The Role of T Cells in Multiple Sclerosis: Implications for Therapies Targeting the T Cell Receptor

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Abstract. The cause of multiple sclerosis (MS) is unknown, but an immunopathological process with both endogenous and exogenous factors contributing to disease seems likely. Considerable recent attention, triggered predominantly by findings in the animal model, experimental allergic encephalomyelitis (EAE), which resembles MS, has focused on the role of T cells in MS. Findings in the animal model have raised the possibility that demyelination could be produced by CD4+ T cells specific for myelin proteins and expressing a limited set of T cell receptor (TCR) molecules. Thus, specific therapies targeting T cells or more specifically the TCR could represent an effective treatment of MS as has been demonstrated in EAE. However, current studies of patients with MS indicate that the immunological mechanisms in MS are considerably more complicated than in EAE. The evidence for a pivotal role for T cells in MS and the characteristics of these T cells particularly with respect to TCR usage and potential for therapies directed at the TCR will be examined in this review.

Key Words: Demyelination; Experimental allergic encephalomyelitis; Multiple sclerosis; T cell receptors; T lymphocytes.

INTRODUCTION

The etiology of multiple sclerosis (MS) is not known but both exogenous and endogenous factors seem to contribute to disease susceptibility. The influence of the genetic makeup is apparent in the increased concordance rate for monozygotic (approximately 25%) versus dizygotic twins (1 to 5%)(1,2). Although an association between disease and certain HLA genes exists (3,4), this does not fully explain the genetic influence; most likely multiple genes may contribute. Additional candidate genes include those for T cell receptors (TCR), although, as will be discussed, this association is controversial. Evidence for exogenous factors comes from epidemiological studies demonstrating the effects of geographic location and migration on the manifestation of disease (5). Clusters of MS, particularly in the Faroe islands, argue for an influence of exogenous factors, and their existence is additionally supported by the large number of monozygotic twins discordant for the disease. So far, the nature of potential exogenous factor(s) remains unresolved but a link with viral infections as well as the involvement of superantigens of viral or bacterial origin has been suggested.

The pathology of MS is characterized by an inflammatory process that resembles a delayed-type hypersensitivity reaction. This evidence together with the similarities observed between MS and an experimental animal model for autoimmune disease, experimental allergic encephalomyelitis (EAE), support the notion of an immunopathological process underlying MS. EAE can be induced by immunization of susceptible animals with myelin or protein components of myelin such as myelin basic protein (MBP) or proteolipid protein (PLP) (6-8). EAE is mediated by CD4+ T cells and can be transferred into healthy animals with T cells specific for MBP (9,10) and PLP. The role of T cells in EAE has been the focus of considerable work over the last several years. It is now understood that the interaction between TCR expressed on encephalitogenic T cells and antigen presented by proteins of the major histocompatibility complex (MHC, the equivalent to HLA molecules in humans) plays a crucial role in the disease. The characterization of this trimolecular complex composed of TCR, MHC and antigen has led to innovative therapeutic concepts. Considerable effort is currently invested in determining whether immunological findings in EAE can be reproduced in patients with MS. This review will examine the involvement of T cells and, in particular, the TCR in the pathogenesis of MS and will discuss therapies targeting the TCR and the trimolecular complex.

INFLITRATING T CELLS IN MS LESIONS

Characteristic perivascular lymphocyte infiltration in brain lesions of MS patients supports an immunopathological mechanism in the pathogenesis of MS. T cells and macrophages comprise the majority of infiltrating cells at the sites of active demyelination (11). Characterization of the T cells in the inflammatory infiltrate indicate that both CD4+ and CD8+ T cells are present, but that CD4+ T cells predominate at the edge of active demyelination (12-14). The T cells appear activated as they express IL-2 receptors and HLA class II molecules (15).

Antigen, presented in conjunction with MHC molecules, is recognized by the TCR molecule on T cells. Most T cells express a TCR molecule comprised of one α and one β chain. A smaller number of T cells express a TCR comprised of one γ and one δ chain. The recent detection of T cells in MS lesions that express γδ TCR has led to speculations about an active role of this T cell

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subset in MS. γδ T cells are unable to recognize antigen presented by classical class I or II molecules of the MHC, as αβ T cells do. They are speculated to be evolutionarily older than αβ T cells and to recognize antigen in the context of non-classical MHC class I molecules as a first line of defense against bacterial infections. Selmay et al (16) studied CNS tissue from 13 patients with MS, ten patients with other inflammatory CNS disorders or other neurologically diseases (OND) and three control individuals. Twenty-eight of the 43 MS lesions that were investigated contained γδ T cells. They were mostly localized in areas, characterized as chronic active plaques, which, in contrast, contained only few αβ T cells. More active lesions showed a predominance of αβ over γδ T cells.

