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Multiple Sclerosis: Possible Immunological Mechanisms[1]

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Multiple sclerosis is the principal demyelinating disease of the central nervous system. Although the prevalence of the disease is moderately low, averaging about 40 cases per 100,000 people in high risk areas, it is a particularly devastating disease. It primarily affects young adults, is chronic, and has an unpredictable course. Most discouraging, the cause of the disease is not known and an effective treatment has not been identified. Recently, however, research has yielded some important findings concerning the etiology of MS. Much evidence now points to an immunological process as one of the major elements in the disease. It is also likely that an environmental influence, possibly an infectious process, may contribute to the disease. Finally, it is now certain that genetic makeup influences susceptibility to the disease. At present, the strongest evidence is for a polygenic effect, not the effect of a single gene or gene locus. This review will examine some of the possible immunologically mediated disease processes that could be involved in MS, especially those that could account for a role for infectious and genetic factors in the disease.

INTRODUCTION

Multiple sclerosis (MS) is the principal demyelinating disease of the central nervous system (CNS). Although the prevalence of the disease is moderately low averaging about 40 cases per 100,000 people in high risk areas, it is a particularly devastating disease. It primarily affects young adults, is chronic, and has an unpredictable course. Most discouraging, the cause of the disease is not known and an effective treatment has not been identified. Recently, however, research has yielded some important findings concerning the etiology of MS. Much evidence now points to an immunological process as one of the major elements in the disease (1). It is also likely that an environmental influence, possibly an infectious process, may contribute to the disease. Finally, it is now certain that genetic makeup influences susceptibility to the disease. Presently, the strongest evidence is for a polygenic effect, not the effect of a single gene or gene locus.

Since an excellent review of the various immunological studies relevant to MS has recently been published (1), this review will examine some of the possible immunologically mediated disease processes that could be involved in MS, especially those that could account for a role for infectious and genetic factors in the disease.

Despite the focus on an immunological process in MS, the evidence for this is largely circumstantial. Supporting an immunological mechanism in MS are the

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abnormalities of immunoglobulin (Ig) found in the cerebrospinal fluid (CSF) of patients with the disease (2, 3). The alterations in CSF Ig represent the most consistent immunological changes found in the disease and this is reflected in their diagnostic importance. These changes include elevations in the levels of IgG, IgM, and possibly IgA in a majority of MS patients (2). This Ig is largely synthesized locally in the CSF and is not merely a reflection of a breakdown of the blood–brain barrier (3). The Ig is usually oligoclonal as demonstrated by electrophoresis or isoelectric focusing (4). The oligoclonal nature of the Ig has led to the supposition that the antibody specificity of this Ig may be directly related to the disease process: the antibody may be directed to an infectious agent in the brain or the disease may be caused by antibody to myelin or oligodendrocytes. Despite extensive study, a clear association between CSF Ig reactivity and the disease has not been established. Increased antibody levels to numerous viruses have been found, and in almost every case, they represent only a small fraction of the Ig present. An exception is the recent report demonstrating that a significant portion of CSF Ig from some MS patients is directed to SV5, a paramyxovirus (5). This finding awaits confirmation.

Small amounts of antibody to myelin components have been described and it has generally been thought that these antibodies are unlikely to be directly or singularly responsible for demyelination (6). Importantly, evidence is now emerging from experimental models of cell-mediated demyelination that the presence of antibody to components of myelin may augment disease and demyelination. This will be discussed at greater length later in this review.

If most or all of the CSF Ig is not directly related to the cause of the disease, why do elevated levels occur in the CSF? A likely explanation is that the CSF Ig reflects the specificity of B cells that are found in greatest number in the blood, and therefore, have the greatest chance of migrating into an inflammatory site in the CNS. The antibody specificities found in the CSF of MS patients are generally those with high titers in the blood such as antibodies to viruses that are associated with lifelong immunity. Although the accumulation of these B cells may be random, the conditions permitting their differentiation into Ig-secreting cells must be present within the CNS. Generally, differentiation of and Ig production by B cells requires two signals, one of which is the perturbation of the Ig antigen receptor. If the antigens to which these antibodies react are not in the CNS, the continued differentiation of B cells must be due to factors in the CNS milieu that are capable of overriding the need for antigen binding to the Ig receptor. This could include lymphokines produced by the ongoing immune response or to the effect of neurotransmitters with immunostimulatory activity.

