Multiple sclerosis immunology for clinicians

Makoto Matsui  MD  PhD

Department of Neurology, Kanazawa Medical University, Uchinada, Japan

Abstract

Immunological factors found to be relevant in the pathogenesis of multiple sclerosis include T H1 cells and B cells that react with components of myelin in the central nervous system, as well as impairment of the regulatory mechanism caused by regulatory T cells. In addition, viral etiologies and genetic predisposition also have roles.

INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) in which immunity to CNS myelin has been implicated. A number of approaches to elucidate the immunopathogenesis of this disorder have been attempted, however, no specific target antigen that is initially attacked by the immune system in patients with MS has been defined. On the other hand, whatever the early pathological processes might be, the mechanisms by which inflammatory reactions in the CNS leading to demyelination have been clarified, thanks to recent advances in molecular immunology as well as studies of animal models of human MS experimental autoimmune encephalomyelitis (EAE). New treatment strategies for patients with MS established recently were developed on the basis of pathomechanisms inferred from findings obtained in studies of EAE models.

As a result, much has been learned about MS through EAE studies, including the major target myelin proteins myelin basic protein (MBP), proteolipid protein (PLP), and myelin oligodendrocyte glycoprotein (MOG). However, major questions remain regarding whether results obtained with EAE models are readily applicable to events occurring in the CNS of humans. In fact, the theoretically ideal method of treatment with monoclonal antibodies (MoAbs) against aberrant immunological factors involved in development of an EAE model has not been necessarily successful in MS patients, because results obtained from one strain of inbred mice are only applicable to an individual case, since human beings are out-bred. Therefore, clinicians must be aware of immune status heterogeneity in individual patients, even though several immunological disturbances are shared by the majority of patients with MS. With these points in mind, better treatment options might be chosen. Herein, several key elements in MS immunology are described.

EPIDEMIOLOGY

Epidemiological studies of MS are very important, as results obtained have revealed two major factors in the pathogenesis of MS. One is a genetic predisposition, including a strong association with the HLA-DR2 haplotype, while the other is a high prevalence of disease development in higher latitude regions. The former factor suggests a certain human subpopulation who possess a specific type of immune response gene are susceptible to MS development, while the latter indicates the relevance of some environmental factors. Considering that temperature and climate change in association with latitude, prevalent infectious agents, especially viruses, may have a role in the pathogenesis of MS prevalent in higher latitudes. However, these two factors are not mutually exclusive, since a certain type of immune response to some viruses, directed by HLA-DR2, may result in autoimmunity to CNS myelin proteins. Indeed, molecular mimicry between a peptide that is a constituent of Epstein-Barr virus (EBV) and the middle portion of MBP in terms of antigen presentation by HLA-DR2 has been shown.

In MS typically seen in western countries, a majority of CNS lesions exist in the cerebrum and cerebellum. However, Asian researchers of MS have long been aware of the presence of a subtype of MS in which major symptoms are restricted to the optic nerves and spinal cord. It was revealed that the western type of MS has an association with the HLA-DRB1*1501 allele, while the Asian type of optocarpal spinal MS is associated with HLA-DPB1*0501. These findings suggest that...
there may be two types of MS with different immunological backgrounds. In addition, the recent discovery of the anti-aquaporin 4 (AQP4) antibody has had great impact on the definitions of western and Asian types of MS\(^6\), as a majority of patients with opticospinal MS as well as some with western type MS have been found positive for this antibody.\(^7\) Presently, we are awaiting clarification of the biological and pathological significance of this autoantibody before utilizing it in routine tests in MS clinics.

