Brief Definitive Report

T Cell Receptor (TCR) Usage Determines Disease Susceptibility In Experimental Autoimmune Encephalomyelitis: Studies with TCR Vβ 8.2 Transgenic Mice

By Vijay K. Kuchroo,* Mary Collins,‖ Ahmad Al-Sabbagh,* Raymond A. Sobel,¶ Matthew J. Whitters,‖ Scott S. Zamvil,* Martin E. Dorf,‡ David A. Hafler,* J. G. Seidman,‡ Howard L. Weiner,* and Ilonna J. Rimm§

*From the *Center for Neurological Diseases and the Department of Neurology, Harvard Medical School and Brigham and Women's Hospital; the ‡Departments of Pathology and Genetics, Harvard Medical School; the §Division of Pediatric Hematology/Oncology and Department of Pediatrics, Dana-Farber Cancer Institute, Children's Hospital and Harvard Medical School, Boston, Massachusetts 02115; ‖Genetics Institute, Cambridge, Massachusetts 02140; and the ¶Department of Pathology, Stanford University School of Medicine and Laboratory Service, Veterans Affairs Medical Center, Palo Alto, California 94304*

Summary

Experimental allergic encephalomyelitis (EAE) is an autoimmune disease that can be induced in laboratory animals by immunization with the major myelin proteins, myelin basic protein (MBP) and proteolipid protein (PLP). We analyzed the role of the T cell receptor (TCR) repertoire in susceptibility to EAE induced by these two autoantigens. Autoreactive T cells induced after immunization with MBP use a limited set of TCR. In contrast, we demonstrate that T cell clones that recognize the encephalitogenic PLP epitope (PLP 139-151) use diverse TCR genes. When the TCR repertoire is limited by introduction of a novel rearranged TCR Vβ 8.2 chain in transgenic SJL mice, EAE could be induced in the transgenic mice by immunization with the encephalitogenic epitopes of PLP, but not with the encephalitogenic epitope of MBP. Thus, skewing the TCR repertoire affects the susceptibility to EAE by immunization with MBP but not with PLP. These data demonstrate the biological consequences of the usage of a more diverse T cell repertoire in the development of an autoimmune disease.

Experimental autoimmune encephalomyelitis (EAE), an animal model of human multiple sclerosis (MS) (1), can be induced in laboratory animals by immunization with the major myelin proteins, myelin basic protein (MBP) or myelin proteolipid protein (PLP) (2, 3). The EAE that results from immunization with MBP is mediated by T cells that utilize limited sets of TCR (4–6). PLP, which constitutes the bulk of the myelin proteins in the central nervous system (CNS), is an equally important candidate antigen for MS. A panel of T cell clones specific for the encephalitogenic epitope of PLP 139-151 was recently isolated and characterized (7). Cloning and sequencing of the TCR genes reveals that diverse TCR α/β chains are used by these clones. We demonstrate the consequence of the diversity of TCR gene usage in response to PLP and MBP by analyzing the effect of skewing the TCR repertoire on the pathogenesis and susceptibility to EAE in SJL-TCR Vβ 8.2 transgenic mice.

Materials and Methods

Animals. Female SJL/J mice (4–8-wk-old) were from the Jackson Laboratory (Bar Harbor, ME). Transgenic mice were produced by injecting the TcR β chain construct (Vβ 8.2-Dβ 1.1-Jβ1.1-Cβ2) (8), derived from an OVA-specific T cell hybridoma, into the product of a (C57BL/6 × SJL)F_1 mating. The founder animal was backcrossed twice to SJL/J mice and the offspring were H-2 typed. The H-$2^{s/s}$ homozygotes were then backcrossed an additional four times to SJL/J mice. This strain was termed SJL transgenic and was maintained by backcrosses to SJL mice. In all experiments, nontransgenic mice were littermates of transgenic mice.

Antigens. Whole mouse myelin was prepared from the brains and spinal cords by the method of Norton and Poduslo (9). The MBP and PLP peptides used in the study were: MBP 89-101 (VHFFKNIVTPRTP), MBP 17-27 (TASTMDHARH), MBP 1-11 (ASQKRPSQRHG), MBP 35-47 (TGILDSIGRFFSG), PLP 139-151 (HSLGKWLGHPDKF), PLP 178-191 (NTWTTCQSIAFPSK), and PLP 103-116 (YKTTICGKGLSATV). Peptides were syn-

 J. Exp. Med. © The Rockefeller University Press • 0022-1007/94/05/1659/06 $2.00
Volume 179 May 1994 1659–1664

thesized in the laboratory of Dr. Richard Laursen (Boston University, Boston, MA) or by Hans Freisheim (Medical College of Ohio, Toledo, OH).