Obviously, an alternative explanation is that the antigen necessary to drive these B cells is in the CNS. This would suggest that multiple viruses could contribute to the disease process in some manner. Direct evidence for this is lacking. Probably the most consistent antiviral antibody found in CSF of MS patients is that to measles virus (7). Although measles virus genome has been demonstrated in brain material from some MS patients (8), the finding is not specific for MS and efforts to demonstrate the virus by other means have been unsuccessful. It is unlikely that the elevation in antimeasles antibody can be explained by cross-

reactivity between the virus and antigens in the nervous system since antibodies to at least four of the five protein components of the virus are elevated (Dhib-Jalbut and McFarland, unpublished data).

With the exception of the CSF Ig abnormalities, other evidence for an immunological process in the pathogenesis of MS points to a cellular immune mechanism. The perivenular inflammatory response comprised of lymphocytes and monocytes is certainly consistent with an immunologically mediated disease and resembles the pathological changes seen in postvaccinal encephalomyelitis, a disease of certain immunological cause.

Similarities between MS and a model of cell-mediated immunopathological disease of the CNS, experimental allergic encephalomyelitis (EAE), support a similar mechanism in MS. The objections to the appropriateness of EAE as a model for MS have been partially overcome by the demonstration of an experimentally produced relapsing remitting disease with close pathological similarities to MS (9). Although the relationship between MS and EAE remains uncertain, it is clear that the initiating events in MS are far more complex.

Finally, a number of abnormalities in lymphocyte distribution and function have been described in MS. These have been reviewed in detail elsewhere (1). These changes tend to be nonspecific and, in some cases, inconsistent, but in general they support the supposition of an abnormality in cellular immunity in MS.

There remain, however, fundamental unanswered questions regarding the nature of a putitive immune-mediated process in MS. These include: what is the actual mechanism of myelin destruction; what is the antigen or antigens responsible for initiating the disease process; how is antigen presented to immune T cells in the CNS and is the genetic influence on susceptibility involved at this stage; what is the role of an environmental or infectious agent in the disease; and finally, what accounts for the fluctuating nature of the disease? Although there are no definitive answers to these questions, recent studies have begun to provide some insight into these problems.

POSSIBLE MECHANISMS OF MYELIN DAMAGE

Several components of the immune system have been suggested as the effector mechanism producing demyelination. These have included antibody or other poorly characterized serum factors, lymphocytes, particularly cytotoxic T cells, and macrophages. The eloquent ultrastructural studies of acute lesions in MS by Prineas provide strong evidence that demyelination is macrophage mediated (10). These studies, as well as similar studies of demyelination in EAE, indicate that myelin disruption follows an interaction between myelin and macrophages and that characteristic coated pits are found at the point of myelin–macrophage contact. These coated pits most likely represent the migration of receptors within the macrophage membrane. A critical question is what are the receptors that are concentrated in the coated pit? Included among the receptors expressed on macrophages are those for the Fc portion of the Ig molecule and for complement.

Either of these receptors could contribute to the myelin–macrophage interaction seen in MS. As pointed out previously, antibodies to various components of myelin occur in MS and those antibodies recognizing components of myelin ex-

posed to the outer lamelle could form a means for macrophage attachment via Fc receptors. Antibody to glactocerebroside (11) and possibly other myelin components have been shown to contribute to the induction of EAE in the guinea pig. Also, transfer of antibody against components of myelin to mice with a relapsing form of EAE seem to augment demyelination and enhance progression of the disease (12). These findings suggest that antibody to myelin if not necessary for disease may at least contribute to the severity or progression of the process.

Complement may also serve as a ligand between myelin and macrophages. This could involve complement fixed to antibody bound to myelin or complement bound directly to myelin, since myelin has been shown to bind or fix complement in the absence of antibody. Macrophages express two types of complement receptors, CR3 and CR1. In addition to being up-regulated on activated macrophages, the CR1 receptor becomes mobile in the macrophage membrane and associates with clathin-coated pits (13).

A final consideration in the demyelinating process concerns a more direct role of viruses. Demyelination occurs in association with infections with several viruses in the retrovirus family. Infection of sheep with Visna virus produces an encephalitis that is characterized by inflammation and demyelination (14). Demyelination can also be a prominent finding in AIDS-related dementia caused by infection with HIV (15). Finally, abnormalities of white matter have been demonstrated by MRI in tropical spastic paraparesis (TSP) due to infection with HTLV-I (16). In Visna and AIDS, virus is found in the CNS in macrophages and this may form the basis for entry into the nervous system (17, 18). HTLV-I has also been isolated from lymphocytes from patients with TSP and this may provide a similar basis for entry into the CNS in this disease (19). The cause of demyelination in these diseases is uncertain and may be due to infection of oligodendrocytes. The possibility that macrophages infected with viruses, particularly retroviruses, can cause destruction or damage to myelin directly must be considered as well. A possible mechanism could be production of cytokines toxic to myelin. At least in Visna, this seems unlikely, since disease is reduced by treatment with immunosuppressive drugs indicating that demyelination may be immune mediated (42). Although a similiar process would seem unlikely in AIDS which is associated with profound immunosuppression, a role for an immunopathological process in this disease must still be considered.

