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Multiple Sclerosis
Mechanisms of Disease and Strategies for Myelin and Axonal Repair

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INTRODUCTION
Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) with a variety of clinical presentations. The profound heterogeneity of MS is not limited to the symptoms but to neuroradiologic and histologic appearances of lesions and response to therapy. As expected, the pathogenesis of MS is controversial, and there is no effective treatment that halts the neuro-axonal damage.

KEYWORDS
- Multiple sclerosis
- Autoimmune
- Immune
- Axon
- Remyelination

KEY POINTS
- Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system with a variety of presentations and unclear pathogenesis.
- Multiple sclerosis has been associated with the term autoimmunity as a surrogate for pathogenesis.
- Still, multiple sclerosis is an organ-specific disease with immune-mediated myelin destruction.
- Understanding the complex etiology of multiple sclerosis (autoimmune induced, virus induced, or immune mediated) and the importance of axon integrity is critical for clinicians who treat the disease.

INTRODUCTION
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or promotes remyelination. As a leading cause of disability, MS affects 400,000 people in the United States and 2.5 million of people worldwide.2

The demyelinating plaque, the main pathologic hallmark of MS, contains a prominent immunologic response dominated by CD8+ and CD4+ T cells.1,3 Moreover, the presence of oligoclonal bands in the cerebrospinal fluid of MS patients shows the presence of immunoglobulin-producing B cells suggesting their participation in the pathogenesis of the disease.4 These findings suggest that MS is an immune-mediated disorder involving multiple antigens of the CNS5,6 and, further, that MS is an autoimmune disease of the CNS. Understanding the mechanism of MS is essential to elucidate possible strategies to repair myelin and axonal structures.

**AUTOIMMUNITY VERSUS IMMUNE-MEDIATED DEMYELINATION**

Several criteria have been established to determine whether a disease can be classified as autoimmune.7,8 First, an autoantigen must be present in all patients with a proven immune response directed against it. Second, one must identify autoantibodies within a lesion or serum of patients with a direct correlation to disease activity or observed clinical improvement after immunosuppressive treatment. In systemic lupus erythematos (SLE), a well-characterized autoimmune disorder, the presentation of autoantigens by T cells promotes antibody formation and hence, the clinical manifestations.9 It is also critical to reproduce the clinical and histopathologic aspects of the human disease after administration of the autoantibody or autoantigen within an animal. For example, when transferring anti-DNA antibodies to naïve recipient mice, there is an immunologic reaction against glomerular antigens leading to nephropathy similar to that seen in SLE.10 Diseases like SLE have an experimental-based extensive literature that meets all the criteria and proves the role of autoimmunity in the pathophysiology.

MS is also an organ-specific disease (the brain and spinal cord) with immune-mediated myelin destruction. Nevertheless, after extensive research, confirmation of a specific auto-antigen in MS is lacking. The absence/presence of an infectious agent in patients with MS has also not been proven. Other organ-specific immune-mediated diseases such as herpes encephalitis have a persistent exogenous antigen (in this case, the herpes virus) that resides in the CNS and drives the development of acute inflammation and necrotizing lesions.11 However, the absence of any consistent viral or bacterial antigen in MS patients suggests the presence of an autoantigen that drives this disease. Antibodies directed against CNS myelin proteins, lipids, and carbohydrates (possible candidates as autoantigens) can be identified in the tissue and serum of patients with MS.

Extensive literature is devoted to identifying antibodies against the myelin oligodendrocyte glycoprotein (MOG) in MS patients with inconsistent results. Enzyme-linked immunosorbsorbent assay–based binding studies using a synthetic MOG peptide to identify antibodies found an increase in the frequency of MOG-binding IgGs in patients with MS compared with controls.12,13 In contrast, other studies using enzyme-linked immunosorbsorbent assay binding to the recombinant human immunoglobulin domain of MOG showed no difference in the levels of bound antibodies in patients with MS or healthy controls.14 When using other techniques, such as immunoblot to detect antibodies directed against the recombinant human immunoglobulin domain of MOG in patients with MS, the results are inconsistent.15,16 Antibodies that bind to other antigens such as alpha-B-crystallin, alu repeats, myelin basic protein, and myelin-associated glycoprotein have been reported but not rigorously studied.17–20 Despite several published attempts to detect and quantify antibodies directed against
myelin and nonmyelin antigens in patients with MS, there is no consensus. This lack of a self-directed immune response producing antibodies argues against the hypothesis of MS as an autoimmune disease (Fig. 1).

