from HLA genes, single nucleotide polymorphisms within genes such as RNA helicase DEAD box polypeptide 39B (DDX39B), tumor necrosis factor receptor super family 1A (TNFRSF1A), ecotropic viral integration site 5 (EVI5), and other polymorphisms in TNFSF113B, IL2RA, IL7RA, and CD58 were found to confer MS risk (56–58). In summary, while HLA gene variants are thought to affect the T cell repertoire, non-HLA-risk genes modulate immune cell activation, collectively shaping the immune response directed against the CNS (4).

Nongenetic factors linked to MS include vitamin D levels (59), obesity (60), circadian disruption (61), and smoking habits (62). Indeed, it has been proposed that smoking contributes to MS risk by activating proinflammatory pathways in the lungs, where CNS autoreactive cells may potentially be activated (63). Along with smoking, EBV infection is the greatest environmental risk-conferring factor for MS (64). Previous studies showed that anti-EBV antibodies are increased in MS patients, especially against EBV nuclear antigen 1 (EBNA-1), and, in fact, infectious mononucleosis increases the risk of developing MS (65). Interestingly, EBNA-1 serologically negative individuals positivize prior to MS onset (63). Several mechanisms have been proposed to explain the contribution of EBV in MS. For example, it has been suggested that inflammatory events associated with infections may activate autoreactive CNS cells. It has also been suggested that molecular mimicry between EBV and CNS antigens may trigger or boost CNS autoimmunity in MS (2). However, the mechanisms by which EBV contributes to MS pathology have not been completely elucidated.

Peripheral Activation of Pathogenic T Cells

MS onset is thought to be triggered by the activation of CNS-reactive T cells in the periphery. Two main hypotheses have been put forward to explain the activation of CNS reactive T cells in MS: (*a*) immune cross-reactivity with foreign antigens and (*b*) recognition of CNS-derived antigens that leak to deep cervical lymph nodes (1) (**Figure 2**).

Foreign antigens in tissues such as the lungs, intestine, or skin are captured by APCs, which migrate to draining lymph nodes and may activate pathogen-reactive T cells cross-reactive with CNS self-antigens (66). Following their activation and polarization into proinflammatory subsets, these self-reactive T cells migrate to the CNS to cause tissue damage as described below. It is also possible that CNS soluble antigens present in the CSF that bathes the CNS activate T cells in the deep cervical lymph nodes (67).

Regardless of the specific initiating event involved, an important aspect of the pathology of MS and other autoimmune diseases is epitope spreading, a phenomenon by which the immune response generated against a single epitope is spread to other epitopes within the same antigen or even to other peptides (68, 69), further expanding the pathogenic autoimmune response.

Central Nervous System Migration

The CNS is delimited by the BBB, which limits the passage of circulating cells and large molecules, transforming the CNS into a relatively immunologically privileged site. Hence, following their peripheral activation, autoreactive T cells should migrate across the BBB to cause CNS damage.

Even though the mechanisms by which immune cells are guided into CNS remain unclear, it is thought that peripheral T cell activation triggers the expression of molecules that facilitate