**IMMUNOLOGY OF MULTIPLE SCLEROSIS PLAQUE**

Demyelinating MS lesions have been termed MS plaque. In microscopic examinations, typical plaques usually form oval-shaped lesions adjacent to high endothelial venules, as inflammatory cells, including lymphocytes, macrophages, and plasma cells, infiltrate the CNS through this type of vessel. Since MS plaques are sites of demyelination, many investigators have attempted to clarify which immune cells are involved in ongoing demyelination, and it has been reported that both CD4\(^+\) helper and CD8\(^+\) cytotoxic T cells exist in active plaques, with CD4\(^+\) cells in the plaque edge area and CD8\(^+\) cells in the perivascular region.\(^8\) Furthermore, macrophages appear to directly strip the myelin sheath and phagocytize myelin debris. During the 1980s, the concept of T helper type I (Th1) cells that produce proinflammatory cytokines, including IFN-\(\gamma\) and IL-2, as opposed to T helper type II (Th2) cells that secrete anti-inflammatory cytokines, such as IL-4, IL-5, and IL-13, was not firmly established. Therefore, additional studies for elucidating the function of infiltrating CD4\(^+\) cells were insufficient, as were those in regard to CD8\(^+\) cells.

In the 1990s, Th1 cells became a major target of MS research, with a rapid advance in EAE research techniques that emphasized the relevance of Th1-cell mediated autoimmunity to MBP and PLP. Humoral immunity seems to play some role in lesion formation only in the case of MOG-induced EAE, as injection of antibodies to MOG worsens the course of EAE. However, a sophisticated pathology method that uses monoclonal antibodies for detecting molecules associated with activation and function of the immune system has clarified the distinct processes that occur in patients with MS. Using biopsy specimens, investigators successfully demonstrated that plaques form as a result of cellular immunity in which T cells and macrophages have a major role, while there are also plaques with different etiologies in which antibodies and complements are heavily involved.\(^9\)

**IMMUNOLOGY OF CEREBROSPINAL FLUID IN MULTIPLE SCLEROSIS**

Although biopsy specimens can provide detailed information regarding ongoing immunological reactions in the CNS of MS patients, obtaining them is not feasible in daily practice. In contrast, a lumbar puncture can be performed more easily to obtain cerebrospinal fluid (CSF) for determining an event occurring in the CNS and the results are more accurate than those obtained with peripheral blood. Actually, in inflammatory CNS conditions including acute MS relapse, T cell subsets appearing in the CSF seem to reflect immune reactions in the CNS.\(^10\) Based on advances in basic immunology, a number of MoAbs have been produced and used for defining functional lymphocyte subsets. Furthermore, flow cytometric analyses of CSF lymphocytes using MoAbs revealed that acute relapses are characterized by an increase in CD4\(^+\)CCR5\(^+\)Th1 cells\(^11\) and decrease in CD8\(^+\)CD11a\(^+\)cytotoxic T cells.\(^12\) In addition, there is a definite increase in CD4\(^+\) cells possessing CD25 antigens (\(\alpha\) chain of IL-2) in association with active disease status, though recent studies have shown that those are CD25\(^{high}\)Foxp3\(^+\)regulatory T (Treg) cells. These findings support a 20-year old hypothesis that Th1 cells infiltrating the CNS are relevant in demyelination, as well as an older hypothesis that CD8\(^+\) cells have a protective role in the CNS.\(^13\) Also, Treg cells in patients with MS may be functionally defective\(^14\) or unable to cope with an overwhelming immune attack, as their increased number in the CSF does not halt the pathological processes. Flow cytometric studies of peripheral blood lymphocytes in active MS patients have shown an increase in Th1 cells positive for CCR5 and CXCR3 chemokine receptors,\(^11,12\) as well as decreases in CD4\(^+\)CCR4\(^+\)Th2 cells\(^11,15\) and IL-4-producing CD4\(^+\)Th2 cells.\(^15\) However, alterations in such T cell subsets are not as clear as those found in the CSF.