Antibodies. The following antibodies were used: anti-Vβ8.1 and 8.2 (KJ 16-133, obtained from Phillipa Marrack and John Kappler, National Jewish Center of Immunology and Respiratory Medicine, Denver, CO); anti-Vβ6 (46-6-B5, from Hans Hengartner, University of Zurich, Zurich, Switzerland); anti-Vβ4 (KT 10.4, from Dr. Robert Clark, University of Connecticut, Farmington, CT); anti-Vβ11 (RR 3-15, from Dr. Ed Palmer, National Jewish Center of Immunology and Respiratory Medicine); and anti-CD4 (GK 1.5, from Dr. Frank Fitch, University of Chicago, Chicago, IL).

T Cell Clones and Hybridomas. The five T cell clones used have been described (7). Hybridomas were prepared (10) from each of the clones and were used to isolate some TCR genes.

Cloning and Sequencing of TCR Genes. Full-length cDNA clones for TCRα from 5B6, 7A5, and 4E3 and for TCRβ from 7A5 and 4E3 were isolated from unamplified λZap (Stratagene, La Jolla, CA) libraries, and the DNA sequence of multiple clones were determined. The SPL1.1 TCRα was identified using inverse PCR (11) using two Cα primers. The full-length cDNA clone was then isolated by using a primer specific for the predicted Vα15 leader sequence (AAATTTGAATTCATGAAGACATCCCTTCACACTGTA) with 3′ Cα (AAATTTGAATTCAACTGGACCACAGCCTCA) primers. The 2E5 TCRα clone was identified by PCR using a degenerate Vα primer (12) and a Cα primer and independently cloned by PCR with the above Vα15 and Cα primers and sequenced. The 2E5 and SPL1.1 TCR β chains were isolated by PCR with a Vβ17a specific primer (ATGGGTGCAAGACTGCTCTGCTGTGTAGCA) or Vβ2 primer (ATGTGGCAGTTTTCCATTCTGTGCCTCTGC), and a 3′ Cβ (AAATTTGAATTCTGATGTTCTGTGTGACAGGT) primer. The 5B6 TCRβ clones were isolated by PCR using a degenerate Vβ oligonucleotide (13) and the 3′ Cβ primer; sequence of clones from a second PCR reaction with Vβ6 and Cβ primers confirmed that this was derived from a full-length transcript.

In Vitro Proliferation. Mice were immunized subcutaneously with 100 μg of PLP or MBP peptides in 0.1 ml of CFA containing 200 μg of heat killed *Mycobacterium tuberculosis* H37RA (Difco Laboratories, Detroit, MI). Cells from inguinal, prescapular, and paraaortic lymph nodes were dissociated and cultured at 5×10^5 cells/well with peptide in DMEM (GIBCO BRL, Gaithersburg, MD) containing 10% FCS in 96-well plates for 72 h and then pulsed with 1 μCi of [^{3}H]thymidine for 16–18 h. Mean thymidine incorporation from triplicate wells was calculated. Antibodies were used as culture supernatants for blocking studies.

EAE Studies. Mice were injected subcutaneously in the flank with 2 mg of whole mouse myelin or 50 or 70 nmol of peptide and 400 μg of *M. tuberculosis* H37Ra (Difco) in an emulsion consisting of equal volumes of water and CFA. Each mouse was also injected intravenously on day 0 and days 2, 3, or 4 with 10^9 heat killed *Bordetella pertussis* bacilli (Pertussis vaccine lot no 264; Massachusetts Public Health Biological Laboratories, Boston, MA) or 200 ng pertussis toxin (List Biological Laboratories, Inc., Campbell, CA). Clinical assessment was carried out daily as described (7).

Brains and spinal cords were removed and fixed in 10% phosphate-buffered formalin, and paraffin-embedded sections were stained for light microscopy. Histological disease was quantified by counting inflammatory foci in meninges and parenchyma (7). For evaluation of TCR Vβ expression in the tissues, the brains and samples of spleen and thymus were frozen in OCT compound (Miles Laboratories, Naperville, IL) and stored at −70°C. 4–6 μm-thick cryostat tissue sections were immunostained with undiluted anti-TCR Vβ hybridoma culture supernatants using avidin-biotin immunohistochemical staining kits (Vector Laboratories, Inc., Burlingame, CA).

