Multiple Sclerosis

Mechanisms of Disease and Strategies for Myelin and Axonal Repair

Hernan Nicolas Lemus, MD[a], Arthur E. Warrington, PhD[a,*], Moses Rodriguez, MD[a,b]

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

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.[1] As expected, the pathogenesis of MS is controversial, and there is no effective treatment that halts the neuro-axonal damage

Financial Support: Authors are supported by grants from the Minnesota Partnership Award for Biotechnology and Medical Genomics, Mayo Clinic Center for Multiple Sclerosis and Autoimmune Neurology (CMSAN) through a gift from Dr and Mrs Moon Park.
Competing Interests: Patents for human antibodies that promote remyelination and CNS repair are issued and owned by Mayo Clinic. A.E. Warrington and M. Rodriguez have a potential conflict of interest.
[a] Department of Neurology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA; [b] Department of Immunology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA
* Corresponding author. Department of Neurology, Mayo Clinic, Guggenheim Building 401, 200 First Street Southwest, Rochester, MN 55905.
E-mail address: Warrington.Arthur@mayo.edu

Neurol Clin 36 (2018) 1–11
https://doi.org/10.1016/j.ncl.2017.08.002 **neurologic.theclinics.com**

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 CNS[5,6] 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 erythematous (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 immunosorbent 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 immunosorbent 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