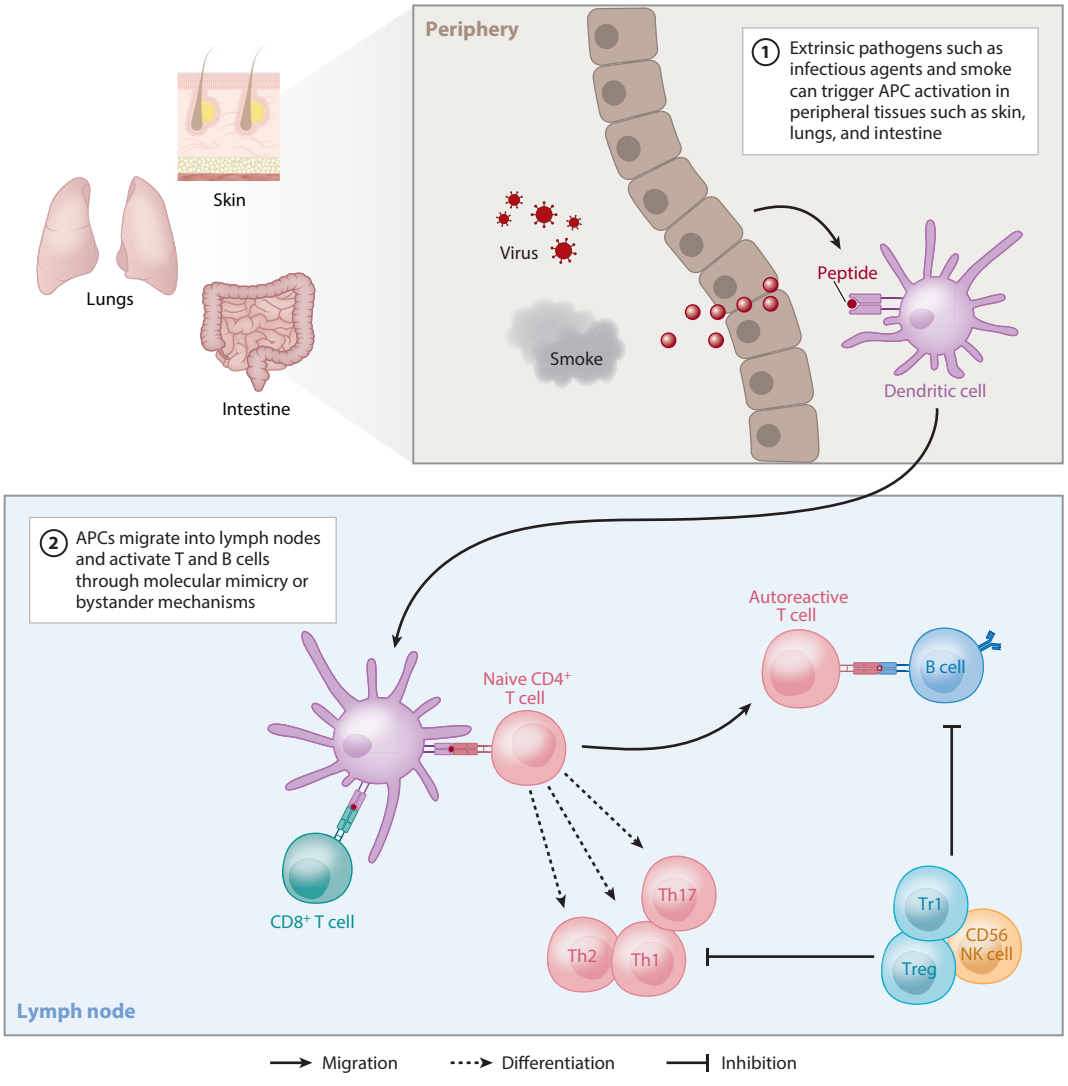

Figure 2

Autoreactive immune cells are activated in peripheral lymph nodes. One theory posits that T cells are activated following the presentation of cross-reactive antigens derived from pathogens by APCs. Following their activation, $CD4^+$ T cells may migrate to the CNS to cause tissue damage. Abbreviations: APC, antigen-presenting cell; CNS, central nervous system; NK, natural killer; Tr1, type 1 regulatory T cell; Treg, regulatory T cell.

their arrest on endothelial cells in the CNS (70). In addition, endothelial cells in proximity to damaged tissue express chemokines that promote integrin activation (71), which is responsible for immune cell rolling. Moreover, selectin stimulates autoreactive cell tethering and arresting, thus contributing to its migration (**Figure 3**).

MS lesions display an increased expression of endothelial adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin. Interactions between these adhesion molecules and their ligands ICAM-1/LFA-1 and VCAM-1/VLA-4 promote T cell migration across the BBB (70). Indeed, it has been shown that

