Rationale for Immunotherapy in Multiple Sclerosis

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The presumed but unspecified immune-mediated basis for the pathogenesis of multiple sclerosis (MS) has led to therapeutic attempts to modify the immune system in general and in selective ways in patients with MS. In general, antiviral, anti-inflammatory, immunosuppressant, and immunomodulatory therapies have been considered. More specifically, these treatments have involved the use of glucocorticoids; immunosuppressant drugs and physical agents such as irradiation; modifications of the immune environment with therapeutic plasma exchange and intravenous immunoglobulin; and more recently, alteration of events surrounding antigen presentation and stages of the immune response of cellular proliferation, recruitment, and infiltration of the central nervous system. The more selective approaches have dealt with attempts to interfere with elements of the trimolecular complex through blocking MHC class II, modifying T-cell receptor functions, interfering with co-stimulatory recognition steps, and altering cytokine effects or lymphocyte adhesion. The rationale for the current therapeutic trials of antigen-driven peripheral tolerance, MHC class II blockade, and immunomodulation, especially with interferon-β, illustrate the progression from broad immunosuppressive treatment to targeting specific activities of the immune system. The combination of new strategies in immunotherapy and sensitive disease monitoring of their effects should allow for more rapid identification of beneficial and tolerated treatment for MS.

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To quote from Waldmann and Cobbold [1]:

> The ideal form of therapeutic immunosuppression would be one that could be given over a short-term period to achieve long-term unresponsiveness to the desired antigen, without impairing the response to infectious agents.

It is sometimes useful to examine what events and beliefs have led us to our current position from which we attempt to devise a rational strategy for therapeutically altering multiple sclerosis (MS). If my good friend Dale McFarlin were present, he would likely be urging such an examination. Information continues to accumulate on the immunologic basis and etiologic mechanisms of MS [2, 3], leading to different opinions about the available evidence. On the one hand, there is the restrained position that acknowledges that something is awry with immune function in MS. The abnormality of immune function might be causal but could be an epiphenomenon. In contrast, there is the less restrained position from which MS is viewed as developing in the genetically susceptible individual through a viral infection that initiates a T cell–mediated immune response during an early phase of life. The genetic susceptibility presumably occurs on the basis of a polygenic influence but is mediated especially through genes encoded by the major histocompatibility complex (MHC) and the T-cell receptor (TCR). Through molecular mimicry and a recurrent or fixed dysregulated immune system, an autoimmune response to an endogenous myelin component such as myelin basic protein, proteolipid protein, or myelin oligodendrocyte glycoprotein, ensues and is perpetuated by a combination of cellular and humoral mechanisms.

Neuropathological and immunopathological observations underscore the principle that in MS the central nervous system (CNS) is infiltrated by lymphoid tissue that establishes an in situ immune apparatus [4, 5]. The most commonly postulated evolution of MS lesions (Fig 1) begins with an initial systemic event, most likely a viral infection, that leads to organ-specific CNS perivenular inflammation. Directed against an endogenous or cross-reactive exogenous antigen, sensitized and activated T cells circulate and adhere to endothelial cells in the CNS. The initial wave of lymphocytes mediating these events are T-helper cells that carry CD3 and CD4 markers. The adherence and properties of these cells alter the blood–brain-barrier so that they may penetrate. Thereafter follows recruitment of a diverse population of lymphoid cells with subsequent cell-mediated damage. Cytokines are secreted as are mediators and other enzymes such as proteinases and lipases. Antibodies are induced and synthesized by the recruited B cells, which transform into plasma cells. In-

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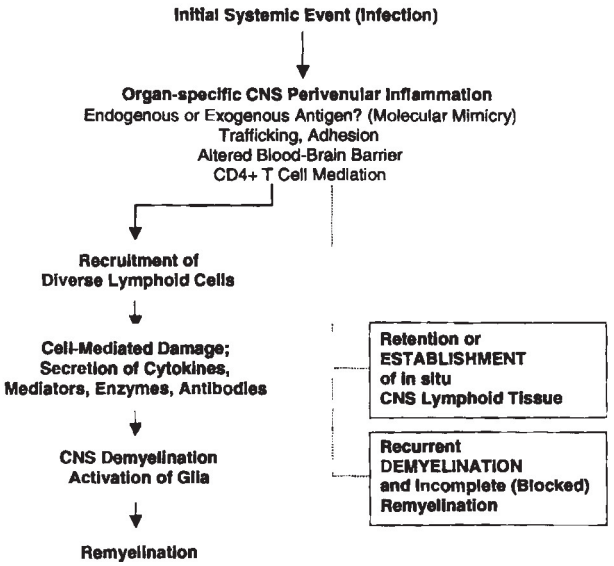

Fig 1. A postulated immunopathogenesis for evolution of lesions in multiple sclerosis. CNS = central nervous system.

