Hypothesis

Genetically determined failure of activation-induced apoptosis of autoreactive T cells as a cause of multiple sclerosis

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I postulate that multiple sclerosis is an autoimmune disease that involves genetically determined failure of activation-induced apoptosis of autoreactive T cells in the central nervous system. Activation of central-nervous-system-reactive T cells in peripheral lymphoid organs by exposure to crossreacting antigens or superantigens derived from common infectious agents may trigger attacks of multiple sclerosis. In normal individuals these activated T cells are deleted by activation-induced apoptosis, but in individuals predisposed to multiple sclerosis they survive, proliferate, and damage the central nervous system. The clinical course of multiple sclerosis may vary according to the antigens in the central nervous system being targeted: targeting of myelin antigens leads to a relapsing-remitting course of clinical recovery due to remyelination or other mechanisms; targeting of axonal antigens leads to a progressive course from onset because axonal regeneration is limited in the central nervous system. This hypothesis can account for many characteristics of multiple sclerosis and has predictions that can be tested.

Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system and is a common cause of disability in young adults. Typically, multiple sclerosis starts with a relapsing-remitting course that changes to a secondary-progressive course; less commonly the course is progressive from onset (primary-progressive multiple sclerosis). The cause of multiple sclerosis is unknown, but similarities to experimental autoimmune encephalomyelitis (EAE) suggest that it might have an autoimmune basis. Here I hypothesise that multiple sclerosis is an autoimmune disease that involves a genetically determined failure of activation-induced apoptosis of autoreactive T cells in the central nervous system.

The role of T cells

T cells reactive to myelin antigens, such as myelin basic protein, can be isolated from normal healthy individuals.[1] These cells have the potential to induce damage to the central nervous system because of their cytotoxic capacity. In rats, EAE can be induced by the intravenous injection of T cells reactive to myelin basic protein derived from the lymph nodes of normal rats.[2] Given the array of antigens derived from infectious agents to which human beings are exposed, it would be surprising if autoreactive cells were not activated in peripheral lymphoid organs in some individuals by crossreactivity (molecular mimicry). Viral peptides can efficiently activate human T-cell clones specific for myelin basic protein.[3] Bacterial and other superantigens may also activate T cells reactive to myelin antigens in an antigen-non-specific way. Activation of autoreactive T cells by crossreacting environmental antigens or superantigens may explain the occurrence of acute disseminated encephalomyelitis associated with viral and bacterial infections, since proliferation of peripheral-blood lymphocytes is increased in response to myelin basic protein in acute disseminated encephalomyelitis. A similar mechanism may be responsible for triggering more attacks of multiple sclerosis at the time of common viral infections than at other times.

Activated T cells of any specificity, including autoreactive T cells, enter the normal central nervous system parenchyma[4] and seem to be continuously present. Why, then, doesn't everyone develop autoimmune disease of the central nervous system? In normal individuals, the autoreactive T cells may be deleted in the central nervous system. This mechanism stops the immune attack on the central nervous system in acute EAE.[5-9] In most animals EAE has a self-limited acute monophasic course similar to acute disseminated encephalomyelitis in human beings because apoptosis selectively eliminates autoreactive T cells from the central nervous system.[8,9] T cells interact with central-nervous-system non-professional antigen-presenting cells, such as astrocytes or microglia, which do not deliver the costimulatory signal needed for the T cells to produce sufficient interleukin-2 and Bcl-2-related-proteins to inhibit Fas-mediated apoptosis (figure 1).[10] It is thought that the costimulatory signal received by the T cell through CD28 results in an increased production of interleukin-2 with resultant increased expression of the antiapoptotic protein Bcl-2, which inhibits activation-induced apoptosis through the Fas pathway. Non-professional antigen-presenting cells do not deliver the costimulatory signal.