On the other hand, neuromyelitis optica (NMO), an autoimmune astrocytopathy, is a CNS disease driven by the presence of antibodies against aquaporin 4 (AQP4), a plasma membrane–based water-transporting protein (see Fig. 1). AQP4 is the most abundant water channel in the brain, expressed primarily in astrocytes and highly involved in neuroexcitation.[21] The discovery of pathogenic immunoglobulin G directed to AQP4 in almost 70% of the patients with NMO was the first evidence that this disease was an inflammatory autoimmune disease of the CNS.[22,23] The pathogenicity of the anti-AQP4 IgG in NMO patients has been reproduced in vivo and their presence confirmed in pathologic lesions.[24,25]

IS MULTIPLE SCLEROSIS AN AUTOIMMUNE DISEASE?

When comparing MS with other autoimmune diseases like neuromyelitis optica, it is clear that MS does not meet the full definition of autoimmune disease (Table 1). Although NMO meets 6 of 8 autoimmune disease criteria, MS meets only 2. Although there are some data for several of the other criteria, the evidence is controversial. For example, multiple studies focused on measuring the level of precursor T cells before and then during clinical exacerbations. However, none of these studies found a difference from the prevalence in healthy controls or are not confirmed using other patient populations.[26] It is clear that the data are weak to make a definitive conclusion that MS is an autoimmune disease.
IS MULTIPLE SCLEROSIS A VIRUS-INDUCED DISEASE?

Viral microorganisms are postulated by many investigators to be causal agents of MS. The idea is plausible because other demyelinating diseases of the CNS like progressive multifocal leukoencephalopathy are caused by a virus: the JC virus in immune-compromised individuals.\textsuperscript{37} Recently, much attention has focused on Epstein-Barr virus (EBV) because EBV antigens are expressed at significantly higher levels in the cerebrospinal fluid and serum of some MS patients compared with controls.\textsuperscript{36} However, studies show an absence of intrathecal anti-EBV antibody synthesis in nearly 93% of patients with MS, which argues against this hypothesis.\textsuperscript{39} Hence, the association of EBV with adult MS is not well established, and its role in pathogenesis remains to be determined. Other viral agents like varicella zoster and rubella are considered as possible risk factors but not causal agents.\textsuperscript{40,41} Of note, vitamin D

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Table 1

| Criteria for Autoimmune Disease\textsuperscript{7} | NMO | MS |
|-------------------------------------------------|-----|----|
| Immune response to a precise autoantigen in all patients | aquaporin 4\textsuperscript{22,23} | Multiple antigens have been described, not present in all patients\textsuperscript{12,13,17–20} |
| Lesion reproducibility after administration of autoantibody or T cells | Exacerbation of EAE model after adoptive transfer of neuromyelitis optica Abs\textsuperscript{27} | EAE model: induced by myelin oligodendrocyte glycoprotein, proteolipid protein, myelin basic protein\textsuperscript{26} and reactivated CD4+ T cells\textsuperscript{29} |
| Animal: induction of lesion by antigen immunization | | |
| Autoantibody or T cell isolation form lesion or serum | aquaporin 4 antibodies\textsuperscript{27,30} | |
| Autoantibody titers or T-cell levels associated with disease activity | Higher antibody titers during relapse than during remission\textsuperscript{31} | |
| Autoimmune disorders or autoantigens associated with the disease | Sjogren syndrome, SLE\textsuperscript{32} | No association in population-based cohort studies\textsuperscript{33} |
| Immune absorption with purified autoantigen abrogates pathogenic autoantibody or T cell | | |
| Reduction of autoantibody or T cell associated with clinical improvement | Plasma exchange\textsuperscript{34} | Plasma exchange\textsuperscript{35,36} |

Abbreviations: EAE, experimental autoimmune encephalomyelitis; MBP, myelin basic protein; PLP, proteolipid protein.