The γδ T cells appeared to localize near oligodendrocytes expressing activation markers including heat shock proteins (hsp). This finding has raised the possibility that γδ T cells may contribute to the destruction of oligodendrocytes in chronic active plaques and thus eliminate the potential for remyelination. Wucherpfennig et al (17) have studied γδ T cells in more active MS plaques and have attempted to characterize the TCR chain genes used by these γδ T cells. They identified Vδ1, Vδ2, Vγ2 and Vγ9 as being predominantly used. This limited use of only two variable region genes for each chain was attributed to a clonal expansion of cells in the lesions. Expression of hsp was observed by both groups. Selmay et al (18) demonstrated expression of hsp65 on oligodendrocytes, while Wucherpfennig et al (17) found hsp90 being expressed by astrocytes and hsp60 by foamy macrophages.

In a very recent study Hvas et al (19) investigated brains from 12 MS patients, ten normal and three OND controls. The lesions were examined for γδ T cells by the polymerase chain amplification technique (PCR) using Vγ- and Vδ-specific primers. All 23 areas from MS brains studied tested positive for γδ T cells. The observed preference for Vγ2 and Vδ2 was consistent with the results of Wucherpfennig et al (17). Only one of the ten samples from normal brains showed evidence of a presence of γδ T cells. Sequence analysis of the junctional regions of amplified γδ TCR demonstrated clonal expansion only in one MS patient and in the normal control brain that contained γδ T cells, and the sequences differed between the cases. The occurrence of γδ T cells in MS lesions is undisputed. Their frequency and exact localization, whether they are more prominent in acute or chronic lesions, and the question of clonal expansion are, however, less clear. The differences in localization are probably due to differences in pathological staging and the limited pathological material available for studies. This might also explain the varying observations about the presence of γδ T cells in cerebrospinal fluid (CSF). No significant differences in the incidence of γδ T cells in the CSF were observed in one study comparing 18 MS patients with ten OND (20), whereas a second study reports the cultivation of γδ T cells from CSF only of recent-onset MS patients, but not chronic patients or controls (21). γδ T cells have been shown to lyse oligodendrocytes, fetal astrocytes and brain-derived microglia in vitro independent of hsp expression (M. Freedman, Montreal, see 22). Other investigators have argued, however, that oligodendrocytes are not necessarily destroyed in MS lesions and that recruitment of γδ T cells and expression of hsp are features of inflammation not specific for MS (H. Lassmann, Vienna, see 22). The potential role of γδ T cells specific for hsp in MS was the subject of a recent workshop, which has been reviewed (22).

The relationship between disease and the trimolecular complex raises numerous therapeutic possibilities, many of which have been tested and found effective in the EAE model. These include T cell vaccination (discussed later in this review), antibodies to MHC molecules, and peptides designed to bind to the MHC molecule that render the T cell unresponsive upon engagement. Consequently, there has been considerable interest in determining whether a similar relationship between T cell reactivity, TCR usage, and HLA makeup exists in MS. An evaluation of the results of the extensive efforts to examine frequency, HLA restriction and epitope specificity of MBP- or PLP-specific T cells from MS patients or healthy controls is beyond the scope of this review. However, most studies have demonstrated that MBP-specific T cells can be isolated from the peripheral blood of MS patients and healthy controls, and that the frequencies are similar or only slightly increased in MS. Several areas of the MBP molecule appear immunodominant in both patients and controls. Those areas also contain the major epitopes that are encephalitogenic in susceptible animals such as the 87-106 region, which is encephalitogenic in SJL mice, and the C-terminal portion, which contains the encephalitogenic region for non-human primates. HLA restriction studies have also provided similar results in patients and controls. The major restriction elements used, regardless of disease, are DR2, DR4 and DR6; each of these have been reported to be overrepresented in MS in various geographic regions. These findings indicate that if MBP-specific T cells contribute to disease, it is not based on higher frequencies, a unique reactivity or HLA restriction found only in MS patients. The focus therefore shifted from HLA and antigen to the TCR, the part of the trimolecular complex that is expressed on the effector cells. First attempts focused on the investigation of TCR on the germline level. In parallel, new technologies allowed a large scale investigation of TCR used by MBP-specific T cells and T cells present at the site of myelin destruction in the brain.
TCR GERMLINE POLYMORPHISMS

