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Multiple Sclerosis: A Coordinated Immunological Attack against Myelin in the Central Nervous System

Review

Lawrence Steinman, M.D.*†
*Department of Immunology
The Weizmann Institute of Science
76100 Rehovot
Israel
†Department of Neurology and Neurological Sciences
Beckman Center for Molecular and Genetic Medicine
Stanford University School of Medicine
Stanford, California 94305

Multiple sclerosis (MS) is the most common autoimmune disease involving the nervous system. In the United States ~250,000 individuals suffer from MS. The first clinical signs of MS typically begin in young adulthood, and women with the disease outnumber men 2:1. The cause of the disease is unknown, but genetic factors are important. The concordance rate among monozygotic twins is 30%, a 10-fold increase over dizygotic twins or first-degree relatives (Ebers et al., 1986, 1995). The higher incidence rate among monozygotic twins emphasizes the importance of genetic factors, but the discordance rate of 70% among identical twins illuminates the role of nongenetic factors on disease penetrance. The fact that the prevalence of MS among nonbiological first-degree relatives of MS index cases is similar to that in the general population strongly supports a genetic basis for familial clustering (Ebers et al., 1995). Among genetic factors, HLA class II genes exert an influence, with HLA DR2 carrying a 4-fold relative risk for northern European caucasoids (Altmann et al., 1991; Oksenberg et al., 1993a, 1993b). Geography plays an interesting role in determining susceptibility to MS. Among white populations, the prevalence of MS is highest in the temperate regions of the world (Kurtzke, 1983). Migration from a location of high disease incidence to a location of low disease incidence after the age of 15 years carries with it the risk associated with the location where one dwelled during the first 15 years, while migration before the age of 15 years carries the risk associated with the immigrant's destination (Kurtzke, 1983).

A typical presentation of MS involves an initial course, running for several years to more than a decade, manifest by episodes of relapse followed by remission. Relapses often follow an episode of a viral infection of the upper respiratory system or gastrointestinal tract. In about one half of MS cases the disease progresses to a more chronic phase. The clinical symptoms of the disease are entirely attributable to pathology in the central nervous system. Clinical problems may include disturbances in visual acuity, sometimes culminating in blindness; double vision; motor disturbances affecting walking and use of the hands; incoordination; bowel and bladder incontinence; spasticity; and sensory disturbances including loss of touch, pain, and temperature and proprioception. Cognitive function is not impaired in MS. The pathology of the disease lies entirely in the central nervous system and is characterized by a classic picture of inflammation surrounding venules and extending into the myelin sheath. Understanding the pathogenesis of the disease allows for the rational design of therapeutic strategies.

Myelin-Reactive T Cells Are Present in Normal Blood; Once Activated They May Penetrate the Blood–Brain Barrier

T cells reactive to the major constituents of the myelin sheath, such as myelin basic protein (MBP) and proteolipid protein (PLP), are easily detectable in specimens of peripheral blood from normal individuals (Wucherpfennig et al., 1994; Steinman et al., 1995). Some exons of MBP encoded in the Golli–MBP gene (Pribyl et al., 1993) are actually expressed in the thymus during the development of the immune system and into adulthood. T cell epitopes of MBP that are pathogenic in various strains of mice are expressed in the thymus (Mathisen et al., 1993). Thus, there is an escape from negative selection for T cells reactive to certain myelin constituents. The revelation that MBP is expressed in the thymus has overturned the idea that this antigen, which comprises ~30% of the protein in the myelin sheath, somehow represented a special example of an antigen that was altogether sequestered from the immune system. It had generally been assumed that antigens such as MBP were "protected" from the immune system by virtue of their predominant expression in the central nervous system, which is separated in part from the immune system by the blood–brain barrier.

