PERSPECTIVE

Do Myelin-Directed Antibodies Predict Multiple Sclerosis?

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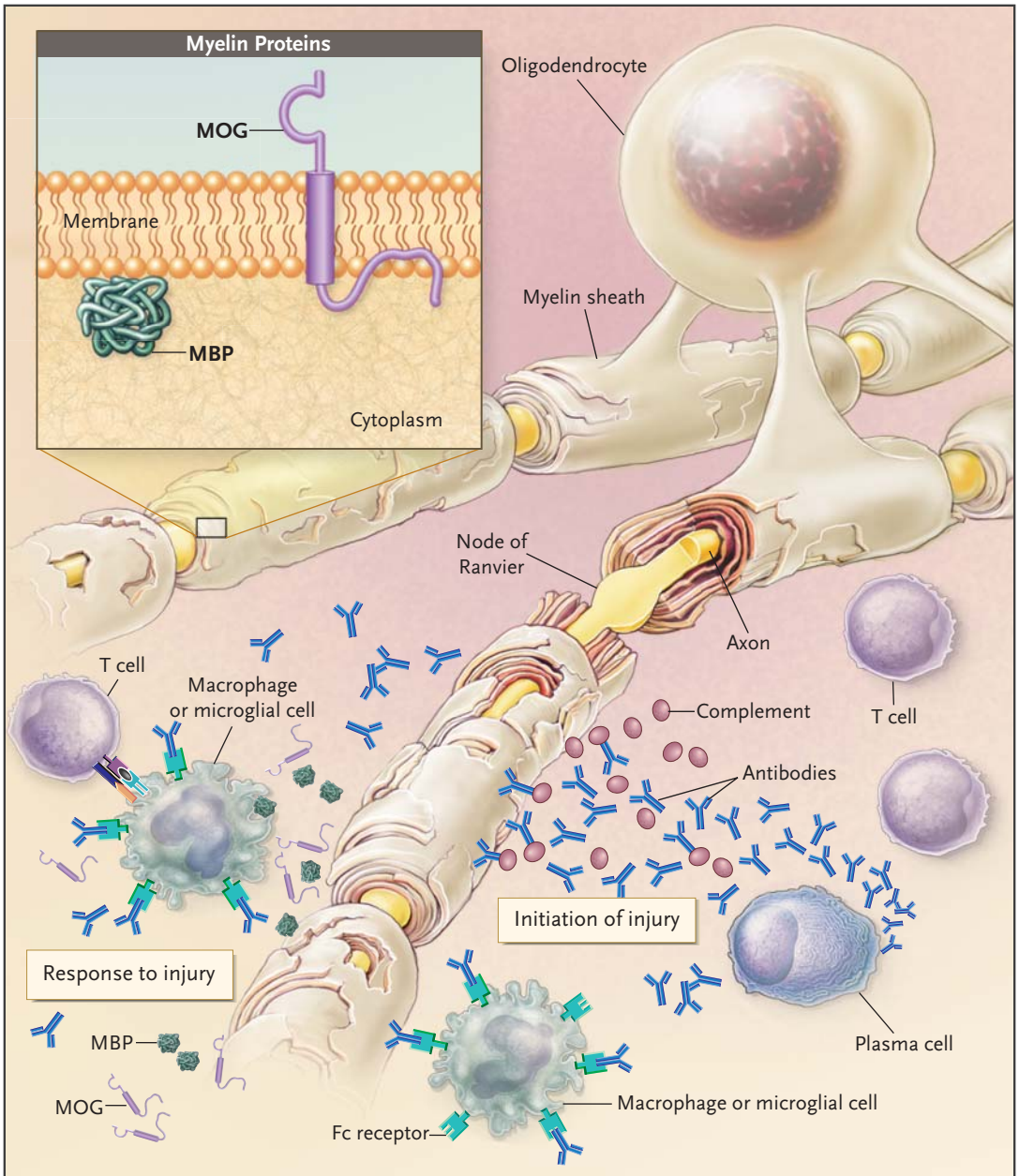
Multiple sclerosis is characterized by recurrent neurologic events (clinical relapses) that are attributable to multifocal lesions within the central nervous system. Lesions referred to as "active plaques" are characterized by the presence of inflammation and active myelin degradation and phagocytosis. These lesions have been subtyped according to the relative presence of immunoglobulin (i.e., antibodies) and according to whether the primary injury is directed at the myelin itself or its cell of origin, the oligodendrocyte. Pathological and magnetic resonance imaging (MRI) studies show that axonal injury occurs early in the course of disease. The potential for remyelination is greatest at this early stage. Thus, for the purposes both of disease prevention and of recovery, early diagnosis and therapeutic intervention are the goals. Experience with current immunomodulatory therapies for multiple sclerosis indicates that they have greater, albeit limited, efficacy if begun early. Decisions regarding the initiation of these therapies continue to be influenced by concern about adverse effects, the difficulty of drug administration, and cost–benefit considerations.

An ongoing challenge in the field is the prediction of whether and when a single neurologic episode suggestive of central nervous system demyelination (i.e., a clinically isolated syndrome) will evolve into a recurrent course of disease (i.e., clinically definite multiple sclerosis). Uniphasic disorders typified by acute disseminated encephalomyelitis have been recognized since Pasteur introduced his rabies vaccine containing spinal cord tissue. The advent of MRI has provided a means by which patients who have a clinically isolated syndrome can be assigned a relative risk of recurrent disease, on the basis of the number and size of central nervous system lesions at their initial presentation. No criteria currently permit ascertainment of whether lesions observed on an initial MRI scan developed at different times. In multiple sclerosis, unlike type 1 diabetes, no early biologic measure of either cellular or humoral immunity (in cerebrospinal fluid or in blood) has yet been established as a useful predictor of the onset or severity of disease.