Adapted from Paul WE, Schwartz RS, Datta SK. Autoimmunity and autoimmune diseases. In Fundamental immunology. New York: Raven Press; 1989. p. 819-66; and Rodriguez M, Warrington AE, Pease LR. Invited article: human natural autoantibodies in the treatment of neurologic disease. Neurology 2009;72(14):1269–76.
deficiency has been linked as a causal agent in relapsing remitting MS. Vitamin D has a role in regulating immune function. Low levels of this vitamin could produce an immune-deficient state against viral agents. Although clinical trials and observational studies using high levels of vitamin D have only shown modest reductions in the levels of interleukin 17, it has not been seen in other inflammatory markers. 42,43 The fact that high dose treatment of vitamin D in MS patients has scant effect on the overall course of the disease does not support this theory.

Demyelinating disease nearly identical to human MS can be consistently established in animals using well-characterized viral agents. Theiler’s murine encephalomyelitis virus (TMEV) is a mouse enteric pathogen that belongs to the picornavirus family. It produces a chronic progressive demyelinating condition similar to what is seen in humans with progressive MS. 44 This model presents with an immune response to virally infected cells and an autoimmune response to CNS antigens. 45 Novel therapies like natural human antibodies that induce either remyelination or neuroprotection have been successfully evaluated in this model of virus-induced demyelination. 46–48 Other virus-induced models with a persistent viral infection without dramatic animal mortality are coronavirus (JHM and MHV-4) and Semliki Forest affecting mice, distemper virus specific for canines, and visna virus in sheep and goats.

**MECHANISMS OF MULTIPLE SCLEROSIS: DEMYELINATION VERSUS AXONAL DAMAGE**

Demyelination, the major pathologic hallmark of MS, is not sufficient to explain the deficits seen in these patients. In 1969, the first observation of demyelination and complete axonal dysfunction in the CNS was made, 49 and since then, many have considered it as a unique event. Recent studies found that in MS, damage to myelin is not enough to produce the spectrum of symptoms. In humans, levels of demyelination are not strictly correlated to disease stage, neurologic deficits, or lesion pathology. 50–52 Imaging studies in postmortem brains using MRI have shown how axonal injury is the primary event leading to clinical deficits (more than demyelination). 53,54

On the other hand, murine models of demyelination have also questioned the role of demyelination as the sole event in MS. Despite profound demyelination seen with TMEV murine model, in the absence of major histocompatibility complex (MHC) class I, there is no deficit in motor function. 55 Moreover, there is preservation of axonal transport in these mice despite demyelination. 56 CD8+ T cells direct recognition of MHC class I is a well-known mediator of axonal injury and dropout. In murine models of demyelination and murine culture of neurons, CD8+ T cells injure demyelinated axons selectively. 57,58 CD8+ clones are the dominant cells in active MS lesions and have direct correlation with accumulation of amyloid precursor protein, a marker of acute axonal damage. 59

Perforin, a critical mediator in cell cytotoxicity and apoptosis, is released by CD8+ T cells after recognition of the MCH class I complex. 60 Once inside the cell, perforin creates a pore in the membrane and delivers granzymes that initiate a cascade of signals causing death of cells. 61 During viral infection with TMEV and in electrically silent neurons in vitro, both have an increased expression of MCH class I complex. 62,63 More importantly, axon injury secondary to demyelination is mediated by inflammatory factors, especially, perforin. 65 Perforin-deficient mice had an increased number of large-diameter axons and better functional motor abilities when compared with perforin-competent controls, despite having the same levels of demyelination.