Myelin-reactive T cells in the peripheral blood may become activated by microbes. The similarities between infectious pathogens and self-antigens may lead to inadvertent autosensitization, in the course of an immune response to a microbe. This concept is called molecular mimicry. Molecular mimicry refers to structural homologies between a self-protein and a protein in a viral or bacterial pathogen. For example, MBP shares extensive homologies at the amino acid level with a number of common pathogens including measles, hepatitis B, influenza virus, and adenovirus (Wucherpfennig and Strominger, 1995). Residues 84–101 of MBP share stretches of four to six amino acids with influenza, Epstein–Barr virus, herpes viruses, papilloma virus, and various bacteria including pseudomonas (Wucherpfennig and Strominger, 1995). Various critical contact residues for binding to major histocompatibility complex (MHC) molecules and the T cell receptor (TCR) are present in these microbial sequences. Microbes having appropriate amino acids at critical MHC and TCR contact sites can stimulate MBP-specific T cell clones from MS patients (Wucherpfennig and Strominger, 1995). It has been shown that one can induce EAE by immunizing with a peptide sequence from a pathogen with homology to MBP (Fujinami and Oldstone, 1985). Homology may be necessary at only a few of the amino acids comprising a T cell epitope. Conservation of the native amino acid sequence at only four of eleven amino acids of an MBP epitope is sufficient to induce EAE (Gautam et al., 1992). Thus, tolerance to myelin components could be broken by an immune response to a microbe. This would be