T CELL ACTIVATION

If activated macrophages serve as the final effector arm in demyelination and if macrophage activation is immune mediated, what is the antigen specificity of the immune response producing the activation and why doesn't demyelination follow every inflammatory response in the brain such as those associated with viral infections? The answer to the second question may be that a true delayed-type hypersensitivity (DTH) reaction is necessary for macrophage activation. As mentioned previously, the presence of antibody to myelin may also contribute to the potential for demyelination.

The antigen specificity or specificities of T cell initiating the local immune reaction in the MS lesion are not known but either neural or viral antigens would

seem to be reasonable possibilities. EAE, a disease characterized by inflammation, and in some species, demyelination, can be induced by inoculation of experimental animals with myelin basic protein (MBP). The most compelling objections to viewing EAE as a model for MS have been based on the relatively acute and monophasic form of the experimental disease as compared to the relapsing course frequently found in MS. Recent studies of EAE have now demonstrated fluctuating courses under several experimental conditions. Importantly, a relapsing form of EAE has been produced in mice following the transfer of T cells from mice sensitized to MBP (9). Further, the pathological appearance of the CNS of these mice closely resembles that found in patients with MS. That MBP can be the relevant antigen in relapsing EAE is supported by the finding that this form of disease can be produced following transfer of T cell clones specific for the amino terminal portion of the MBP molecule (20).

As expected, the demonstration that MBP induces an experimental disease with similarities to MS has stimulated extensive studies of MBP reactive T cells in patients with MS. Evidence indicating an enhanced cellular immune response to MBP in MS, however, is meager. A recent study of a large number of patients using lymphoproliferation to measure reactivity to MBP found the response to be only slightly greater than that of a control group (21). The response to two other immunogenic components of myelin, myelin-associated glycoprotein (MAG) and proteolipid protein (PLP), were not significantly different between the patients and the controls. In a separate study using T cell clones generated from the CSF and blood of MS patients, MBP reactive clones could not be recovered from the CSF of MS patients but were generated from CSF lymphocytes obtained from patients with postinfectious encephalomyelitis (22). In the same study, T cell clones were generated from lymphocytes obtained from the brain of a patient with MS who had died. None of the clones reacted with MBP. These findings suggest that, even at the site of demyelination, MBP reactive T cells cannot be readily demonstrated. This study probably does not provide a definitive answer to this problem since it can be argued that if lymphocytes were obtained at the very earliest stages of disease, T cells with more relevant specificities might be recovered. Also, in studies of viral infections in the brain in which the inflammatory response is known to be generated by viral reactive T cells, only very small numbers of cells with the relevant specificity have been recovered from the inflammatory site (43). This indicates that a very small number of antigen reactive T cells are capable of initiating an inflammatory response and that the recovery of these cells from the site may be extremely difficult. The evidence for a role for MBP reactive T cells in MS is unconvincing but unfortunately the question is not completely resolved.

The other major category of antigens that has been considered in postulating an immunopathological process in MS is viral antigens. A relationship between a virus and MS has been supported by epidemiological studies showing a variation between incidence of disease and geographic region and by the apparent occurrence of small focal epidemic phase of disease (23). In addition, elevations in antibody to various viruses have been found in the CSF of patients with MS (44). Additional support for a relationship between MS and a virus comes from studies of

various experimental models of virus-induced demyelination. One of the most important of these models is Theiler's murine encephalomyelitis virus (TMEV) infection in mice (24). Infection of some strains of mice with TMEV, a picornavirus, produces, after one to several months, a neurological disease that is characterized pathologically by inflammation and demyelination. The disease appears to be immunologically mediated and susceptibility is influenced by the genetic makeup of the mouse (25). The genetic factors include genes in the MHC and probably another genetic locus, possibly genes coding for the β chain of the T cell receptor (25). Susceptibility to disease correlates closely with the ability to generate a DTH response to the virus. Consequently, it has been proposed that T cells recognize virus in the CNS and trigger a DTH response. The subsequent recruitment and activation of macrophages then leads to demyelination. A process of this nature would not require persistence of infectious or complete virus. Persistence of the viral genome and production of a single polypeptide that contains an epitope recognized by T cells would be sufficient to elicit a response. If the polypeptide was incomplete or present in small amounts, it might escape detection by conventional antibody staining.