The known association of certain HLA haplotypes with susceptibility to MS and the potential role of T cells in the disease have led to speculations about possible disease-promoting TCR haplotypes. T cell receptors, unlike immunoglobulins, do not undergo somatic mutations, which has facilitated the study of haplotypes. This allowed the investigation and comparison of the germline TCR repertoires through an analysis of the length and pattern of restriction fragments generated by the digestion of genomic DNA with specific endonucleases. The presence of susceptibility gene(s) within the TCR Vβ locus was suggested by a study of 40 sibling pairs that were concordant for relapsing-remitting MS (23). One TCR Vβ haplotype was found to be significantly overrepresented in MS, while some other inherited haplotypes were found to be slightly increased. The haplotype sharing in unaffected siblings was random. Other investigators have examined 14 different Vβ subfamilies (Vβ1-14) and the constant region and have shown that all 15 loci were present in the TCR germlines of both MS patients and controls. However, a specific haplotype was found to be significantly overrepresented in MS patients. This overrepresentation was more pronounced when DR2-positive MS patients (84% in the study) were compared with DR2-positive normals (24). In an extension of this study, the Vβ15 region, which lies between Vβ11 and the constant region, was further characterized (25). An association could only be found with the Vβ8–Vβ11, but not the Vβ11–Vβ15 haplotype, excluding an influence of genes for the constant, junction or diversity regions. A recent study with 197 Caucasian controls and 83 Caucasian MS patients in the chronic progressive stage compared six restriction fragment length polymorphisms that spanned 600 kb of the TCR Vβ locus. Again, differences could only be found in a region spanning 175 kb and covering the area from Vβ8.1 to Vβ11 and only for DR2-positive individuals (26). These results suggest that a complementation between HLA class II gene(s) and TCR Vβ gene(s) might be necessary for susceptibility to MS. A study of 97 MS patients from Spain confirmed an association between MS and the TCR Vβ8 and Vβ11 loci (27). In contrast to these results, examination of the implicated loci at Vβ8, Vβ11 and Cβ in 100 Swedish MS patients, 23 suffering from chronic progressive and 77 from the relapsing-remitting form of the disease, and 100 control individuals failed to confirm a disease association even when the individuals were grouped according to their HLA or the clinical form of the disease (28). Also, a recent study of 48 twin pairs and 63 unrelated MS patients from France failed to identify significant differences in the TCR Vβ germline (29). Explanations for the disparity of TCR Vβ associations in MS are uncertain, but geographic differences in the populations studied could contribute.

Susceptibility genes within the TCR Vα locus have also been reported (30, 31). An investigation of Australian MS patients showed significant association between MS and Vα, but the strongest association was between MS and Cα (p < 0.001). The relative risk of a DR2-positive individual with a specific Cα haplotype was found to be 47. Subsequently, however, three independent research groups have reported a lack of any disease association (32–34). Hashimoto et al (32) found no increase in haplotype sharing in the affected siblings of 30 MS families. Hiltet et al (33) examined the previously reported Cα and Vα regions and concluded that germline genes for TCR α chains did not seem to contribute to susceptibility in MS. Lynch et al (34) studied TCR α chain gene restriction fragment length polymorphisms in 99 individuals from 14 multiplex families. Thirty-four individuals had definite MS, two had probable MS and six had abnormal cranial MRIs. The penetration ranges and LOD scores assuming either an autosomal recessive or a dominant model did not support a direct role of TCR α in the inheritance of MS.

The multigenetic nature of genetic predispositions in most autoimmune diseases could complicate the evaluation of single genetic linkages. The involvement of the TCR locus in MS susceptibility could be masked if mixed ethnic populations are studied, and a linkage with different TCR haplotypes in different populations that is not solely based on the HLA type could be possible. For a recent review of this topic see Robinson and Kindt (35).