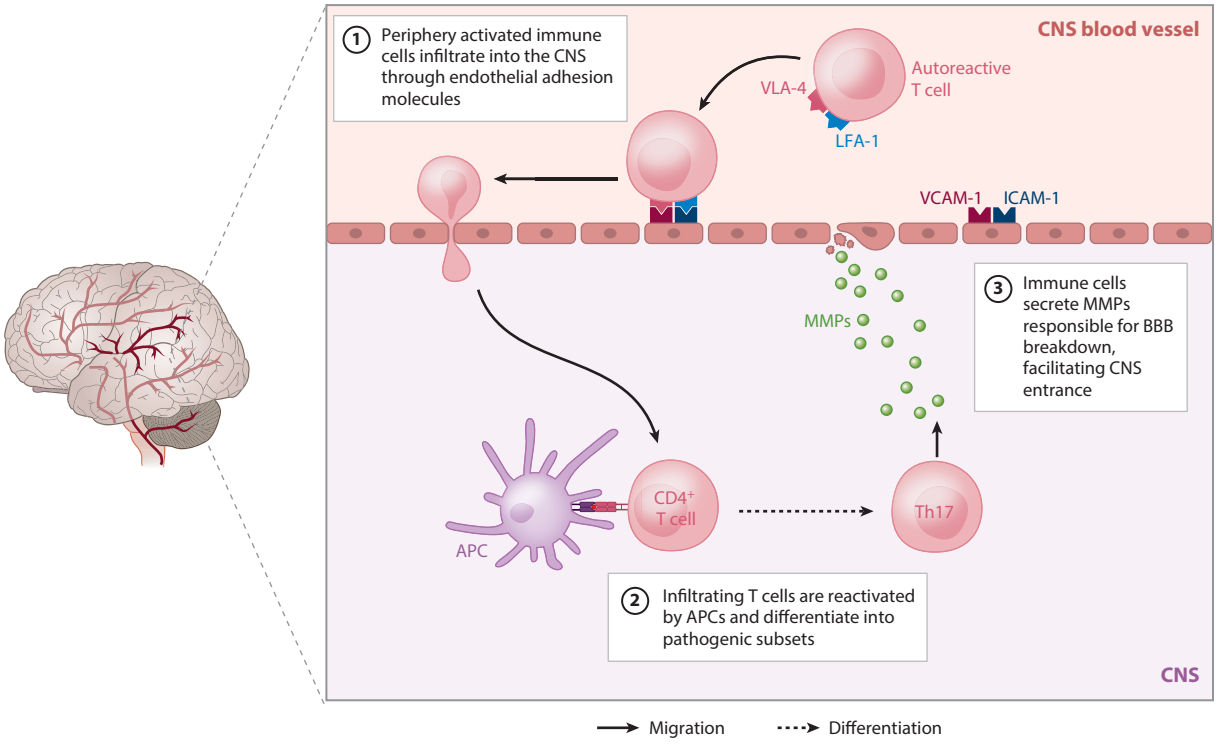

Figure 3

Immune cells are reactivated in the CNS to trigger tissue damage. Autoreactive immune cells extravasate into the CNS as a result of interactions with adhesion molecules (LFA-1/ICAM-1 and VLA-4/VCAM-1) and the secretion of MMPs, thereby damaging vessels and boosting immune cell infiltration. Antigen presentation by dendritic cells, microglia, and other cells in the CNS reactivates T cells. Abbreviations: APC, antigen-presenting cell; BBB, blood–brain barrier; CNS, central nervous system; ICAM-1, intercellular adhesion molecule 1; LFA-1, lymphocyte function-associated antigen 1; MMP, matrix metalloproteinase; VCAM-1, vascular cell adhesion molecule 1; VLA-4, very late activation antigen 4.

autoreactive T cells fail to migrate into the CNS in VLA-4-deficient mice (72), a finding that supports an important role for VCAM-1/VLA-4 in BBB transmigration. In fact, a VLA-4 blockade with natalizumab prevents lymphocyte entry into the CNS and suppresses disease activity (73). Taken together, these findings suggest that complex interactions between the local microenvironment of CNS lesions and activated immune cells promote, amplify, and sustain CNS inflammation.

Lymphocyte Reactivation and Tissue Damage

Infiltrating autoreactive immune cells are reactivated in the CNS by dendritic cells, microglia, and other cells in the CNS (74). Indeed, T cell reactivation by microglia (75), dendritic cells at the BBB (76), and Tbet$^+$ B cells at the perivascular space (77) is needed for the development of CNS pathology.

T cell restimulation in the CNS triggers the clonal expansion of CD4$^+$ Th subsets. Th1 and Th17 cells secrete proinflammatory cytokines such as IFN-γ, TNF-α, IL-17, and GM-CSF, which activate macrophages, dendritic cells, astrocytes, and microglia that are responsible for further

activating resident astrocytes and microglia, while recruiting additional $CD8^+$ T cells, B cells, and mast cells that boost CNS pathology. Once in the CNS, infiltrating immune cells and brain resident cells secrete soluble neurotoxic and oligotoxic mediators including reactive nitrogen species, nitric oxide synthase, glutamate, perforin, granzyme, MMPs, and inflammatory cytokines (78–83). Moreover, this proinflammatory environment interferes with the ability of astrocytes, and potentially oligodendrocytes, to support neuron metabolic needs (84), amplifying the damage to neurons. In addition, autoantibodies secreted by activated B cells trigger complement fixation and ADCC, contributing to demyelination (85). Of note, B cells have also been shown to secrete neurotoxic molecules (27), which in combination with the abovementioned factors induce myelin and oligodendrocyte damage, promoting neurodegeneration (86) (**Figure 4**).

