

# Multiple Sclerosis Is an Inflammatory T-Cell-Mediated Autoimmune Disease

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**T**HE ETIOLOGY AND pathogenesis of multiple sclerosis (MS) have been much debated during the past 50 years. It is now recognized that MS is a complex disease with different clinical and pathological phenotypes, perhaps reflecting different pathways to tissue injury. Thus, MS may not be a single disease entity. Nonetheless, with recent advances in immunology and magnetic resonance imaging and the demonstration that immunomodulatory treatment can have an ameliorating effect on the disease process, it is now clear that the core process in MS is inflammatory, with T cells and their mediators triggering injury of axons and their myelin sheaths through a complex sequence of events. The T-cell-mediated inflammation is driven by an autoimmune process, which in turn can trigger a degenerative phase that is immune independent. As described below, a large body of evidence suggests there is a Th1-type bias in MS (interferon [IFN] gamma, interleukin [IL]12, IL-18, and osteopontin) and that factors associated with Th2-type (IL-4 and IL-10) or Th3-type (transforming growth factor  $\beta$ ) responses are beneficial in MS.

Immune abnormalities in MS include activated T cells in the blood and cerebrospinal fluid, T-cell reactivity to myelin antigens, Th1-type inflammation in the brain (IL-12 and chemokine expression), local central nervous system (CNS) immune reaction (Ig-G), linkage of immune abnormalities to clinical course and magnetic resonance im-

aging, and major histocompatibility complex linkage.

## PATHOLOGIC FEATURES

The pathologic features of MS reflect a Th1-type delayed hypersensitivity reaction consistent with a cell-mediated immune process, as does expression of IL-12 and Th1-type chemokines in the CNS.<sup>1</sup> Other forms of injury to the CNS may be associated with inflammation (eg, stroke), but these are not characterized by the Th1 bias seen in MS (notably, IL-12 expression).<sup>2</sup> Also, increased levels of gamma globulin and the presence of activated T cells in the cerebrospinal fluid demonstrate a localized immune response in the CNS.

## AUTOIMMUNITY DIRECTED AGAINST MYELIN COMPONENTS

Direct proof that autoimmunity drives inflammation in MS requires the demonstration of autoantibodies or autoreactive T cells against a self-antigen in the nervous system. Obvious candidates are one or more components of myelin. Such evidence is often available for antibody-mediated autoimmune diseases, including myasthenia gravis, lupus, antiglomerular basement membrane disease, and idiopathic thrombocytopenic purpura. In these situations, the pathogenic potential of autoantibodies can be demonstrated by passive transfer of immune serum to animals. Although antibodies directed against self-antigens have been identified in MS, passive transfer of these antibodies does not cause MS in animals. Because of the need to cross histocompatibility barriers, this experimental approach is limited for putative T cell-mediated autoimmune disorders. Nonetheless, T cells reac-

tive to myelin components are found in a state of heightened activation in patients with MS but not controls.<sup>3</sup> Furthermore, a trial of an altered peptide ligand of myelin basic protein showed increased disease activity linked to increased MBP reactivity.<sup>4</sup> This directly demonstrates a link between MBP autoreactivity and MS.

## MAJOR HISTOCOMPATIBILITY COMPLEX ASSOCIATION

Genetic studies have repeatedly shown association (and subsequently linkage) between MS and class II (and class I) alleles of the major histocompatibility complex. The class I and II major histocompatibility complex molecules are directly involved in T-cell activation and shaping the T-cell immune repertoire. This implicates a crucial role for the immune system in the disease.

## RESPONSE TO THERAPY

If MS is truly a Th1-type T-cell-mediated autoimmune disease, therapy that down-regulates the Th1 component of the immune system must have an ameliorating effect on the disease process, with the converse also being true. Indeed, several immunomodulatory drugs that decrease Th1-type responses reduce disease activity and limit the accumulation of disability in MS, whereas those that increase Th1 responses increase disease activity in MS.

## INTERFERON BETA

Treatment with interferon beta decreases clinical relapses, reduces gadolinium-enhancing lesions, decreases accumulation of T2 lesion burden, decreases accumulation of brain atrophy, and delays onset of progression. Interferon beta appears to have multiple immune effects, including decreasing IFN- $\gamma$ ,

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increasing IL-10, and affecting movement of T cells into the CNS by inhibiting the activity of T-cell matrix metalloproteinases.<sup>5</sup> On the other hand, administration of interferon gamma caused worsening of MS.