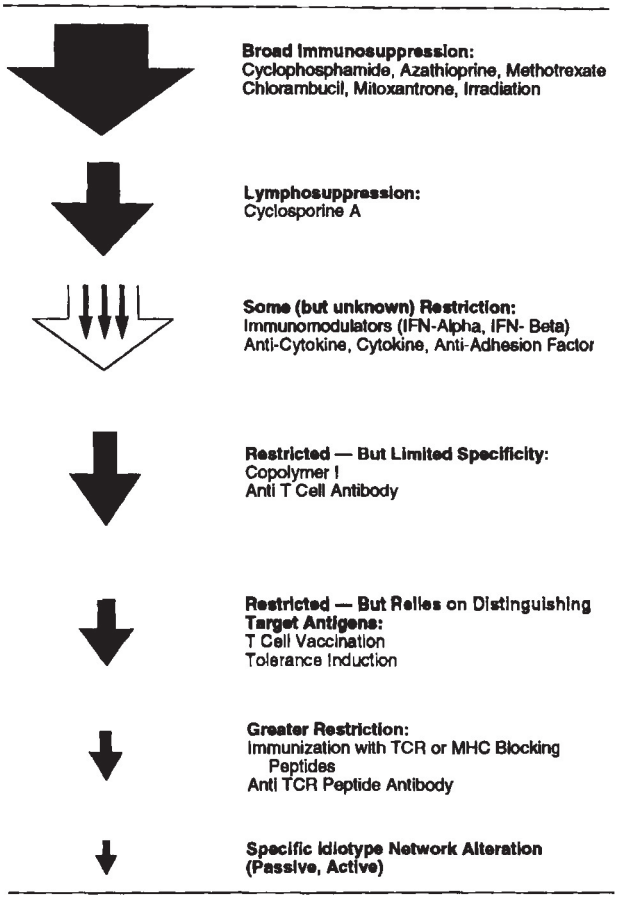

Fig 2. Considerations for the move toward selectivity of immunosuppression. IFN = interferon; TCR = T-cell receptor; MHC = major histocompatibility locus.

flammation and demyelination result. Microglia and astrocytes are activated. In early lesions oligodendrocytes also rapidly proliferate. Remyelination may then occur. As a result of this process or in parallel with it, the cells that have been attracted to the CNS are retained so that in situ lymphoid tissue is in place for further activation leading to recurrent demyelination. At some point, the cumulative events, possibly through extensive astrocytosis or other membrane changes in axolemma or oligodendrocyte, preclude or restrict remyelination.

It is on the basis of these observed tissue changes and postulated mechanisms that therapy is considered. The general stategies for treating MS may be divided into three categories. First, efforts may be directed at limiting demyelination through systemic immunomodulation with consideration given for what reagents and drugs will penetrate into the CNS so as to have an effect on the lymphoid function in situ. Most of the treatment administered heretofore and currently would fall within the category of limiting demyelination through limiting inflammation and suppressing the immune response [3]. Second, efforts may be directed to enhance remyelination [6]. Although stimulatory agents may be found for inducing this phenomenon, it is likely that limiting demyelination and oligodendrocyte injury may enhance remyelination. Third, one can attempt to improve conduction in demyelinated fibers. This is the objective of the use of potassium channel blockers such as 4-aminopyridine [7]. In attempting to effect the general strategies just mentioned, numerous therapeutic claims have been made [8].

A number of therapeutic regimens are available to attempt to alter the immune system. These may be generally classified into physical approaches, drugs, and biological materials. Treatments involving physical approaches include surgery to remove the thymus, apheresis, such as therapeutic plasma exchange or leukapheresis, to alter the internal milieu, and total lymphoid irradiation. Drugs that have been used to alter the immune system include the antiinflammatory glucocorticoids and the immunosuppressants. Biological agents, which are gaining more attention, are intravenous immunoglobulin, monoclonal antibodies to different markers or subsets of lymphocytes, therapy directed at the trimolecular complex (see below), and immunomodulatory agents and other materials that may act on the trimolecular complex or distal to it in the sequence of events following immune activation.