Results and Discussion

We examined TCR usage in a panel of T cell clones specific for the encephalitogenic PLP epitope 139-151 (7). These PLP-specific T cell clones use a variety of TCR Vα, Jα and Vβ, Dβ, and Jβ segments (Fig. 1). Two of the T cell clones (2E5 and SPL1.1) used the same Vα15 segment in combination with different Jα segments, thereby creating diverse junctional regions. The Jα8 segment was used by clones SPL1.1 and 5B6 in combination with different Vα segments. The Vβ segments were all different, with only two of the clones using the same Jβ segment. A conserved junctional motif was not observed in the CDR3 region of the TCR α or β chains. In the TCR α chain, the threonine at position 2 within the conserved GXGT motif adjacent to the predicted CDR3 region, may be selected in that it is in four of the five sequences and is present in a minority (6/47) of germline Jα segments (14). Thus, a wider variety of the TCR genes is used in response to this PLP epitope than in response to encephalitogenic MBP epitopes. TCR β chain diversity has also been observed with two other encephalitogenic PLP epitopes in SJL (15) and in (PL/J × SJL)F_1 mice (Kuchroo, V. K., unpublished data).

The difference between the limited TCR diversity in response to MBP determinants and the diverse response for PLP epitopes could affect susceptibility to EAE induced by these two myelin autoantigens. One prediction would be that limitation of the TCR diversity would have a profound effect on the ability of MBP, but not PLP, to induce EAE. We examined the ability of encephalitogenic MBP and PLP epitopes to induce EAE in transgenic SJL mice containing a single rearranged TCR β chain transgene (8, 16). The transgene is expressed on >95% of peripheral T cells in the transgenic mice. This transgene, which is not specific for either MBP or PLP, was chosen because the TCR Vβ8.2 is deleted in

	Vα	Jα	TCRα JUNCTIONAL SEQUENCE	
2E5:	Vα15	Jα4	HITATQPEDSAIYFCA	ASPGANTG.KLT FGHGTILRVHPN
SPL:	Vα15	Jα8	HITATQPEDSAIYFCA	ASTGGNMGYKLT FGTGTSLLVDPN
5B6:	Vα4	Jα8	QKASVQESDSAVYFCA	L..VGSMGYKLT FGTGTSLLVDPN
7A5:	Vα13	Jα27	KKSPAHWSDSAKYFCA	L..EVSNTDKVV FGTGTRLQVSPN
4E3:	Vα11	Jα12	HIRDAQLEDSGTYFCA	VLYQGGRA..LI FGTGTTVSVSPN

	Vβ	Dβ	Jβ	TCRβ JUNCTIONAL SEQUENCE	
2E5:	Vβ17A	Dβ1	Jβ1.2	SSEEDDSALYLCAS	SLVRGNS.DYT FGSGTRLLVI
SPL:	Vβ2	Dβ2	Jβ2.5	VANMSQGRTLYCTC	SAVQGQD.TQY FGPGTRLLVL
5B6:	Vβ6	Dβ2	Jβ2.6	SAQKNEMAVFLCAS	SRGGRSSYEQY FGPGTRLTVL
7A5:	Vβ10	Dβ2	Jβ2.4	SVELEDSAVYLCAS	SHWGVQN.TLY FGAGTRLSVL
4E3:	Vβ16	Dβ2	Jβ2.5	PTALEDSAVYFCAS	SFGGLQD.TQY FGPGTRLLVL

Figure 1. Predicted amino acid sequence of V(D)J junctions of TCR α and β chains from PLP-peptide 139-151 specific T cell clones. Boxed residues correspond to predicted CDR3 regions (25). The asterisk marks the threonine residue that may be selected in TCRα. Assignments to V, D, and J segments are based on references (14, 26, 27). Sequence data are available from EMBL/GenBank/DDBJ under accession numbers (U07653–U07662).

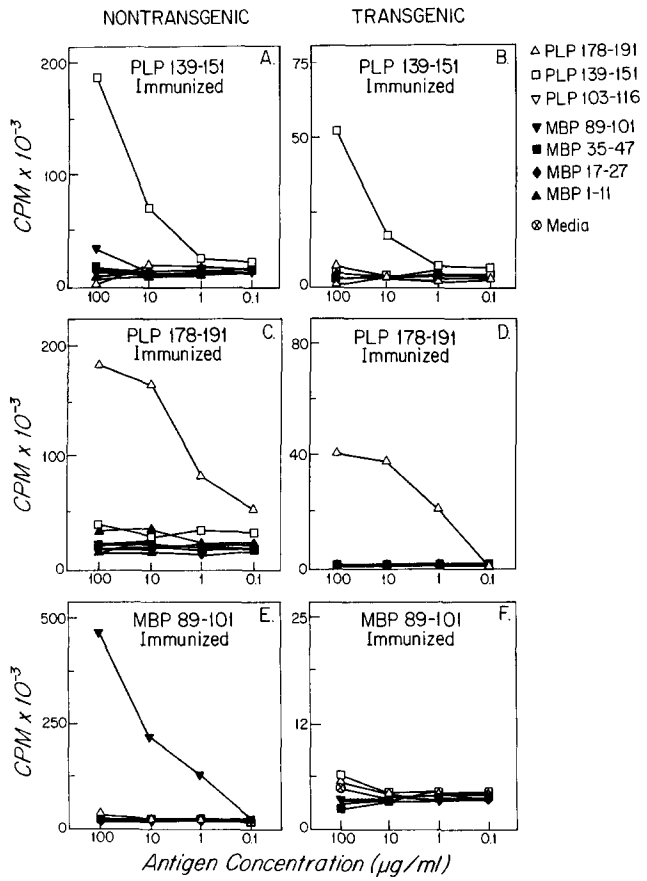
Table 1. *Clinical and Histological EAE Induction in SJL Transgenic and Nontransgenic Mice*