I propose that activation-induced apoptosis (pathways 1 and 2) of autoreactive T cells occurs in the central nervous system in normal individuals and generally leads to deletion of these T cells before any significant damage or neurological deficit occurs. In acute disseminated encephalomyelitis, an increased autoreactive-T-cell population may temporarily overwhelm the central nervous system's protective mechanism and result in a neurological deficit before activation-induced apoptosis stops the attack. I suggest that a genetically determined failure of activation-induced apoptosis of autoreactive T cells in the central-nervous-system occurs in multiple

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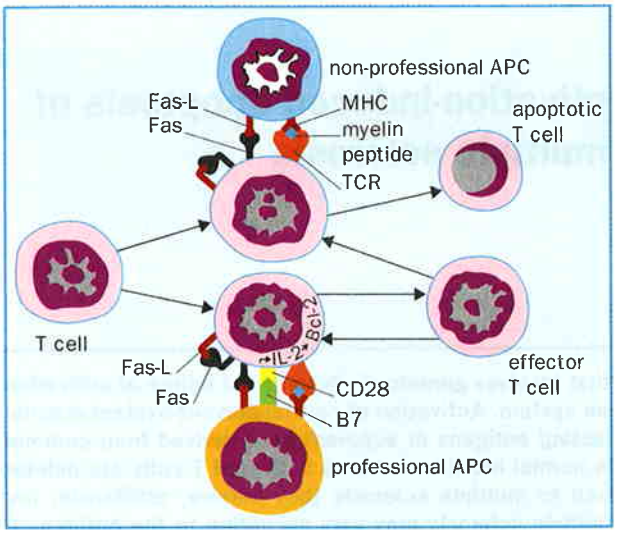

Figure 1: **Professional antigen-presenting cell interaction and non-professional antigen-presenting-cell interaction with activated T cell**

APC=antigen presenting cell; Fas-L=Fas ligand; TCR=T cell receptor; MHC=major histocompatibility complex; B7 represents costimulatory molecules, and CD28 represents their receptors on T cell.

sclerosis, so that these T cells survive, proliferate, and induce central-nervous-system damage (pathway 3) by secretion of lymphocytes or recruiting macrophages, or direct killing of oligodendrocytes (figure 2). Indeed, apoptotic T cells have been found in patients with multiple sclerosis,[11,12] but these may have been non-autoreactive T cells destroyed by corticosteroid-induced apoptosis. One study found that T cell apoptosis was strikingly infrequent.[12]

Activation-induced T cell apoptosis may fail in the central nervous system because of two broad types of abnormality. First, an abnormality in central-nervous-system antigen-presenting cells with increased costimulatory ability or decreased Fas-ligand expression. Second, an abnormality in the T cells leading to underactivity of the proapoptotic Fas-mediated (or other) pathways or overactivity of the antiapoptotic Bcl-2-related protein family. Note that abnormalities of the second type would affect T cells in general and lead to autoimmunity in other organs and enhance immune responses to environmental antigens.

Target antigens

Much attention has been given to the possible role of myelin basic protein as a target antigen in multiple sclerosis. However, when EAE is induced in animals by inocula containing myelin basic protein, major abnormalities occur in the peripheral and central nervous systems[13,14] because myelin basic protein is present in both systems.

Since multiple sclerosis is essentially restricted to the central nervous system, myelin basic protein is unlikely to be the main target antigen. A more likely target is myelin proteolipid protein, which is the most abundant myelin protein in the central nervous system, and does not occur in the peripheral nervous system. When inoculated into animals, this myelin protein results in disease restricted to the central nervous system.[14] Patients with relapsing-remitting or secondary-progressive but not primary progressive multiple sclerosis, have increased peripheral-blood T-cell proliferative responses to two overlapping proteolipid-protein peptides (PLP184–199 and PLP190–209) but not to myelin-basic-protein peptides.[15] This region of proteolipid protein is immunodominant in human beings and encephalitogenic in mice. These findings suggest that the PLP180–209 region may be a target in multiple sclerosis. However, only 27% of patients with relapsing-remitting or secondary-progressive multiple sclerosis of less than 6 years' duration had increased reactivity to this region, which suggests that other regions of proteolipid protein or other myelin antigens may be targeted during this period. A variety of myelin antigens are probably targeted, even in the same patient.[16] The immune response may eventually spread to involve PLP180–209, in a similar way to antigenic-determinant spreading in chronic EAE.