Analyses of immune cells in the CSF have provided information in regard to aberrant cellular immunity in the CNS, though another approach used to detect oligoclonal IgG bands revealed B cell activation in the CNS.\(^16\) This finding corresponds to the fact that there are a substantial number of plasma cells in MS plaque. However, it is unfortunate that all attempts to
elucidate the specific immune target with which those IgG bands react have been unsuccessful. Concerning humoral immunity, it was recently reported that lymphoid follicle-like structures can be found in the meninges of patients suffering from secondary progressive MS, which may be closely associated with EBV infection. In this regard, it is notable that a clinical trial using an anti-CD20 MoAb for reducing acute relapses of MS reported successful results, as that reagent deprives B cells from the blood for a long period, providing further evidence of B cell involvement in the pathogenesis of MS.

IMMUNOLOGY OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

Summarizing findings obtained with EAE models, there may be four steps in the development of demyelinating lesions in the CNS. First, lymphocytes are activated by a specific antigen presented by antigen-presenting cells (APCs) including dendritic cells in the peripheral lymphoid tissues. As a second step, activated T cells easily go into the CNS through the blood-brain barrier (BBB) via interactions between surface integrins and adhesion molecules expressed by endothelial cells. Then, if those T cells do not detect relevant antigens, they leave from the CNS. On the other hand, if they encounter a specific antigen presented by microglia that is an APC in the CNS, then Th1 cells begin to produce IL-2 and IFN-γ, while Th2 cells secrete IL-4 and IL-5, which is the third step. The antigen may not be a myelin antigen itself, since there is a possibility that short peptides constituting a portion of a virus or even bacteria can mimic a part of myelin protein. If Th1 responses are predominant, IFN-γ activates endothelial cells to upregulate adhesion molecules, which in turn recruit inflammatory cells including macrophages from the blood. IFN-γ also activates microglia to express additional class II MHC to efficaciously present autoantigens to Th1 cells. Furthermore, TNF-α secreted by Th1 cells and macrophages directly damage the myelin sheath or oligodendrocytes, while nitric oxide produced by macrophages is also toxic to myelin. This is the effector phase of demyelination and final step. Based on an understanding of these processes, a number of treatment options have been presented. However, in an EAE model, the pathological relevance of autoantibodies plus complements as well as that of CD8 cells is ignored, though both immunological components exist in MS plaques.

Recently, Th17 cells that produce IL-17 have been found to be important in at least MOG-induced EAE. However, additional studies are needed before concluding whether this is the case with MS patients or a marker for separating a subgroup of MS.

MOLECULAR IMMUNOLOGY OF MULTIPLE SCLEROSIS

The immunological disturbances observed in patients with MS are mostly compatible with those found in EAE models. In 1990, autoimmunity against MBP was shown to occur in human MS patients using the method of generating MBP-reactive T cell clones that function as either helper T cells or cytotoxic T cells, while T cell clones reactive with PLP were also found. However, treatment trials including oral tolerance induction for the suppression of specific immune reactions to myelin have been unsuccessful. Nevertheless, it is noteworthy that those studies revealed T cells that react with myelin proteins not only in patients with MS but also in healthy subjects, though there is a slight difference in precursor cell frequency. This important finding indicates that immunoregulatory mechanisms that prevent healthy subjects from the development of MS must exist. Although Th3 cells that produce TGF-β, Tr1 cells that secrete the inhibitory cytokine IL-10, and Treg cells are known to exert regulatory functions in immune responses, none of those have been found to be a promising target of immunological intervention. Furthermore, whether CD8+ cells protect or harm myelin has not been clarified to date. Finally, humoral immunity against myelin including anti-MBP and anti-MOG antibodies was reported to have a role in the development of MS, though that has not been confirmed by other investigators.

CONCLUSION

In MS, the belief that Th1 cells react with yet defined components of CNS myelin that trigger inflammation in the CNS, which leads to demyelination, still persists. However, humoral immunity against myelin also has a role in the pathogenesis of MS, though the target antigens have yet to be defined. In addition, anti-AQP4 antibodies require further clarification before being used in MS clinics. Therefore, restoration of impaired immunoregulatory mechanisms in MS, which may not be antigen-specific, is a feasible method for immune manipulation.
REFERENCES