Limitation of the Immune Response

A clinical landmark of MS is that following the onset of symptoms, patients usually recover fully or partially as a result of multiple physiologic anti-inflammatory processes that include, among other factors, the apoptosis of inflammatory cells (25). In addition, anti-inflammatory cytokines produced in the CNS such as IL-27 and IFN-β are thought to act on lymphocytes and APCs to suppress inflammation (2, 87), while microglia clear debris and dead cells (88). Furthermore, several studies point to Tregs as important agents involved in remission via the production of immunosuppressive cytokines and the expression of additional anti-inflammatory molecules such as CD39 (89). In fact, Tregs expressing IL-10 and FoxP3 cells are increased at the remission stage of MS (90, 91). In this context, it has been proposed that the relapsing-remitting course of MS reflects the expansion of CNS antigen-specific effector T cells (relapse); this stage is followed by the expansion of Tregs directed against the same antigen, resulting in the control of the initial pathogenic response (remission) until effector T cells with a different antigen specificity are activated, initiating the cycle again (69).

Remyelination

Following myelin and axon destruction, most lesions show signs of remyelination. However, oligodendrocytes remyelinate damaged axons only partially after a relapse, and the original myelin thickness is never achieved again. The oligodendrocytes responsible for myelin repair are thought to be newly differentiated from resident oligodendroglial precursor cells, which are widespread all over the CNS (92).

Interestingly, immune cells may influence myelin regeneration. For example, microglia and macrophages showing an immunoregulatory profile (M2) are thought to promote remyelination through multiple mechanisms, including the phagocytosis and proteolysis of myelin debris, the secretion of regulatory factors such as IGF-1 and activin A, metabolic and trophic support, and iron handling (93, 94).

Some studies also suggest a beneficial role of autoantibodies in remyelination. Indeed, antibodies directed against CNS molecules that interfere with axonal elongation, such as neurite outgrowth inhibitor, enhance myelin repair (95) and are therefore considered attractive therapeutic targets. Additional pathways involved in the inhibition of myelin regeneration are also considered potential therapeutic targets, including Notch signaling, LINGO-1, Wnt, muscarinic receptor signaling, hyaluronan, semaphorin 3A, fibrinogen, and chondroitin sulfate proteoglycan (93, 96) (**Figure 5**). In fact, it has been reported that treatment with anti-LINGO-1 antibodies diminishes clinical symptoms, improves axonal integrity, and enhances myelination in experimental autoimmune encephalomyelitis (97). Remyelination-targeting strategies in isolation or combined with other approaches are of particular interest for the treatment of MS.