Lymphocytes from MS patients have been studied extensively for abnormal reactivity to a wide variety of viruses. Most of these studies have used lymphoproliferation to measure reactivity and the results have generally been inconsistent (45). Because of the substantially elevated antibody titers to measles virus in the CSF of MS patients, measles virus has been the focus of numerous studies. Recently, the generation of virus specific cytotoxic T cells (CTL) was examined in patients with MS and in appropriate control groups (26). The findings demonstrated that a substantial number of patients had a significant reduction in their ability to generate measles virus-specific CTL. In contrast, their ability to generate influenza virus-specific CTL was normal. The abnormality in measles virus CTL is due to a 5- to 10-fold reduction in the precursor frequency of the population and not due to their complete absence (27). Importantly, measles virus CTL are $CD4^+$ lymphocytes and recognize measles virus antigens in conjunction with class II HLA molecules. This is in distinction to most other well-characterized virus-specific CTL which are predominantly $CD8^+$ and HLA class I restricted. It remains uncertain if the abnormality seen in the generation of measles virus CTL is specific for measles virus or if it reflects a more general abnormality in a population of $CD4^+$ lymphocytes. If the abnormality is virus specific, it may reflect a defect occurring at the time of initial exposure to the virus or to an abnormality in maintaining normal long-term immunity. It is also tempting to speculate that these cells are reduced in the peripheral blood because they are sequestered within the CNS following recognition of viral antigens. Recognition of a brain antigen that cross-reacts with measles virus is unlikely, since there is a reduction in the ability to generate CTL using several of the measles virus proteins: the reduction is not specific for a particular viral polypeptide (Dhib-Jalbut and McFarland, in press). Although the possibility of T cell recognition of viral antigens in the CNS triggering an immune response with subsequent demyelination remains an attractive hypothesis, proof is lacking.

An alternative means by which a virus could elicit a disease such as MS is by

causing sensitization to a neural antigen either by altering tolerance to the antigen during infection or through molecular mimicry. The coronavirus, JHM virus, when inoculated into rodents produces a subacute demyelinating disease. This disease is probably due to infection of oligodendrocytes with virus. An important finding, however, has been that lymphocytes taken from rats with this subacute disease and transferred into normal rats can elicit an EAE-like disease that does not seem to be due to transfer of virus (28). These animals can subsequently be shown to have a cellular immune response to MBP. These findings indicate that infection with JHM virus leads to sensitization to MBP. A similiar observation has been made in the same laboratory using rats infected with a neurotrophic strain of measles virus (29). Although this virus also produces encephalitis, it replicates mostly in neurons and does not cause demyelination. This suggests that the inflammatory response in the brain may be sufficient for sensitization to MBP to occur. Sensitization to MBP following viral infections has also been reported in humans. Studies of children with complicated or uncomplicated measles virus infections have demonstrated that many of the children acquire a lymphoproliferative response to MBP greater than that found in controls (30). It is not known if this sensitization follows infection of the nervous system with measles virus or if it is due to some form of cross-reactivity. Some minor degrees of sequence homology have been reported between MBP and several viruses that infect humans (31). Despite extensive study, however, immunological cross-reactivity between measles virus and MPB has not been demonstrated. Regardless of the mechanism, some viral infections apparently can produce enhanced T cell reactivity to neural antigens.

PRESENTATION OF ANTIGEN WITHIN THE NERVOUS SYSTEM

If MS is due to a local DTH response, the relevant antigen(s) is most likely presented to T cells in the nervous system. The essential requirements for cells to serve as antigen-presenting cells are that they are capable of processing antigens and that they can express HLA class II molecules on their surface. Two cell populations, astrocytes and brain endothelial cells, have been shown to have these qualities (32, 33). It also seems reasonable to assume that microglia may also be able to serve as antigen-presenting cells (46). Neither astrocytes nor CNS endothelial cells normally express HLA class II molecules but both can be induced to do so using interferon-γ. Also endothelial cells from mice with EAE express HLA class II molecules and studies of astrocytes from various strains of rats or mice have found a correlation between the ability to induce HLA class II molecules and susceptibility to EAE (34).

MHC class II antigens can also be induced on rat astrocytes with viruses (35). Even inactivated virus seems to be capable of inducing MHC class II antigen on astrocytes and this could be achieved more easily on astrocytes derived from strains of rats susceptible to EAE. These findings indicate that persistent infection could contribute to expression of MHC molecules and that this, in turn, could lead to presentation of either viral or neural antigens. This provides an alternative mechanism by which a viral infection could lead to sensitization to CNS antigens. Importantly, this suggests that a persistent infection could be instrumental to

disease production triggered by T cell reactivity to nonviral antigens. A diminished cellular immune response to the virus might increase the likelihood of this since there would be a reduced ability to eliminate virus.