In the field of immunology there is a strong determination to become more selective with therapy for immunosuppression [3] (Fig 2). Broad immunosuppression with a variety of drugs or physical treatment can be more focused by selective lymphosuppression with cyclosporine A and progressively more directed treatment with immunomodulators, anti–T-cell regimens,

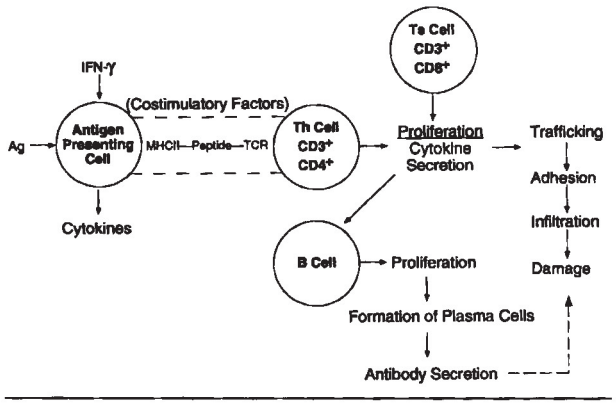

Fig 3. General principles of the immune response and the cells and their components involved. This figure should be used in reference to the information presented in the Table. IFN-γ = interferon-γ; MHC = major histocompatibility complex; Ts = T suppressor cell; Th = T helper cell.

tolerance induction and immunotherapy altering the TCR, MHC class II, or components of the idiotype network. Concurrent with this drive on the part of the immunotherapist to use more selective treatment is the generation of nonspecificity during an immune response [9]. In animals where experimental conditions can be rigidly controlled, specific immune activation is initiated. There soon follow amplification and recruitment of cells, much as described for MS (see Fig 1) and then the cascading phenomenon of cytokine secretion, formation of antibodies, enzymes, and mediators. Within the antigenic molecule having major and dominant epitopes there may be a spread of specificity to other portions of the same molecule to less dominant and sometimes cryptic (inaccessible in the intact molecule) epitopes. It is also possible for there to be spreading to other molecules besides that which produced the initial response. Thus, the desire to be selective with immunotherapy and avoid complications must be balanced with the need to be broad based enough to cover the widening immune response that is likely to have been in place by the time MS is diagnosed and therapy started.

In the sequence of steps involved in an immune response [10], an antigen-presenting cell, commonly a macrophage or a monocyte, takes up an antigen and degrades it and presents it on its surface in the context of an MHC class II molecule (Fig 3). The antigen-presenting cell may elaborate cytokines such as interleukin-1, and different cytokines may up-regulate the MHC class II expression on professional antigen-presenting cells such as the macrophage, or induce "nonprofessional" antigen-presenting cells such as the astrocyte or endothelial cell, to express MHC class II and become antigen presenters. In the context of MHC class II, the TCR on the T-helper lymphocyte ($CD3^+$, $CD4^+$), working in conjunction with a host of costimulatory factors, leads to activation of the T-helper cell so that it proliferates and secretes cytokines. The cytokines may then stimulate other cells within the T-cell series, stimulate B cells, and the activated T and B cells carry out the cellular and humoral components of an immune response. Other cells, especially the $CD3^+$, $CD8^+$ T-suppressor cell, may suppress these phenomena.

Glucocorticoids have been used in MS since the early 1950s. Glucocorticoids have many effects [11] and among those include inhibition of secretion by antigen-presenting cells and T cells of the cytokines tumor necrosis factor-α and interleukin-6. Glucocorticoids may in turn interfere with synthesis or secretion of interferon-γ (IFN-γ) and interleukin-2 by activated T cells. This plethora of effects of glucocorticoids indicate that in those trials of other agents that permit glucocorticoid usage for treatment of exacerbations, effects may also be noted that might be ascribed to glucocorticoids themselves.

The typical immunosuppressive agents [3] that have been used in MS include (1) the thiopurines, such as azathioprine and 6-mercaptopurine, which work through inhibiting nucleic acid synthesis; (2) methotrexate, an antifolate; (3) alkylating drugs, such as cyclophosphamide and chlorambucil, which bind to purine bases of DNA; (4) mitoxanthrone, which cross-links DNA and binds to mRNA; and (5) cyclosporine, which interferes with cytokine secretion. Each has been used in MS or is currently being tried without clear and persuasive evidence that they work [3].