### GLATIRAMER ACETATE

Glatiramer acetate is a specific immune modulator that decreases relapse rate and magnetic resonance imaging measures of disease activity in MS. Glatiramer was developed as a medicine based on its ability to modulate the experimental allergic encephalomyelitis (EAE) animal model of MS, in which it shifted the immune repertoire by induction of Th2- and Th3-type responses that mediate bystander suppression in the brain. It has demonstrated similar immune effects in patients with MS.<sup>6</sup>

### NATALIZUMAB

If MS is a T-cell-mediated inflammatory disease, treatment that blocks the movement of T cells from the blood into the CNS should be efficacious in treatment of the disease. This has been shown both in the EAE animal model and in patients with MS.<sup>7</sup> Gadolinium-enhancing lesions and relapses are both reduced in patients with MS who are treated with natalizumab, which is an alpha 4 integrin inhibitor.

### IMMUNOSUPPRESSION

If MS is an inflammatory disease sustained by autoimmunity, immunosuppressant drugs should have beneficial effects. It is now clear that immunosuppressant drugs such as mitoxantrone, cyclophosphamide, and Campath-1H have a profound effect on MS relapses.<sup>8-10</sup> Mitoxantrone has Food and Drug Administration approval for patients with worsening MS. The immune effects of cyclophosphamide, decrease in IL-12, immune deviation with eosinophilia in the peripheral blood, and increases in cells secreting IL-4 and transforming growth factor  $\beta$ <sup>10</sup> are consistent with the immune paradigm of MS, as previously described.

### PREGNANCY

Other evidence supporting MS as an inflammatory autoimmune disease includes the effect of pregnancy. Disease activity in MS is reduced during pregnancy but rebounds during the puerperium, coinciding with the shift from a predominant Th1 to Th2 immune polarity.

### ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

Autoimmune diseases are overrepresented in family members of individuals with MS, mainly because of an excess of autoimmune thyroid disease.

### CORRELATIONS BETWEEN CLINICAL FEATURES AND BIOMARKERS

The relapsing remitting character of MS, magnetic resonance imaging activity, and the accumulation of disability have been shown in numerous studies to be matched by changes in immune system biomarkers. For example, elevated percentages of IL-12+ monocytes in the blood correlate with gadolinium-enhancing lesions on magnetic resonance imaging,<sup>11</sup> and decreased IL-10 and increased IL-12 are associated with disease activity and different stages of disease.<sup>12</sup>

### RELATIONSHIP OF MS TO EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS

Experimental allergic encephalomyelitis has served as a model for MS and, although imperfect, has suggested therapies (such as glatiramer acetate) that subsequently were licensed on the basis of randomized clinical trials. Experimental allergic encephalomyelitis is induced by a variety of myelin antigens and exhibits markedly different clinical patterns depending on the strains used to induce disease. By varying the protocols, each feature of MS can be modeled in animals, including acute relapsing, chronic progressive, and, in the MOG-T-cell receptor transgenic mouse, isolated idiopathic optic neuritis.<sup>13</sup> Degenera-

tive changes that are triggered by inflammation but then become independent of the immune system have also been demonstrated in the EAE animal model, and neuroprotective agents can have a beneficial effect on the disease.<sup>14</sup> Thus, the EAE model replicates both the inflammatory and degenerative stages of the disease. Experimental allergic encephalomyelitis is not an exact model of MS because not all treatments that are effective in EAE are effective in MS, eg, anti-tumor necrosis factor therapy. Also, there are paradoxical effects in EAE, such as increased disease severity in IFN- $\gamma$ -deficient animals.

### PROGRESSIVE MS

There are types of MS or stages in which anti-inflammatory or immunomodulatory drugs are not helpful. This is true for primary progressive MS and the later stages of secondary progressive MS. Dissociation between the inflammatory and degenerative components is illustrated by studies with the humanized anti-CD52 monoclonal antibody Campath-1H and cladribine, a purine nucleoside analogue resistant to the action of adenosine deaminase. Despite substantial effects on clinical and surrogate markers of inflammation, patients with secondary progressive MS show sustained accumulation of disability due to uncontrolled progression marked by increasing cerebral atrophy, attributable to ongoing axonal loss apparently independent of concomitant cerebral inflammatory activity.

### CONCLUSIONS

Multiple sclerosis is a T-cell-mediated autoimmune disease in which inflammation is sustained by autoreactive T cells directed against components of myelin. There may be minor noninflammatory subtypes.<sup>15</sup> Inflammation precedes and triggers a degenerative phase of the disease that may not be affected by anti-inflammatory therapy. More effective therapy of MS will require identifying those subtypes in which aggressive treatment shuts down inflammatory responses and repair de-

fects in immune tolerance either in time to prevent the further cascade of events or with the administration of drugs to check the degenerative process. As stronger and more specific immune modulators are developed and given at the very onset of the disease, better control of the disease will be attained.