Differences in the ability to induce HLA molecules in humans similar to those demonstrated in those experimental animals could represent one of the components of the genetic susceptibility to MS. Clearly, the mechanisms regulating expression of the molecules may be critical to understanding MS.

REGULATION OF THE IMMUNE RESPONSE

One of the striking characteristics of MS is its frequent relapsing remitting course. This has led to speculation that the disease may be related to an abnormality of suppressor cell function with reduced suppression resulting in episodes of disease activity followed by return of suppressor function or local regulation of the response. In fact, deficiencies of suppressor cells have been demonstrated in several experimental, *in vitro,* systems (1). The finding that a reduced number of $CD8^+$ T cells, which includes suppressor cells, occurs during periods of worsening has been inconsistent. Functional studies have shown, however, that there is reduced suppression during progression or exacerbation. These studies have measured suppression as generated by mitogens such as concanavalin A or OKT3 which binds to the T cell receptor (36). Similarly, the ability of $CD8^+$ T cells to suppress Ig production following PWM stimulation is reduced while other functional parameters of the $CD8^+$ T cells such as CTL activity are normal (37). A subset of $CD4^+$ cells, the 2H4 cells, which acts to induce suppression through $CD8^+$ T cells, has been shown to be reduced in MS patients with active disease (38).

The autologous mixed lymphocyte reaction (AMLR) has been considered an important technique for studying immunoregulatory processes and several investigators have examined the AMLR in patients with MS (39, 40, 41). Generally, the response is found to be increased during worsening. It has now been demonstrated that this is due to a reduction in the generation of suppression which normally occurs in the AMLR (40).

The significance of the various abnormalities of suppressor cell function is uncertain. MS is not associated with multiple immunological abnormalities which casts some doubt on generalized suppressor cell deficiency but episodic fluctuations in regulatory mechanisms could be involved in exacerbation. Alternatively, these changes in immunoregulation could occur as a result of the same process that triggers the immune response occurring within the CNS. For example, upregulation in HLA class II antigen expression could lead to increased reactivity in all of these *in vitro* tests and account for the apparent reduction in suppression. Studies of immune regulation are critical to an understanding of the immune process in MS and future studies hopefully will establish if these changes represent reduced suppression or enhanced reactivity secondary to the disease process.

CONCLUSION

The evidence linking the pathogenesis of MS to an immunological process remains indirect and tentative. It seems increasingly certain that the actual de-

struction of myelin is caused by activated macrophages. What is uncertain is the mechanism for activation of these macrophages. Although an immunological mechanism would seem most likely, it is still possible that this activation could occur as a direct result of a viral infection. By extrapolating from observations made in various experimental models, it seems that the most likely immunological process would be the induction of a DTH type response with subsequent macrophage activation. Either a neural or viral antigen could trigger this response and the genetic influence on susceptibility may reflect the genes coding for the HLA class II and T cell receptor makeup necessary for recognition of the relevant antigen. The failure to demonstrate a unique or enhanced T cell reactivity is disturbing, but could be due to the techniques used or to a sequestration of this population within the CNS. This latter possibility seems the least likely and has little support from experimental models.

It is now clear that both astrocytes and endothelial cells can function as antigen-presenting cells *in vitro*. It is also likely that microglia can also express class II HLA molecules and function as antigen-presenting cells. The nonspecific induction of HLA class II antigens on these populations by lymphokines such as interferon-γ provides an attractive mechanism for presenting antigen to circulating cells and triggering a local immune response which leads to demyelination. Periodic increases in HLA class II expression due to nonspecific processes such as viral infections could provide a reasonable explanation for the fluctuating course of the disease. With continued disease progression, the local production of lymphokines may become sufficient to maintain an ongoing immune response.

Demyelination may be enhanced by local production of antibody capable of binding myelin. B cells with appropriate specificities migrating into the inflammatory site would find both antigen and lymphokines necessary for B cell differentiation. The continued differentiation of B cells with production of antimyelin antibody could contribute to the conversion of the disease from a relapsing–remitting course into one of continued progression.

The major unanswered questions concern the antigen and the role for the genetic influence on the immune response. The ability of T cells to recognize epitopes consisting of only several amino acids and which are not recognized by antibody may contribute to the difficulty of answering these questions. It is hoped that the techniques that allow manipulation of HLA genes and identification of characteristics of the T cell receptor makeup along with more specific immunological methods will contribute a greater understanding to these questions.

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