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Research Article



# Significance of Autoreactive T Cells in Diseases such as Multiple Sclerosis Using an Innovative Primate Model

## Editorial

The work published in this issue by Claude Genain and colleagues (1) has important implications for understanding disease mechanisms which may contribute to immunopathological diseases of the nervous system such as multiple sclerosis (MS). The investigators have demonstrated that a form of experimental allergic encephalomyelitis (EAE) can be produced in the nonhuman primate, *Callithrix jacchus,* by adoptive transfer of myelin basic protein (MBP)-sensitized T cells. This marmoset is unusual since the fetuses share a common placenta and are tolerant of their siblings' immune cells, despite being genetically distinct. Thus, T cell lines derived from one sibling can be transferred into a second sibling without fear of rejection. Using this model, the investigators have demonstrated that MBP-specific T cells can be derived from nonimmunized animals and that some of these T cell lines can successfully transfer disease. Over the past several years, several laboratories have examined the occurrence of T cells specific for myelin proteins such as MBP, proteolipid protein, and myelin-associated glycoprotein in patients with MS and controls in order to identify an association between a unique reactivity and MS. Numerous parameters have been studied including frequency, specificity, HLA restriction, and T cell receptor (TCR) usage. Generally, these studies have failed to demonstrate a consistent unique reactivity associated with MS but have shown that T cells specific for various myelin proteins can be demonstrated in both patients and controls (for review see reference 2). An unresolved question has been whether these cells could represent one aspect of the disease process and contribute to disease and, if so, what other factors are necessary? The results of the present study suggests that, after activation, these cells may be capable of inducing disease.

However, the work presented by Genain et al. (1) also raises additional points concerning possible disease mechanisms. First, disease required the administration of *Bordetella pertussis* vaccine, indicating that factors other than the presence of activated MBP-specific T cells were necessary. As Genain et al. (1) point out, similar observations have been made in other animal models. In some strains of mice susceptible to EAE, the majority of encephalitogenic T cells from that animal use the same TCR. When the alpha and beta chains of the TCR are placed as transgenes in an MHC compatible strain, the mice fail to develop EAE despite the expression of the encephalitogenic TCR on $> 90\%$ of the circulating T cells (3). Disease does develop after the administration of *B. pertussis* or in animals kept in non-germ-free conditions. Thus, in this strain the presence of high numbers of potentially encephalitogenic T cells is not, alone, sufficient for disease. In contrast, adoptive transfer of activated MBP-specific T cells in a susceptible strain of mice such as the SJL/J or PL/J results in disease without additional manipulation. Together, these findings argue that additional factors are required for disease production and that these may involve both host and environmental factors or host factors that influence how the host responds to environmental influences. These factors may contribute to opening of the blood brain barrier, to mechanisms of T cell activation such as costimulatory events or the production of cytokines which either amplify or downregulate the inflammatory response. Consistent with such a multifactoral process is the evidence that multiple genes influence susceptibility for MS (for review see reference 2) and probably in EAE. The clinical course in the marmoset after adoptive transfer of MBP-specific T cells was mild and monophasic, which may reflect an absence of host components which contribute to increased susceptibility.

A second important point is that the pathology of the adoptive transfer model in the marmoset is not characterized by demyelination. Although only one example of the pathology is included in the manuscript, the authors describe an inflammatory response associated with necrosis. It is well established that the pathological findings in EAE differ considerably between species and that some species such as the rat, while having considerable inflammation, generally have little myelin damage. Importantly, the lack of demyelination described in this manuscript seems to be related more to the experimental conditions than to unique characteristics of the host. The authors indicate that marmosets immunized directly with whole white matter develop EAE associated with demyelination. They also mention that immunization with MBP alone produced disease but again failed to produce demyelination. Differences in the pathological appearance of the disease depending on the manner in which the disease was induced have been demonstrated in other species as well. These observations provide strong evidence for a multifactoral process in lesion development. Factors influencing entry of activated T cells into the central nervous system, generation of an inflammatory response, demyelination, and possibly regulation of these factors may all contribute to the development of the lesion and determine its characteristics. The authors speculate that the lack of demyelination may be due either to the limited macrophage response in the lesions or to an absence of autoantibodies to myelin which may be a critical element. Both of these are reasonable possibilities. Although the effector mechanism for demyelination is not known, stripping of myelin by activated macrophages and involving a receptor–ligand interaction is supported by ultrastructural studies of both EAE and MS (4, 5). Demyelination in the guinea pig immunized with MBP requires coimmunization with glycolipids such as galactocerebroside, and it is presumed that antibodies to the glycolipids contribute to the destruction of myelin (6). Disease in the adoptive transfer marmoset model, if not due to demyelination, must be related to inflammation and an inflammatory response may be capable of disrupting nerve conduction temporarily. An additional important point is that recurrent or chronic disease that is seen in MS and in the murine model may depend on demyelination with subsequent sensitization to additional myelin proteins or epitopes of these proteins. It will be interesting to learn if disease in the marmoset induced with whole myelin has a chronic form, and publication of the results with the marmoset model using active immunization with either whole myelin or MBP should contribute to our understanding of these differences.

Finally, Genain et al. (1) point out that the encephalitogenic T cells recognize three different regions of MBP and that, in

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this outbred animal, multiple portions of MBP and probably other myelin protein as well can be encephalitogenic. Inbred animals have tended to respond to particular epitopes of a myelin protein such as MBP or proteolipid protein, and the choice of immunodominant encephaltiogenic regions is influenced by the MHC class II makeup. However, there is increasing evidence to indicate that, even in these inbred animals, portions of the molecule other than the immunodominant regions may result in EAE. Still, some caution must be exercised since the data in the marmoset model are limited. The strongest argument for diversity of epitope specificity among encephalitogenic T cells in the work by Genain et al. (1) comes from the results in the first set of animals. In this set of triplets, two encephalitogenic T cell lines were derived from one animal. One of these lines, reacting with amino acids 11–30, produced disease in one sibling, while the other line, reacting with amino acids 153–172, induced disease in the third sibling. Since the MHC makeup of these animals is unknown, the findings do not exclude the possibility that these two specificities are immunodominant for the MHC molecules in the donor animal. Thus, each outbred animal or human may have a limited number of immunodominant epitopes, and the choice of epitopes will depend on MHC makeup. Previous studies of primates have indicated that the major encephalitogenic region was within the COOH-terminal portion of the molecule, and the findings in this study which demonstrate that four of the five encephalitogenic lines recognized epitopes within the COOH-terminal region seem consistent with the previous observations in other primates. Studies of additional animals and analysis of MHC makeup will be required to fully define the extent of diversity of encephalitogenic epitopes in the marmoset. Although this work raises many questions which cannot be completely resolved at present, it provides a model for addressing questions which are essential in understanding immunopathological processes in MS.

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