The absence of increased T-cell responses to PLP180–209 in patients with primary-progressive multiple sclerosis[15] raises the possibility that the main target antigens in this form of multiple sclerosis are not myelin antigens but are, perhaps, axonal antigens such as gangliosides. Primary-progressive multiple sclerosis has less central-nervous-system inflammation than the other forms of the disease,[17] but no pathological study has compared the extents of primary demyelination and axonal damage or loss in the different forms. Increased serum antibody reactivity to gangliosides has been found in patients with primary-progressive multiple sclerosis compared with controls and patients with other forms of multiple sclerosis.[18] T-cell responses to gangliosides may also be increased in patients with primary-progressive multiple sclerosis, but the inflammatory response may be less than that evoked by T cells reactive to myelin proteins. Because axonal regeneration is limited in the central nervous system, repeated immune attack against axonal antigens could account for the progressive course in this form of multiple sclerosis. The transition from relapsing-remitting to secondary-progressive multiple sclerosis may involve the spreading of the immune response to axonal antigens or increased bystander damage to axons near to myelin-directed immune attack.

Mechanisms of remission and relapse

Remission may be due to a general downregulation of the immune response by immunologically non-specific mechanisms, such as the endogenous secretion of corticosteroids. Remyelination by oligodendrocytes and possibly other mechanisms could account for the clinical recovery. Relapses may be triggered by reactivation of the originally aggressive autoreactive T cells, or by activation of other autoreactive T cells by viral infections. Myelin antigens released from the demyelinated lesions may reactivate the originally aggressive autoreactive T cells and also activate T cells specific for other myelin antigens. This activation may occur in the central nervous system or in the deep cervical lymph nodes draining the central nervous system and would perpetuate and amplify the autoimmune attack.

Genetic predisposition

Studies in twins have shown a substantial genetic susceptibility to multiple sclerosis. Many genes are involved, including the major histocompatibility complex genes.[19] Susceptibility to multiple sclerosis based in the major histocompatibility complex genes are likely to be mediated through the effects of major histocompatibility

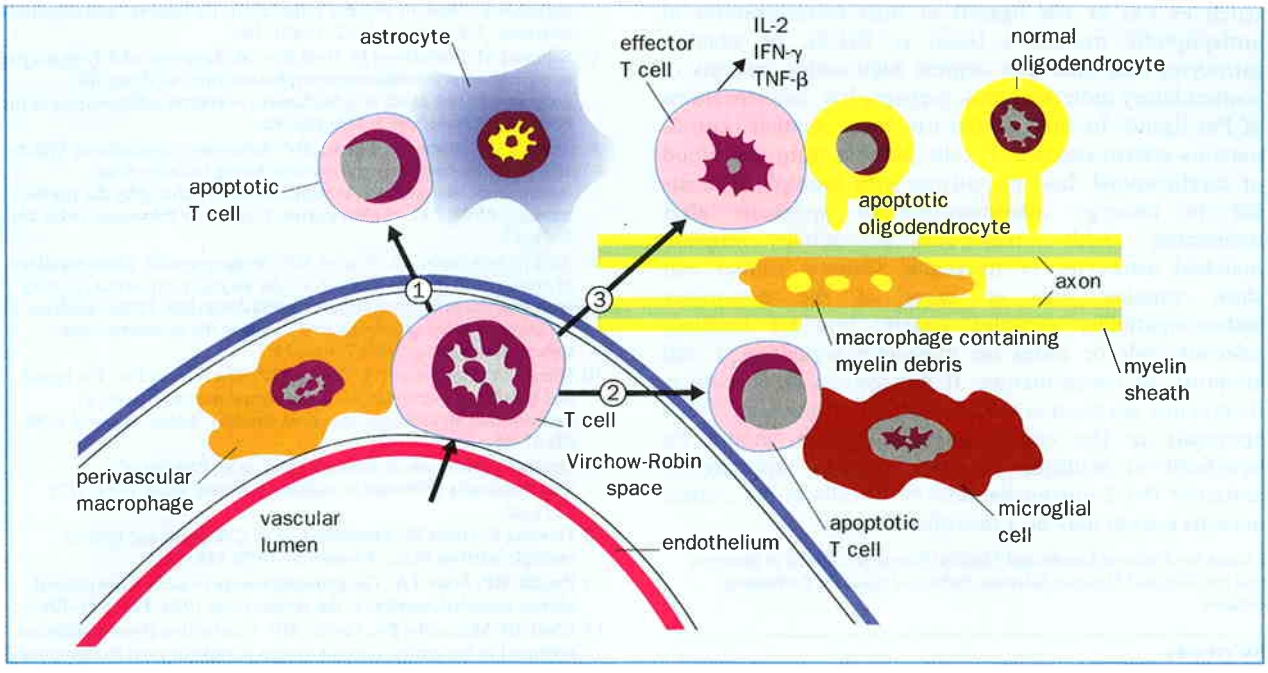

Figure 2: **Autoreactive T cells entering the central nervous system**
IL-2=interleukin-2; IFN-γ=interferon-γ; TNF-β=tumour necrosis factor-β.