RESTRICTION OF TCR USAGE IN MS

A surprising finding has been that in some animals susceptible for EAE encephalitogenic T cells use a restricted set of TCR. Acha-Orbea et al (36) showed that the vast majority of encephalitogenic MBP-specific T cells in PL/J or (PL/J × SIL) F1 mice recognize an N-terminal nonapeptide and use the same TCR Vβ (Vβ8) and TCR Vα (Vα2) chains. The T cell lines nevertheless represented distinct T cell clones with diverse D–J regions. Further, similar Vβ were used by encephalitogenic T cells from the rat, even though these T cells recognized a different epitope, MBP88–98 (37). These findings have raised the possibility that MBP-reactive T cells, if relevant to the disease process in MS, might also use restricted sets of genes in their TCR variable regions. If so, passive or active vaccination directed against those T cells could be used to slow the progression of disease.

The first study of oligoclonality of T cells in the CSF of MS patients was published in 1988 (38). Hafler et al (38) analyzed the TCR Vβ chains of 87 PHA-stimulated T cell clones generated from CSF and blood of two chronic progressive MS patients by Southern blot. Both patients showed recurring TCR rearrangements in T cell

clones derived from CSF and blood. One hundred fifty-three T cell clones from blood or CSF of three control individuals proved unique. As the study merely compared restriction patterns, no assumptions could be made about possible preferential use of a particular Vβ chain. Also, the antigen specificities of these T cell clones were not determined. In contrast, analysis of TCR gene rearrangements in T cells from the CSF of MS patients by Roteveel et al (39) did not reveal a restricted TCR usage.

In a subsequent study, the TCR Vβ usage in T cells with defined antigen specificities that were generated from five MS patients and five controls were compared (40). Seven of these ten individuals were HLA DR2-positive. The T cell lines analyzed recognized two immunodominant regions of MBP (residues 84–102 and 143–168). The majority of the T cell specific for MBP84–102 expressed Vβ17 and to a minor extent Vβ12. This observation was somewhat skewed by the fact that over 80% of the Vβ17-positive T cells had been generated from one individual. Nevertheless, Vβ17 was occurring in varying degrees in four of the five patients and in two of the five controls. T cells specific for MBP143–168 did not preferentially select Vβ17, but instead Vβ12 and Vβ14. A follow-up study by the same investigators found overrepresentation of Vβ12 in MS patients (41). Unfortunately, no Vβ17 analysis was included in this study (41). A different study attempted to characterize 38 MBP-specific CD4+ T cell lines from MS patients with a panel of monoclonal antibodies specific for TCR V regions. In only six of the 38 T cell lines was it possible to identify the TCR Vβ usage (42). Four of the six T cell lines came from one donor, were HLA DR2-restricted and used Vβ5.2, despite varying antigen specificities. The overrepresentation of Vβ5.2 and Vβ6.1 by MBP-specific T cell lines from MS patients as detected by Kozin et al (43) has not been confirmed by other groups (44–47). Ben-Nun et al (44) observed restriction of TCR usage in MBP-specific T cell lines within but not between individuals. Martin et al (45), Giegerich et al (46) and more recently Joshi et al (47) demonstrated that even T cells from the same individual with identical epitope specificity and HLA DR restriction can use different TCR Vα and Vβ chains. An overrepresentation of Vβ12 or Vβ17 by MBP-specific T cells has also not been confirmed.

With the differences in studies of TCR germline associations, disease and patient population heterogeneity could contribute to the diversity of results.