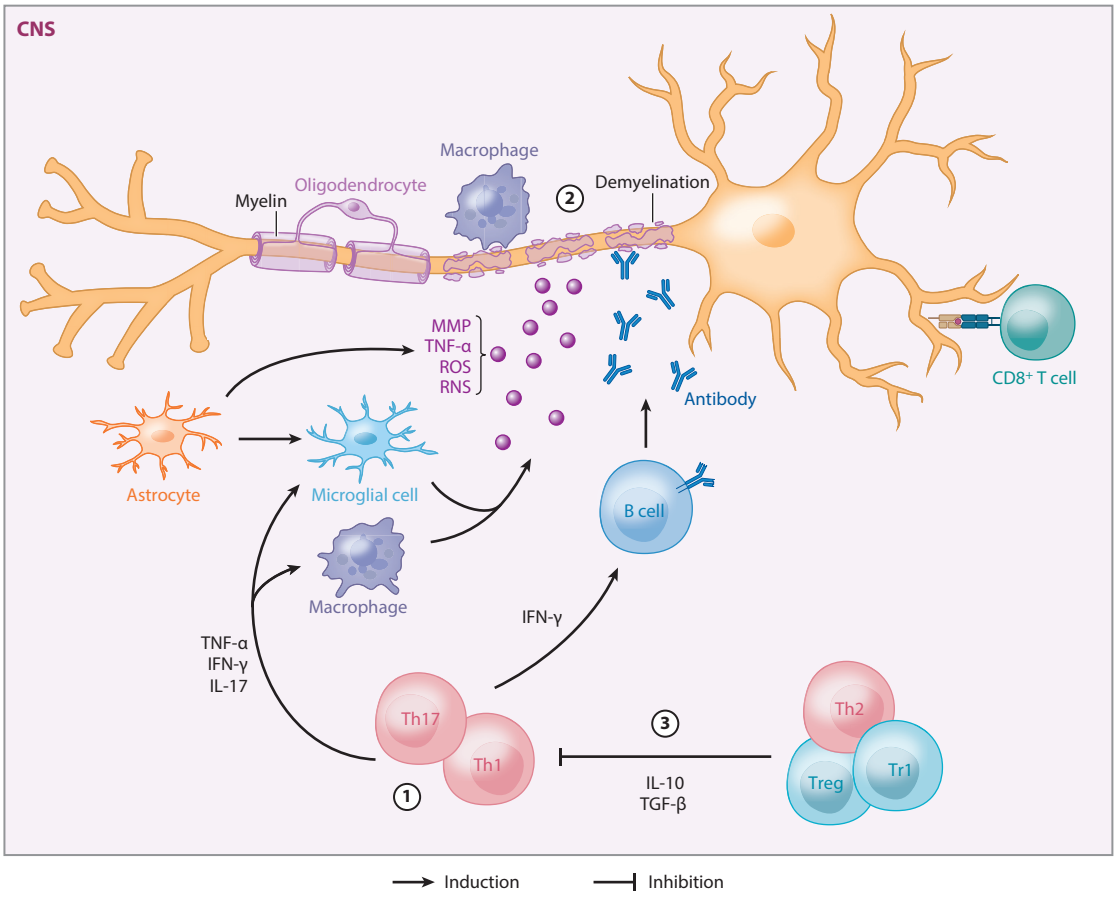

Figure 4

CNS damage driven by activated immune cells in the CNS. (①) Pathogenic Th subsets secrete proinflammatory cytokines such as TNF-α, IFN-γ, and IL-17, which induce microglia and macrophage pathogenic responses. Such immune cell activation and recruitment are supported by astrocyte activity, which promotes an additional immune response by cytokine and chemokine secretion giving rise to microglia activation and monocyte recruitment. This response causes further pathogenic behavior led by macrophages, B cells, and cytotoxic T cells. (②) Multiple mechanisms drive myelin and axonal damage, principally soluble neurotoxic molecule production such as MMPs, TNF-α, ROS, and RNS, which are secreted by astrocytes, macrophages, and microglia, as well as activated $CD8^+$ T cell cytotoxicity, ADCC, and complement. Further damage is facilitated by astrocytes, which not only show neurotoxic activity by NO secretion but also show decreased neurotrophic factor production and diminished metabolic support of neurons, thus contributing to neuronal damage. (③) Local CNS inflammation associated with MS relapses is limited and is resolved by $FOXP3^+$ Tr1 Tregs via the secretion of immunoregulatory cytokines such as IL-10 and TGF-β and additional mechanisms. Abbreviations: ADCC, antibody-dependent cytotoxicity; CNS, central nervous system; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; MS, multiple sclerosis; RNS, reactive nitrogen species; ROS, reactive oxygen species; TGF, transforming growth factor; TNF, tumor necrosis factor; Tr1, type 1 regulatory T cell; Treg, regulatory T cell.

Therapeutic Targets

Although no medication reverses or completely prevents the progressive neurological deficits caused by MS, several drugs have been approved by the US Food and Drug Administration in the last two decades for the treatment of the disease (98, 99). A full review of MS therapies is beyond the scope of this review, and we only briefly mention the treatments and their relationship with the cells and mechanisms mentioned above (**Figure 6**; **Table 1**).