Most of the current therapeutic strategies in MS revolve around directing drugs toward some component of the trimolecular complex that is comprised of the MHC class II of the antigen-presenting cells, digested peptide lying in a groove of the MHC class II molecule, and the TCR on the $CD4^+$ T lymphocyte (see Fig 3; Table). Strategies may be developed for targeting the antigen-presenting cell to interfere with processing and with presentation by MHC class II. This might involve the use of blocking antibodies to MHC class II or the use of modified epitopes such as copolymer-1 to displace peptide and prevent its presentation through MHC class II to TCR [3, 12]. Alternatively, therapy might be directed at the T cell itself through vaccination with T cells or passively administering antibody against the markers CD3 [13] and CD4 [14]. It is also possible to use peptides of the TCR or to direct an antiidiotypic response against TCR [15, 16].

In addition to the trimolecular complex itself, the various costimulatory factors have an important role in making it possible for the T cell to be stimulated. Relevant to a discussion of the role of the costimulatory factors is that of the process of tolerance and anergy [17]. In the usual immune response, a clone of cells is

Cells and Processes as Potential Targets for Immunotherapeutic Reagents in Multiple Sclerosis

Antigen presenting cell	
Processing	Proteinase inhibitor
MHC II (Presentation)	Blocking or displacement antibodies to MHC II; modified epitopes (copolymer-1)
T cell	
Vaccination with T cells	
Antibody to CD3	
Antibody to CD4	
Antibody to T-cell receptor (TCR)	
Immunization with TCR peptides	
Antibody to TCR peptides (passive)	
Generate antiidiotype (active or passive)	
Costimulatory factors	
Antiadhesion molecules	
CTLA-4	
Antiergotopes	
Peripheral tolerance	
Cytokines and cytokine receptors	
Antibodies, soluble receptors, receptor antagonists, interferon-α, interferon-β, transforming growth factor-β	
Trafficking of cells	
Antiadhesion molecules	
Blood–brain barrier	
Prazosin; glucocorticoids	
Promote remyelination	
Intravenous immunoglobulin, apheresis	

MHC = major histocompatibility complex; TCR = T-cell receptor.

expressed and expanded through activation of $CD4^+$ T cells by antigen, which leads to proliferation and secretion of cytokines. The responsive clone may be deleted in the thymus so that the $CD4^+$ T cell is missing in the periphery. In clonal anergy, which appears to result from a peripheral phenomenon outside the thymus, the $CD4^+$ T cell may respond to antigen through proliferation but does not secrete inflammatory cytokines. The lack of participation by costimulatory factors or interference with their usual effect can lead to clonal anergy. Another mechanism for tolerance is the elaboration of suppressor cells that block the response of $CD4^+$ T cells to antigen. One or more of these mechanisms is involved in induction of tolerance so that lessened immune activation may be reestablished. Oral myelin basic protein given to animals [18, 19] or oral myelin given to humans [20] appears to result in tolerance through anergy or suppressor cells. Other agents that may work on costimulatory factors include antibodies to adhesion molecules, the fusion product of CTLA-4 to interfere with the reaction of CD28 and B7, and reagents that react with ergotopes, which are markers of activation of T cells.

Other therapeutic strategies include altering the effects of cytokines through blocking harmful cytokines or inducing or administering cytokines that appear to be immunosuppressive or immunomodulatory themselves. The best studied therapeutic strategies for cytokine modification deal with those for interleukin-1 [21]. Cytokine effects may be abolished or reduced by blocking or inhibiting conversion and release of active cytokine, by neutralizing the released cytokine with antibodies or soluble receptors or by blocking the cytokine receptor with antireceptor antibodies or receptor antagonists. Cytokines may also be blocked nonspecifically with glucocorticoids, interleukin-4, interleukin-10, and transforming growth factor-β. Other immunotherapeutic approaches would be to interfere with the trafficking of activated T cells through the use of antiadhesion molecules or to prevent the penetration of cells through the blood–brain barrier with various drugs altering vascular permeability, such as prazosin [22] or glucocorticoids. Evidence to indicate that remyelination can be promoted therapeutically in humans with MS does not yet exist, although it is an approach that should be considered.

The recent success of the use of interferon-β (IFN-β) for the treatment of relapsing–remitting MS [23, 24] has led to a number of additional studies on the mechanism whereby this beneficial effect of IFN-β was expressed. There is evidence that IFN-β may augment suppressor function [25], reduce the effects of IFN-γ to induce MHC class II molecules [26], and reduce the production of IFN-γ in MS patients [27]. IFN-β does not work by raising the level of glucocorticoids [28]. It is possible that IFN-β has even more diverse sites of action [29]. Even though the goal of specific immunotherapy will continue to motivate immunotherapists, it may be more rational at this point to consider the broad-based therapy, such as with immunomodulators and IFN-β, to deal with the variety of steps envisioned to lead to tissue injury in MS.

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