Sodium channels are also a critical component in demyelinated axons, as changes in their number can influence impulse conduction. 66,67 After an acute injury in peripheral axons, there is a high density of sodium channels. 68 Murine models of
demyelination have also shown how formation of nodes of Ranvier (where action potentials are generated) and saltatory conduction precedes remyelination in axons with demyelination. Demyelinated mice with MHC class I deficiency and normal functional status have been previously described. The normal motor function is caused by a preservation of axons and increased intensities of sodium channels suggesting an upregulation or redistribution of these molecules in the axons. Based on these observations, it can be concluded that axonal injury plays a critical role in the neurologic deficits seen in patients with MS and must be taken into account when considering strategies for MS therapies.

**MYELIN AND AXONAL REPAIR STRATEGIES**

Understanding the complex etiology of MS and the importance of axon integrity is critical for clinicians who expect halting of neuro-axonal damage. When a patient with newly diagnosed MS has the first neurologic symptom, there is already axonal loss. Hence, there is a need to treat early and use multiple strategies that target remyelination and preservation of axons and oligodendrocytes (OL).

The authors’ laboratory has done extensive research in natural human recombinant antibodies formerly known as rHIgM22 and rHIgM12. These molecules, part of human innate immunoglobulin repertoire, are able to bind to oligodendrocytes (rHIgM22) and neurons (rHIgM12). In TMEV and lysolecithin-induced demyelination, rHIgM22 promotes oligodendrocyte remyelination and protects spinal cord axon number. Currently, this molecule is under a clinical trial to establish its tolerance in MS patients after an acute exacerbation. In addition, rHIgM12 protects against axonal injury in TMEV and amyotrophic lateral sclerosis murine models. It also binds to PSA-NCAM and gangliosides of glia and neurons resulting in neurite extension in vitro and neurite outgrowth. Recently, rHIgM12 showed an immune-modulatory therapeutic effect in an MOG-induced experimental autoimmune encephalomyelitis (EAE).

Inhibition of the leucine rich repeat and immunoglobulininlike domain containing NOGO receptor interacting protein-1 (LINGO-1) increases differentiation of oligodendrocyte progenitor cells into mature oligodendrocytes. In TMEV murine model of demyelination, inhibition of this molecule promoted remyelination leading to the discovery of anti-LINGO-1. This was the first drug entering a clinical trial showing how 41% of patients had improvement of nerve signaling and possibly myelin repair. Despite this, anti-LINGO-1 failed to improve disability and cognitive function after 72 weeks of follow-up.

As explained in the previous section, CD8+ T cells and the upregulation of MHC class I complex are critical in the pathogenesis of MS. Dimethyl fumarate (BG-12 or Tecfidera) is a molecule that showed remarkable efficacy in the treatment of relapsing remitting MS and exposure may result in reductions in CD8+ T-cell populations in certain patients. Fingolimod, the first approved oral therapy for active relapsing remitting MS, modulates T-cell proliferation in vitro as well. Together, these results suggest that an immunotherapy against active CD8+ cells using anti-CD8 antibodies could suppress the immune-mediated reactions in patients with MS.

**SUMMARY**

MS is an immune-mediated disease that lacks the presence of a specific antigen that drives the inflammatory process. The extensive characterization of MS pathology, immunology, and serology has misled many investigators to conclude that MS is an autoimmune disease. However, there is a lack of scientific evidence supporting the role of active autoantigens and autoantibodies driving the inflammatory and
demyelinating cascades seen in patients with MS. Understanding the role of axonal injury and its relationship with clinical deficits is essential for a future drug. Future trials should aim a multifaceted approach with several reagents that target remyelination, protections of axons and oligodendrocyte progenitor cell, and suppressive therapies against active inflammatory cell populations.

ACKNOWLEDGMENTS

The authors acknowledge with many thanks support from the Applebaum, Hilton, Peterson and Sanford Foundations, and the McNeilus family.

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