complex molecules on antigen presentation to autoreactive T cells. The increased occurrence of other autoimmune diseases in patients with multiple sclerosis and their relatives[20] suggests that genetic factors predispose to autoimmunity. I propose that one or more of the non-major histocompatibility complex genetic loci for multiple sclerosis code or codes for molecules regulating T-cell apoptosis or involved in costimulation, and that a genetically determined failure of activation-induced T-cell apoptosis predisposes to autoimmunity in general.

Opposite effects of therapies in multiple sclerosis and EAE

The opposite effects of some therapies on multiple sclerosis and EAE may be explained by activation-induced apoptosis of autoreactive T cells in the central nervous system in EAE, but not in multiple sclerosis. Interferon-γ therapy aggravates multiple sclerosis but inhibits EAE. The inhibitory effect on EAE may be due to increased expression of class II major histocompatibility complex molecules by non-professional antigen-presenting cells in the central nervous system and the increased expression of Fas ligand on activated T cells, which leads to increased activation-induced T-cell apoptosis. If activation-induced apoptosis of autoreactive T cells in the central nervous system fails in multiple sclerosis, interferon-γ would have an unopposed proinflammatory effect that would aggravate the disease.

How multiple sclerosis might develop

Throughout life, central-nervous-system T cells are activated in peripheral lymphoid organs by crossreacting or superantigenic environmental antigens derived from infectious agents. In normal individuals these activated T cells are deleted in the central nervous system by activation-induced apoptosis. However, in individuals with genetically determined failure of activation-induced apoptosis, these activated autoreactive T cells survive, proliferate, and attack the central nervous system. If the T cells are specific for myelin antigens, primary demyelination leads to clinical attacks of relapsing-remitting multiple sclerosis. Immunologically non-specific mechanisms such as the endogenous secretion of corticosteroids down-regulate the immune attack on the central nervous system, leading to clinical recovery and remission. Relapses are triggered by reactivation of the originally aggressive autoreactive T cells or by activation of other autoreactive T cells by viral infection. Furthermore, myelin antigens released from the demyelinated lesions reactivate the originally aggressive autoreactive T cells and activate T cells specific for other myelin antigens, which leads to perpetuation and amplification of the autoimmune attack on the central nervous system. This process eventually leads to a dominant immune response against the immunodominant epitopes of proteolipid protein. If the aggressive T cells are specific for axonal antigens rather than myelin antigens, axonal degeneration occurs. Since axonal regeneration in the central nervous system is inherently limited, further immune attack on axons leads to primary-progressive multiple sclerosis. The autoreactive T cells also promote the production of antimyelin or antiaxonal antibodies that contribute to the attack on the central nervous system.

Testing the hypothesis

Apoptotic T cells in the central nervous system can be quantified histologically, but differentiating between activation-induced apoptosis of autoreactive T cells and immunologically non-specific apoptosis of non-autoreactive T cells, for example induced by corticosteroid administration, is difficult. T-cell apoptosis can also be quantified in the cerebrospinal fluid. Immunocytochemical studies can assess whether T cells in the central nervous system of patients with multiple sclerosis express low levels of proapoptotic molecules

(such as Fas or Fas ligand) or high concentrations of antiapoptotic molecules (such as Bcl-2), or whether astrocytes and microglia express high concentrations of costimulatory molecules and, perhaps, low concentrations of Fas ligand. In-vitro studies can show whether central-nervous-system-reactive T cells isolated from the blood or cerebrospinal fluid in patients with multiple sclerosis fail to undergo activation-induced apoptosis after interaction with major-histocompatibility-complex-matched astrocytes or microglia. Genetic studies can show whether one or more of the non-major histocompatibility complex genetic loci for multiple sclerosis code or codes for molecules regulating T cell apoptosis or costimulation. If the hypothesis is correct, therapeutic agents that increase activation-induced T-cell apoptosis in the central nervous system should be beneficial in multiple sclerosis. Finally, targeting of antisense Bcl-2 oligonucleotides to T cells in the central nervous system may be a potential therapy.

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