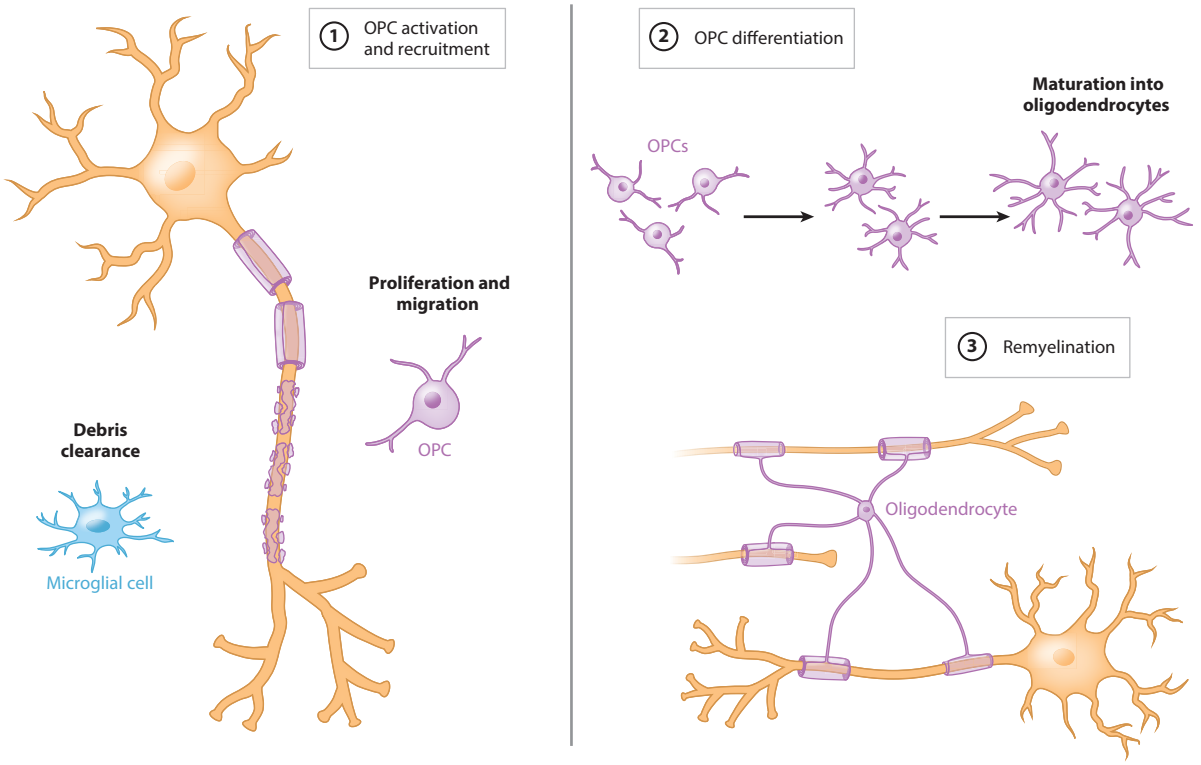

Figure 5

Oligodendrocytes mediate neuron demyelination after relapse. (①) Following myelin damage, OPCs are activated and migrate to lesion sites, together with microglia responsible for debris clearance. (②) Recruited OPCs mature and differentiate into oligodendrocytes, which (③) remyelinate damaged axons. Abbreviation: OPC, oligodendrocyte precursor cell.

IFN-β blocks MMPs; in turn, this blockage stabilizes the BBB (100), reduces proinflammatory cytokine levels, and enhances Th2 cytokine production (101, 102). IFN-β is also reported to induce IL-27 expression, boosting the differentiation of IL-10-producing Tregs while interfering with the generation of effector T cells.

Glatiramer acetate is a copolymer composed of four amino acids (103). Its mechanism of action is not fully understood but is thought to involve the expansion of Tregs and Th2 cells, the enhancement of regulatory $CD8^+$ T cells, and the generation of anti-inflammatory monocytes; it may also interfere with antigen presentation (104, 105).

Mitoxantrone is a chemotherapeutic agent that provides immunosuppression by depletion of activated lymphocytes. Adverse events include cardiotoxicity and hematologic malignancies (106, 107).

Monoclonal antibodies including natalizumab, alemtuzumab, daclizumab, rituximab, ocrelizumab, and ofatumumab provide strong immunomodulatory approaches for MS therapy.

Natalizumab is a humanized monoclonal antibody that binds the adhesion molecule α4-integrin, preventing immune cell infiltration into the CNS (108). Alemtuzumab is a chimeric anti-CD52 monoclonal antibody that induces the prolonged depletion of $CD52^+$ T and B cells, favoring the emergence of Tregs (109). Daclizumab is a humanized monoclonal antibody against CD25, a subunit of the IL-2 receptor, and promotes the expansion of regulatory CD56 NK cells (110).