In a different approach, Oksenberg et al (48) gave priority to the localization of T cells rather than antigen specificity. The TCR of T cells present in brain lesions of MS patients with unknown antigen specificity were analyzed with 18 TCR Vα family-specific PCR primers. Only two to four TCR rearrangements were found in each case. The subsequent analysis of MS plaques with 21 TCR Vβ family-specific primers (49) revealed differences in rearrangement patterns dependent on the HLA phenotype of individuals. Examination of lesions from patients with the phenotype associated with MS (HLA class II: DRB1*1501, DQA1*0102, DQB1*0602) showed T cells with preferential expression of Vβ5, 6, 7, 8, and 12. Only Vβ5.2-positive transcripts were analyzed in more detail, because of the previously reported overrepresentation of Vβ5.2 in MBP-specific T cell lines from the blood of MS patients (43). Five motifs were identified based on the amino acid sequence of the hypervariable region 3 (CDR3), which is created through the rearrangement of genes for a variable, a diversity and a junctional segment. The motifs of Vβ5.2 transcripts isolated from the brain were compared to those of MBP-specific T cell lines. One motif showed some homology with a Vβ5.2-expressing T cell line isolated from a DR2-positive MS patient and specific for MBP87–106 (50). Interestingly, some homology with the CDR3 regions of encephalitogenic T cell lines from rat and mouse could also be identified. However, similarities were also seen with TCR of unrelated specificities, and the importance of a limited number of shared residues in one area of one TCR chain with respect to conferring antigen specificity is unclear. Therefore, the significance of this finding remains uncertain. A more detailed investigation of V region transcripts from MS lesions that additionally attempted to histologically define the areas from which the analyzed T cells were derived and to correlate the findings with lymphokine profiles detected no TCR restriction in active lesions but rather limited sets in chronic lesions (51). The question remains whether activated T cells found in MS plaques of different pathological stages comprise specifically recruited T cells with antigen specificities relevant for the disease. It also is not certain if MBP-specific T cells in the periphery play a role in the disease process. However, a study with monozygotic twin pairs discordant or concordant for MS has demonstrated that individuals affected with disease show a general skewing of their T cell repertoire when compared with their unaffected twin (52). This shift in the T cell repertoire is apparent not only after stimulation with MBP, but also irrelevant antigens such as tetanus toxoid. An impaired T cell regulatory mechanism caused by or initiating the disease course could permit recruitment of greater numbers of autoreactive T cells with multiple epitope specificities. Such epitope spreading has been observed in animal models for autoimmune disease (53–56). Preliminary results point in the same direction for MS (Utz et al, unpublished results). Therefore, a restriction of TCR usage in MS might only be detectable at the very onset of disease.

**TCR Vaccination**

Based on the assumption that, analogous to EAE, MBP-specific T cells would use a restricted set of TCR
genes, a therapy has been proposed that would target the TCR of MBP-specific T cells (57). The effectiveness of such therapies was first tested in the animal model EAE. In early studies (58, 59) animals were shown to be successfully protected against EAE by vaccination with inactivated T cells reactive for MBP. The vaccinations were given before induction of EAE. Only T cells specific for encephalitogenic determinants of MBP were protective (59). The discovery that rat and mouse TCR specific for the encephalitogenic determinant of MBP use similar Vα and Vβ chains even though MHC restriction and encephalitogenic determinants are different (37) raised the possibility that the TCR could be targeted directly. In humans, the same defined MBP-specific T cells could be identified at various times in individual patients (60), arguing that those TCR could be targeted during therapy. This observation does not eliminate the concern that the targets of TCR therapy might change during treatment (see epitope spreading). In EAE, the first therapy targeting the TCR attempted its neutralization with TCR Vβ-specific antibodies (61). The majority of MBP-specific T cells in the B10.PL mouse were positive for Vβ8.2 (84%), whereas the Vα usage proved less restricted. The treatment with Vβ8-specific antibodies reduced the incidence of EAE when administered before and led to a reversal of symptoms when administered after immunization of the animals. Prevention was not absolute, however, and animals that developed disease showed severity similar to untreated animals.

Based on a model by Claverie et al (62) that implicated an antibody-like structure for the T cell receptor, TCR peptides were designed that were predicted to be Vβ region-specific. Those peptides were derived from a hypervariable region of the TCR (termed CDR2) where the different V regions show greatest diversity. Vaccination with peptide TCR Vβ8.39–59 was shown to successfully prevent EAE in Lewis rats (63, 64). Vaccination with a peptide derived from another hypervariable region (termed CDR3) which is involved in antigen recognition also proved effective (64). Suggested mechanisms for protection were the induction of anti-T cell antibodies as well as T cells specific for encephalitogenic TCR (64, 66, 67). CD4+ T cells that recognize peptides derived from the TCR Vβ CDR2 and CDR3 regions of a MBP-specific T cell line have recently been described (68). However, these T cells did not recognize TCR Vβ-expressing T cells. This is not unexpected since CD4+ T cells generally recognize and lyse target cells presenting peptides from the environment and not peptides synthesized within the cell such as TCR. Thus, the role of these CD4+ TCR-specific T cells is unclear.