A particularly appealing biologic marker of the course of disease would be one that was linked to its actual pathogenesis. The role of myelin-autoreactive T cells in initiating the acute lesions of multiple sclerosis was deduced from animal models (e.g., experimental autoimmune encephalomyelitis) in which the adoptive transfer of such cells initiated a paralytic, inflammatory disorder of the central nervous system. To date, the frequency, phenotype, and functional profiles of myelin-reactive CD4 or CD8 T cells in multiple sclerosis remain difficult to determine and are not predictive of the course of disease.

Antibodies that have the capacity to recognize particular targets in the central nervous system (see Figure) may represent another important determinant of the actual extent of tissue injury in patients with multiple sclerosis and in animal models. Such autoreactive antibodies may mediate injury directly, with or without complement fixation, or indirectly, by linking with innate immune effector cells such as macrophages. In vitro studies indicate that human B cells have a capacity even greater than that of T cells to migrate across the blood–brain barrier. The restricted clonality and somatic mutation patterns of immunoglobulin genes expressed by B cells recovered from cerebrospinal fluid and lesions in patients with multiple sclerosis suggest that these cells are stimulated by specific central nervous system antigens.

Antibodies that are reactive with an array of myelin antigens (see Figure), all of which have been used for the experimental induction of autoimmune



The Potential Role of Antibodies against Myelin Oligodendrocyte Glycoprotein (MOG) in Multiple Sclerosis.

Anti-MOG antibodies may initiate oligodendrocyte or myelin injury (by complement fixation or macrophage activation), or they may be generated as a result of tissue injury that releases myelin antigens. The inset shows normal myelinated axons in the central nervous system. MOG is a transmembrane protein distributed on the cell body of the oligodendrocyte and on the outer surface of myelin, whereas myelin basic protein (MBP) is intracellular.

encephalomyelitis, can be detected in the cerebrospinal fluid of patients with multiple sclerosis, and an antibody directed against myelin oligodendrocyte glycoprotein (MOG) has been detected in the lesions themselves. These antibodies do not, however, account for the majority of the oligoclonal immunoglobulin that is a common feature of the cerebrospinal fluid in multiple sclerosis. Although neither B cells nor antibody infusions alone initiate autoimmune encephalomyelitis in animals, the combination of subclinical dosages of T cells with central nervous system–reactive antibody can induce clinically significant demyelination. One could hypothesize that central nervous system–reactive antibodies have a role in directing the phenotype and pathologic process of multiple sclerosis that is similar to the role of peripheral nerve–directed antibodies in peripheral neuritis associated with *Campylobacter jejuni* infection.

The study by Berger et al. in this issue of the *Journal* (pages 139–145) shows that the presence of serum anti-MOG antibodies, with or without antibodies against myelin basic protein (MBP), in patients with an initial event suggestive of central nervous system demyelination and evidence of multifocal lesions on MRI studies of the brain is highly predictive of subsequent clinical events that establish the diagnosis of clinically definite multiple sclerosis. The findings of this study, once confirmed, will improve the quality of the diagnostic and prognostic information that can be used to guide treatment decisions, enhance insight into the pathogenesis of the disease, and possibly identify subgroups of patients for whom B-cell–directed therapies would be indicated. It remains to be established whether these myelin-reactive antibodies contribute to initial tissue injury, reflect a response to injury (i.e., reflect the release of myelin antigens that can be taken up by macrophages and subsequently presented to infiltrating T cells within the central nervous system or be transported to regional lymph nodes), or participate in a protective or remyelinating response to injury. Future studies should also address the question of whether conversion from antibody-negative to antibody-positive status identifies patients at risk for a clinical relapse or for the formation of new lesions on MRI (one of the McDonald criteria for diagnosing definite multiple sclerosis) and whether the presence of anti-MOG antibodies can predict the development of disease in patients at high risk (e.g., monozygotic twins), in a manner akin to the detection of antibody in type 1 diabetes.

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Cancer-Associated Thrombosis

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Thrombosis was identified as a complication of cancer by Trousseau in 1865, and the combination of the two conditions is still often called Trousseau's syndrome. Arterial and, more commonly, venous thrombosis is a frequent complication of cancer and sometimes a harbinger of occult cancer. Moreover, the use of new and aggressive therapy for cancer increases the risk of thrombosis.

There are many causes of thrombosis in cancer. Cancer itself is often the underlying mechanism. When cells of the monocyte or macrophage lineage interact with malignant cells, they release tumor necrosis factor, interleukin-1, and interleukin-6, causing endothelial damage and sloughing of endothelial cells and thereby converting the vascular lining over which blood flows to a thrombogenic surface (see Figure). The interaction between tumor cells and macrophages also activates platelets, factor XII, and factor X, which leads to the generation of thrombin and thrombosis.

Substances in tumor cells such as cysteine proteases and tissue factor (often referred to as cancer-cell procoagulants) have procoagulant, or thromboplastin-like, activity. These procoagulants can directly activate factor X (to factor Xa), whereas tissue factor, including that released by monocytes or macrophages, induces the direct activation of factor VII (to factor VIIa). The sialic acid moieties of mucin from adenocarcinomas cause a nonenzymatic activation of factor X.