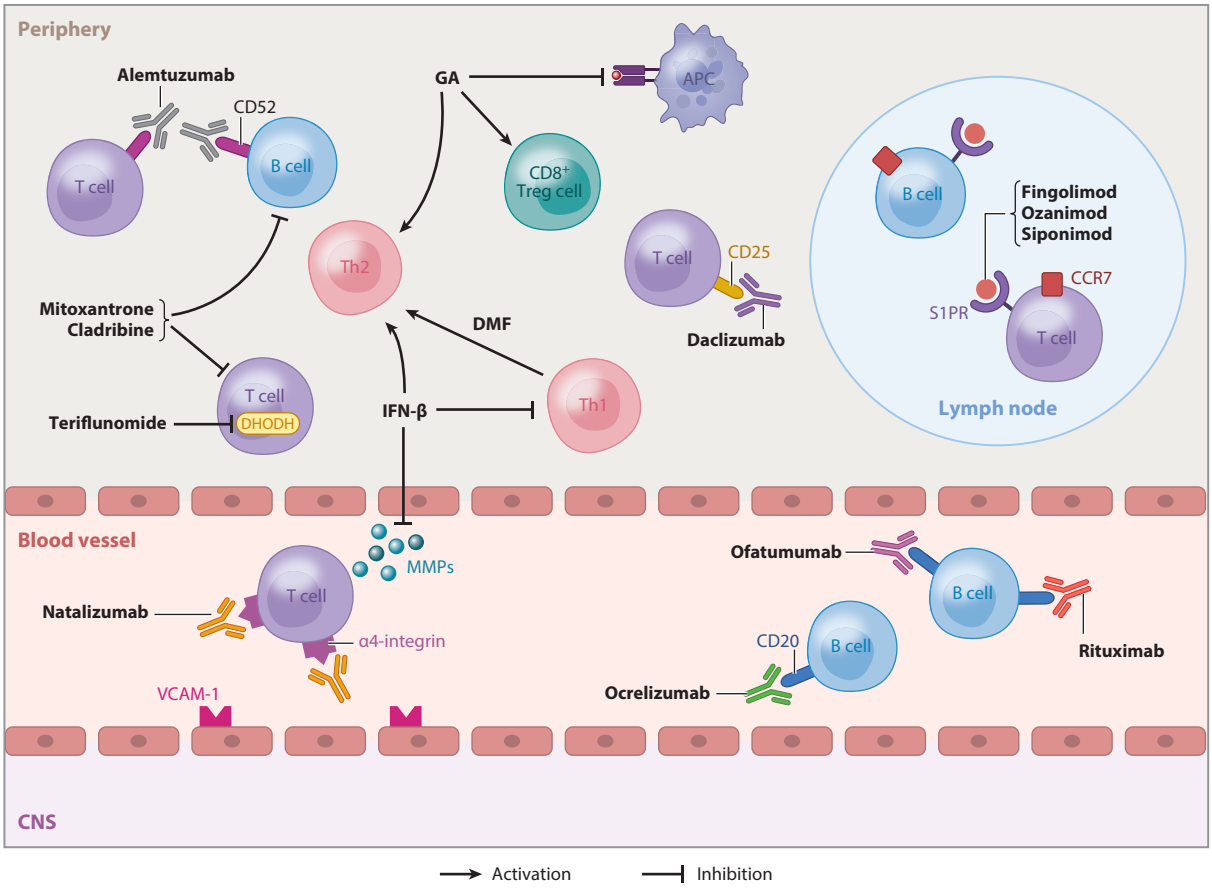

Figure 6

MS therapies and their targets. Different types of therapies are used in MS treatment; among them are monoclonal antibodies, such as alemtuzumab, natalizumab, ofatumumab, ocrelizumab, rituximab, and daclizumab, and immunomodulating treatments, including GA, DMF, IFN-β, fingolimod, ozanimod, siponimod, mitoxantrone, and cladribine. In the figure, the mechanisms of action are simplified. Abbreviations: APC, antigen-presenting cell; CCR7, C-C motif chemokine receptor 7; CNS, central nervous system; DHODH, dihydroorotate dehydrogenase; DMF, dimethyl fumarate; GA, glatiramer acetate; IFN, interferon; MMP, matrix metalloproteinase; MS, multiple sclerosis; S1PR, sphingosine-1 phosphate receptor; Treg, regulatory T cell; VCAM, vascular cell adhesion molecule.