After initial promising results in animals, an extension of TCR peptide vaccination as a therapy of MS was undertaken. Based on earlier data about TCR Vβ usage in human MBP-specific T cell lines (43), Vandenbark proposed to use TCR peptides derived from the CDR2 regions of Vβ5.2 and Vβ6.1. Clinical studies using these peptides are now under way. Since binding motifs can vary between different HLA class I and II molecules, it is doubtful that any one peptide, such as one for the CDR2 region of a specific TCR, will be adequately presented to T cells in all individuals. This could substantially affect the success rate of this approach.

Since many studies have failed to identify a restricted TCR usage by MBP-specific T cell lines in humans or even rats (69, 70), other investigators have elected to immunize with whole inactivated T cells. Zhang et al (71) used MBP-reactive T cell clones generated from six patients with clinically definite MS for vaccination. The use of autologous T cell clones rather than TCR peptides circumvents a characterization of their TCR. The question of a possible restriction of TCR also becomes irrelevant through this approach. Zhang et al (71) demonstrated the presence of anti-clonotypic T cells in vaccinated individuals and, moreover, reported reduced precursor frequencies for MBP-specific T cells. Unfortunately, the effects of this treatment on the disease is not yet known. Whether the vaccinations will prove beneficial for the patients remains uncertain. The crucial point, however, remains that it is not known whether MBP is one of the autoantigens in MS.

ACTIVATION OF T CELLS

Rather than being due to the presence of a population of T cells with unique specificity, HLA restriction or TCR usage, MS could be due to an aberrant regulation of T cells specific for myelin proteins. The T cells found in MS lesions are activated and express IL-2 receptors (15). Activation is thought to be a prerequisite for the penetration of the blood–brain barrier. The specificity of these T cells is unknown. They could represent cytotoxic T cells that specifically recognize a myelin or other central nervous system antigen. They could also be specifically recruited T cells that cause tissue destruction by secretion of lymphokines such as TNF-α. Allegretta et al (72) demonstrated the first evidence that activated MBP-specific T cells are present in MS patients, but not in normal controls. Activation-induced proliferation leads to an accumulation of mutations over time that is absent in resting T cells. Thus, the mutations found in an indicator gene give a measure for the cell cycles a T cell has undergone. Allegretta et al (72) detected such mutations in MBP-specific T cells from MS patients, but not in MBP-specific T cells from control individuals. Further support for the hypothesis that MBP-reactive T cells may be activated in MS comes from studies of Zhang et al (73), who have reported increased precursor frequencies for MBP-specific T cells in MS patients when activated T cells are selected through initial culture with IL-2. Finally, demonstration of increased levels of various cytokines
including IFN-γ, TNF-α and GM-CSF in the CSF and serum of MS patients may argue for increased activation (20).

SUMMARY

Over the past several years considerable research has been directed at attempting to demonstrate a unique T cell reactivity in MS similar to that found in the initial induction phase of EAE. Although some studies have produced some intriguing results, evidence for a unique or restricted TCR usage in MS has not been persuasive. Some important aspects of the EAE model need consideration before conclusions are made about the role of myelin-reactive T cells in the pathogenesis of MS. First, activation of T cells is critical to disease induction in EAE. In the adoptive transfer model, an in vitro culture step is essential for the disease transfer. The critical event during this culture step is probably activation. Recent studies indicate that MBP-specific T cells can also be activated by the superantigen Staphylococcal enterotoxin B. This demonstrates that environmental factors can potentially substitute for autoantigens in supplying the signals necessary for the triggering of an autoimmune reaction. Additional evidence for the importance of activation is shown in animal models with autoreactive TCR transgenes. Autoreactive T cells, even when present in vast abundance and when the appropriate autoantigens and restriction molecules were supplied, did not induce autoimmune disease (74). Only when exposed to exogenous factors, and probably associated with inflammation, is autoimmune disease elicited in these animals. Although inconclusive, evolving evidence supports a role for T cell activation in MS as well.

The second aspect of EAE with particular relevance to MS is that while induction of EAE is clearly related to a T cell response to the respective immunodominant or encephalitogenic epitopes of MBP or PLP, as the disease progresses T cells with other specificities and TCR usage contribute. Consequently, it is not surprising that restricted TCR usage is not found in patients studied long after the onset of disease and with diverse genetic background. Current findings indicate that future research needs to focus more directly on the functional characteristics and state of activation of myelin protein-specific T cells. Further, events within the nervous system such as the expression of HLA and adhesion molecules also need more scrupulous attention.

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