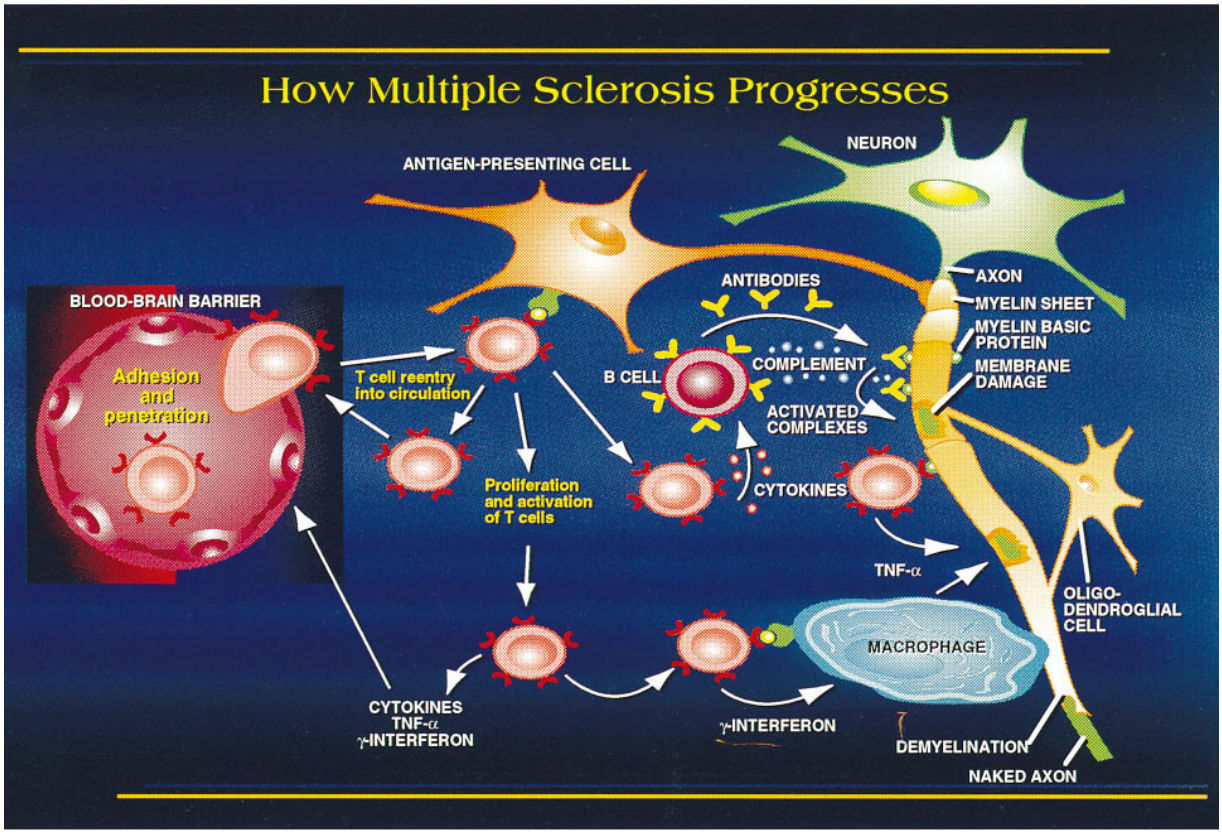

Figure 1. Stages in the Pathogenesis of Multiple Sclerosis

sufficient to trigger a relapse of MS or to initiate disease. Alternatively, superantigens—which are microbial toxins capable of stimulating whole populations of T cells via engagement of the TCR Vβ chain—are capable of inducing relapses in animal models of MS (Brocke et al., 1993) and are also capable of stimulating MBP-specific T cell clones. Thus, microbes may provide the stimulus for induction of disease and may trigger relapses by immunological cross-reactions with myelin.

Penetration of the blood–brain barrier by activated lymphocytes is a multistep process (Figure 1). There are specialized capillary endothelial cells in the central nervous system that are nonfenestrated and connected through tight junctions. Activated lymphocytes are able to diapedese (literally walk through) this barrier by virtue of adhesion molecules such as integrins, particularly α4 integrin, and members of the immunoglobulin supergene family like CD4. Once activated, any T cell expressing very late antigen (VLA)–4 may bind to adhesion molecules on the surface of inflamed endothelium and begin penetration of the capillary endothelium, the first part of the blood–brain barrier (Brocke et al., 1994). Blockade of VLA-4 reverses clinical paralysis in acute experimental autoimmune encephalomyelitis (EAE) and prevents further relapses in the chronic model of this disease (Raine et al., 1990; Yednock et al., 1992). In acute MS lesions, VLA-4 is found on T cells in the perivascular lymphocytic cuff, and vascular cell adhesion molecules (VCAMs), along with class II MHC molecules, are found on inflamed endothelium (Brocke et al., 1994).

Once the activated lymphocytes have extravasated, they still must pass through a barrier of extracellular matrix comprised of type IV collagen. Matrix metalloproteases play a key role in the penetration of this barrier, allowing the activated lymphocytes to gain access to the white matter surrounding axons of the central nervous system. The matrix metalloproteases gelatinase A and B with specificity for collagen type IV, found surrounding inflammed brain endothelium, allow activated lymphocytes to penetrate extracellular matrix. Both gelatinase A and B are detectable in the spinal fluid of MS patients, and gelatinase B immunoreactivity is seen in MS lesions (Gijbels et al., 1992). Gelatinase B is present in MS lesions in endothelial cells, pericytes, macrophages, and astrocytes.

The matrix metalloproteases are regulated in MS patients. Gelatinase A and B are blocked by tissue inibitors of matrix metalloproteases (TIMPs). TIMP-1 is present in the spinal fluid of MS patients and may act to inhibit ongoing demyelination. Spontaneous resolution of most clinical relapses in MS is very common. TIMP-1 is inducible by cytokines including TNFα, which is increased during acute relapses of MS.

When hydoxamic acid inhibitors of matrix metalloproteases are given to animals paralyzed with EAE, disease is reversed and further relapses can be inhibited (Gijbels

et al., 1994). These compounds act by restoring the integrity of the blood–brain barrier. Upon cessation of therapy, disease recurs within 24 hr. These hydroxamic acid inhibitors of matrix metalloproteases inhibit gelatinase B activity in the spinal fluid of MS patients.

Once immune cells have spread to the white matter of the central nervous system, the immune response is targeted to several different antigens on myelin: there is a critical antibody response directed to myelin; the complement cascade is activated with membrane attack complexes appearing in the spinal fluid; and T cells are targeted to certain key portions of various myelin antigens. The T cells in turn produce cytokines and then influence macrophages to attack myelin and phagocytose large chunks of the myelin sheath. This concerted attack leads to areas of demyelination impairing saltatory conduction along the axon and producing the pathophysiologic defect.