Rituximab, ocrelizumab, and ofatumumab are all monoclonal antibodies that target CD20, selectively depleting B cells. Rituximab is thought to induce B cell depletion via ADCC and complement activation. Ocrelizumab is a humanized antibody and ofatumumab is a human antibody, both of which operate via the induction of ADCC and complement (111). B cell depletion diminishes MS clinical and magnetic resonance imaging activity through several mechanisms mostly associated with the reduction of T cell activation by B cells (112). Indeed, the study of the mechanism of action of rituximab has helped researchers to better understand the role of B cells in MS (113).

The use of immunomodulatory oral agents is another therapeutic strategy in MS. Molecular modulators such as fingolimod, siponimod, ozanimod, dimethyl fumarate, and teriflunomide are included in this group. Fingolimod triggers the internalization and degradation of the sphingosine-1 phosphate receptor (S1PR), which is essential for the exit of CCR7-expressing lymphocytes from lymphoid organs. Hence, fingolimod inhibits immune cell migration from lymph

Table 1 Approved disease-modifying therapies for MS

Drug	Relapse reduction	Mechanisms of action	Indication
IFN-β	Low/moderate	MMPs and proinflammatory profile inhibition	CIS and RRMS
GA	Low/moderate	Shift from a proinflammatory profile to a regulatory profile	RRMS
Mitoxantrone	High	DNA intercalator	RRMS and SPMS
Natalizumab	High	Anti-α4-integrin: inhibition of immune cell entrance to the CNS	RRMS
Alemtuzumab	High	Anti-CD52 mAb: depletion of $CD52^+$ T and B cell populations	RRMS
Daclizumab	High	Anti-CD25 mAb: expansion of CD56 NK cells	RRMS
Rituximab Ocrelizumab Ofatumumab	High	Anti-CD20 mAb: proinflammatory and antigen-presenting function inhibited by B cell depletion	RRMS RRMS and PPMS (ocrelizumab)
Fingolimod	Moderate	Sphingosine 1-phosphate receptor inhibitor	RRMS
Siponimod Ozanimod	Moderate	Sphingosine 1-phosphate receptor modulator	CIS, RRMS, and SPMS
DMF	Moderate	Nrf2 pathway induction	RRMS
Teriflunomide	Low/moderate	Dihydroorotate dehydrogenase inhibitor	RRMS
Cladribine	High	Deoxyadenosine analog	RRMS

Abbreviations: CIS, clinically isolated syndrome; CNS, central nervous system; DMF, dimethyl fumarate; GA, glatiramer acetate; IFN, interferon; mAb, monoclonal antibody; MMP, matrix metalloproteinase; MS, multiple sclerosis; NK, natural killer; Nrf2, nuclear factor (erythroid-derived 2)–like 2; RRMS, relapsing-remitting MS; PPMS, primary progressive MS; SPMS, secondary progressive MS.

nodes to the CNS (114). Siponimod and ozanimod are two S1PR modulators that bind to S1PR subtypes 1 and 5, downregulating the expression of S1PR in immune cells (115, 116). The mechanism of action of dimethyl fumarate is thought to involve nuclear factor (erythroid-derived 2)–like 2 (Nrf2)-dependent and Nrf2-independent pathways (117, 118), which control the activity of dendritic cells (119), regulatory B cells (120), and astrocytes. Teriflunomide inhibits dihydroorotate dehydrogenase, an enzyme responsible for pyrimidine synthesis; as a consequence, teriflunomide inhibits the proliferation of activated T lymphocytes (121).

Cladribine is a triphosphorylated deoxyadenosine analog that depletes lymphocytes and is currently used in highly active MS. Lymphocytes are dependent on adenosine deaminase activity to eliminate high amounts of triphosphorylated nucleotides. Cladribine blocks the elimination of triphosphorylated nucleotides, resulting in the accumulation of cytotoxic molecules that promote apoptosis (122).

CONCLUSIONS

Our understanding of the immunology of MS has evolved from a binary Th1/Th2 paradigm to a more complex and realistic scenario. In this scenario, novel pathogenic and regulatory pathways have been identified, including Th17 cells and $FoxP3^+$ and Tr1 Tregs, along with a central role for B cells as APCs. The identification of additional mechanisms of disease pathogenesis will certainly guide the development of more efficacious and specific therapies for MS.

DISCLOSURE STATEMENT

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LITERATURE CITED

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Errata

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