**Accepted for Publication:** June 3, 2004.

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## REFERENCES

1. Sorensen TL, Tani M, Jensen J, et al. Expression of specific chemokines and chemokine receptors in the central nervous system of multiple sclerosis patients. *J Clin Invest*. 1999;103:807-815.
2. Windhagen A, Newcombe J, Dangond F, et al. Expression of costimulatory molecules B7-1 (CD80), B7-2 (CD86), and interleukin 12 cytokine in multiple sclerosis lesions. *J Exp Med*. 1995;182:1985-1996.
3. Zhang J, Markovic-Plese S, Lacet B, Raus J, Weiner HL, Hafler DA. Increased frequency of interleukin 2-responsive T cells specific for myelin basic protein and proteolipid protein in peripheral blood and cerebrospinal fluid of patients with multiple sclerosis. *J Exp Med*. 1994;179:973-984.
4. Bielekova B, Goodwin B, Richert N, et al. Encephalitogenic potential of the myelin basic protein peptide (amino acids 83-99) in multiple sclerosis: results of a phase II clinical trial with an altered peptide ligand. *Nat Med*. 2000;6:1167-1175.
5. Yong VW, Chabot S, Stuve O, Williams G. Interferon beta in the treatment of multiple sclerosis: mechanisms of action. *Neurology*. 1998;51:682-689.
6. Neuhaus O, Farina C, Wekerle H, Hohlfeld R. Mechanisms of action of glatiramer acetate in multiple sclerosis. *Neurology*. 2001;56:702-708.
7. Miller DH, Khan OA, Sheremata WA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2003;348:15-23.
8. Hartung HP, Gonsette R, Konig N, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet*. 2002;360:2018-2025.
9. Coles AJ, Wing MG, Molyneux P, et al. Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. *Ann Neurol*. 1999;46:296-304.
10. Weiner HL, Cohen JA. Treatment of multiple sclerosis with cyclophosphamide: critical review of clinical and immunologic effects. *Mult Scler*. 2002;8:142-154.
11. Makhlof K, Weiner HL, Khoury SJ. Increased percentage of IL-12+ monocytes in the blood correlates with the presence of active MRI lesions in MS. *J Neuroimmunol*. 2001;119:145-149.
12. van Boxel-Dezaire AH, Hoff SC, van Oosten BW, et al. Decreased interleukin-10 and increased interleukin-12p40 mRNA are associated with disease activity and characterize different disease stages in multiple sclerosis. *Ann Neurol*. 1999;45:695-703.
13. Bettelli E, Pagany M, Weiner HL, Linington C, Sobel RA, Kuchroo VK. Myelin oligodendrocyte glycoprotein-specific T cell receptor transgenic mice develop spontaneous autoimmune optic neuritis. *J Exp Med*. 2003;197:1073-1081.
14. Pitt D, Werner P, Raine GS. Glutamate excitotoxicity in a model of multiple sclerosis. *Nat Med*. 2000;6:67-70.
15. Lucchinetti C, Bruck W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann Neurol*. 2000;47:707-717.

# Is Multiple Sclerosis an Autoimmune Disorder?

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**T**HE PATHOGENESIS OF multiple sclerosis (MS) has been debated for decades. At times the arguments have been based on equal parts speculation, fact, and whimsy. (What happened, for example, to the notion that the increased incidence of MS in northern latitudes occurs because people in these colder regions are more likely to be exposed to pet-borne viruses because their animals remain indoors?) As Mark Twain once quipped, "The fascinating thing about science is that one gets such wholesale returns of conjecture out of such a trifling investment of fact." Some speculation is not always bad, of course, because some concept of what is possible is

necessary to develop a model that can be objectively studied.

Both sides<sup>1,2</sup> make valid points here, and there may be more common ground between the authors than is at first apparent. Everyone acknowledges that MS can affect neurons as well as the white matter; the debate is whether the neurons are affected late or early in the process. Acute disseminated encephalomyelitis (ADEM) is a monophasic disorder and may or may not be closely related to MS. Experimental allergic encephalomyelitis does not parallel MS exactly, although the same is true of many animal models of human disease that are nonetheless helpful. And all of the authors acknowledge that MS is a complex disorder with multiple clinical patterns that could be initiated through more than one mechanism. Neither side mentions another intriguing idea: that the immune response in MS could result from a chronic vi-

ral infection rather than autoimmunity in the usual sense.

While the autoimmune model may not explain every aspect of MS perfectly, it is difficult to ignore the considerable evidence that immunity plays a major role in MS. Several immune-based treatments for MS have been shown to be clinically effective, and it seems unwise to dismiss the significance of these drugs just because they do not slow the progressive form of MS or because they are less effective than we would like. And although experimental allergic encephalomyelitis is not a perfect model for MS, it has led to the development of treatments, such as glatiramer, that are licensed for clinical use based on randomized clinical trials. The use of control subjects in randomized clinical trials makes it unlikely that a placebo effect would be mistaken for a therapeutic drug response.

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