The Specificity of the Immune Response to the Myelin Supramolecular Complex

What myelin components are targeted by T and B cells? Immune responses to various components of the myelin sheath have been detected in MS patients: immune responses to MBP, PLP, transaldolase, and 2′,3′ cyclic nucleotide 3′phosphodiesterases (CNP), as well as two members of the immunoglobulin supergene family found in the myelin sheath, myelin oligodendroglial glycoprotein (MOG) and myelin-associated glycoprotein (MAG), are detected in MS patients (Steinman, 1995). Many of these myelin components have been injected into laboratory animals that then develop EAE with inflammation and demyelination in the central nervous system. In addition, some inducible heat shock proteins, including crystallin-αB, can be detected in glial cells in MS lesions and can stimulate an immune response in MS patients. The large number of antigens that can elicit an immune response in MS patients may represent the intermolecular dispersion of an immune response that arose initially to a single component of myelin (Lehmann et al., 1992). Multiple immune responses to several components of a supramolecular structure, like the myelin sheath in MS or the pyruvate dehydrogenase complex in primary biliary cirrhosis, are common in individuals with autoimmune disease involving a discrete organ.

Immunity to some of these antigens is likely to play an important role in the pathogenesis of MS. A key immune response is targeted to certain regions of myelin basic protein. The major T and B cell response in the central nervous system of MS patients who are HLA DR2 (about two thirds of patients) is directed to a region between residues 84 and 103 of MBP (Steinman et al., 1995; Warren et al., 1995). The B cell response to MBP in MS has also been studied extensively. IgG purified from brain lesions reacted with the same region of MBP, p85–96, that is the immunodominant T cell epitope in MS patients who are HLA DR2b (DRB1*1501) and overlaps with the T cell epitope in MS patients who are DR2a (DRB5*0101) (Warren et al. 1995). Overlapping T and B cell epitopes are seen in primary biliary cirrhosis as well (Coppel and Gershwin, 1995). Whether it is a general phenomenon in autoimmune disease is an interesting question that is currently under investigation.

These efforts to determine which antigens trigger the pathologic response in MS brain have very practical consequences. It is now possible to induce immunological tolerance to specific proteins using a variety of strategies including altered peptide ligands, intravenous tolerance, oral tolerance, and blockade of costimulatory molecules. All of these approaches have been effective in suppressing disease in animal models of MS. Moreover, some of these approaches, like the use of altered peptide ligands—which are peptides that are modified so that they engage the T cell receptor in a suboptimal manner, and thereby alter T cell signaling—can influence not only the response to a specific myelin antigen, but can modulate the behavior of an entire inflammatory ensemble. In MS and in EAE, there are diverse collections of T cells in the inflammatory infiltrate in white matter. Targeting a critical T cell in this diverse population with a soluble peptide ligand for the T cell receptor can lead to the rapid disappearance of the entire inflammatory infiltrate within 24 hr (Brocke et al., 1996). The mechanism underlying this observation involves down-regulation of proinflammatory cytokines, like TNFα and interferon-γ, and up-regulation of suppressive cytokines. Apoptosis is also seen during resolution of the inflammatory response in the brain (Bauer et al., 1995).

The role of certain cytokines in MS is well established. T helper type 1 (Th1) cytokines such as interferon-γ were shown to worsen disease when given systemically to patients with MS (Panitch et al., 1987), and TNFα is increased during exacerbations of MS (Sharief and Hentges, 1991). The mechanisms by which Th1 cytokines exacerbate MS may involve the ability of Th1 cytokines to increase expression of MHC class II on endothelium and up-regulate VLA-4. TNFα kills myelinating cells in culture (Selmaj et al., 1991). Therapies aimed at down-regulating TNFα with phosphodiesterase inhibitors or altered peptide ligands (Karin et al., 1994) appear promising for treatment of MS. Most recently, interferon-β, which down-regulates interferon-γ, has been shown to reduce the relapse rate modestly in MS (Paty et al., 1993).

As our understanding of the pathophysiology of MS increases, rational therapies will be devised that will arrest the immunological attack on myelin, without causing widespread immune suppression. Once the immune response is silenced, it will be important to repair the damaged myelin sheath. As possible methods to accomplish this repair, the use of oligodendroglial transplants and growth factors to reinitiate myelination are all currently under intense investigation (Steinman, 1993).

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