Antigen	Nontransgenic				Transgenic			
	Clinical incidence	Mean day of onset	Maximum clinical grade	Number of inflammatory foci	Clinical incidence	Mean day of onset	Maximum clinical grade	Number inflammatory foci
Mouse myelin	8/8	12.1 ± 0.8	3.9 ± 1.0	96	7/7	17.1 ± 4.5*	2.6 ± 1.0*	96
PLP 139-151	4/5	13.3 ± 2.1	3.8 ± 0.5	46	4/5	30.0 ± 10.5*	3.3 ± 1.3	98
PLP 178-191	4/5	12.3 ± 0.9	3.3 ± 1.5	62	4/6	14.3 ± 1.3	2.8 ± 1.5	70
MBP 89-101	6/7	16.2 ± 6.1	3.7 ± 1.2	45	0/7	-	-	0

The SJL transgenic and littermate mice were immunized subcutaneously with 2 mg of whole mouse myelin or 150 μg of the individual peptides emulsified in CFA, and pertussis toxin as described in Materials and Methods. Mice were assessed clinically according to following criteria: 0, no disease; 1, tail atony; 2, hind limb weakness and/or poor righting ability; 3, hind limb paralysis; 4, hind- and fore-limb paralysis; 5, moribund. Mice showing clinical signs were killed at the peak of the disease and paraffin-embedded sections were stained with Luxol fast blue–hematoxylin and eosin for light microscopy. Disease induction was confirmed and quantified histologically by counting the number of inflammatory foci in the white matter in representative mice in each group. Animals were killed within 7–10 d of the initial appearance of clinical signs or at the peak of the disease. Mice that show no clinical signs were killed 40 d after immunization.
The data are presented as mean ± SE. (*) Significant difference ($p < 0.04$–$p < 0.008$) when compared with values obtained with nontransgenic littermates by Student's t test.

SJL mice (17) and the T cell response to MBP is mediated by Vβ8.2 in other mouse strains and in Lewis rats (4–6).

The transgenic mice and the nontransgenic controls that were immunized with either mouse myelin or encephalitogenic PLP peptides 139-151 or 178-191 developed clinical EAE, although the disease occurred earlier and appeared to be more severe in the nontransgenic littermates (Table 1). At the peak of the disease, however, both groups had similar numbers



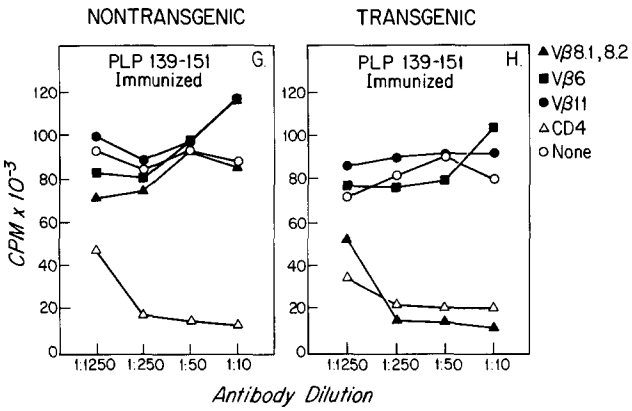


Figure 2. In vitro proliferative response of lymph node cells from SJL transgenic and nontransgenic mice to the encephalitogenic PLP and MBP peptides. (*A–F*) Lymph node cells were isolated from mice immunized 10–12 d earlier with PLP or MBP peptides in CFA and tested with peptides at the indicated concentrations. Proliferative responses were measured as described in Materials and Methods. Data from one of the three experiments is shown. (*G* and *H*) Lymph node cells were isolated as for *A–F*, incubated with 100 μg of PLP 139-151, and the indicated concentrations of anti-TCR Vβ and anti-CD4 antibodies, and proliferation was measured.

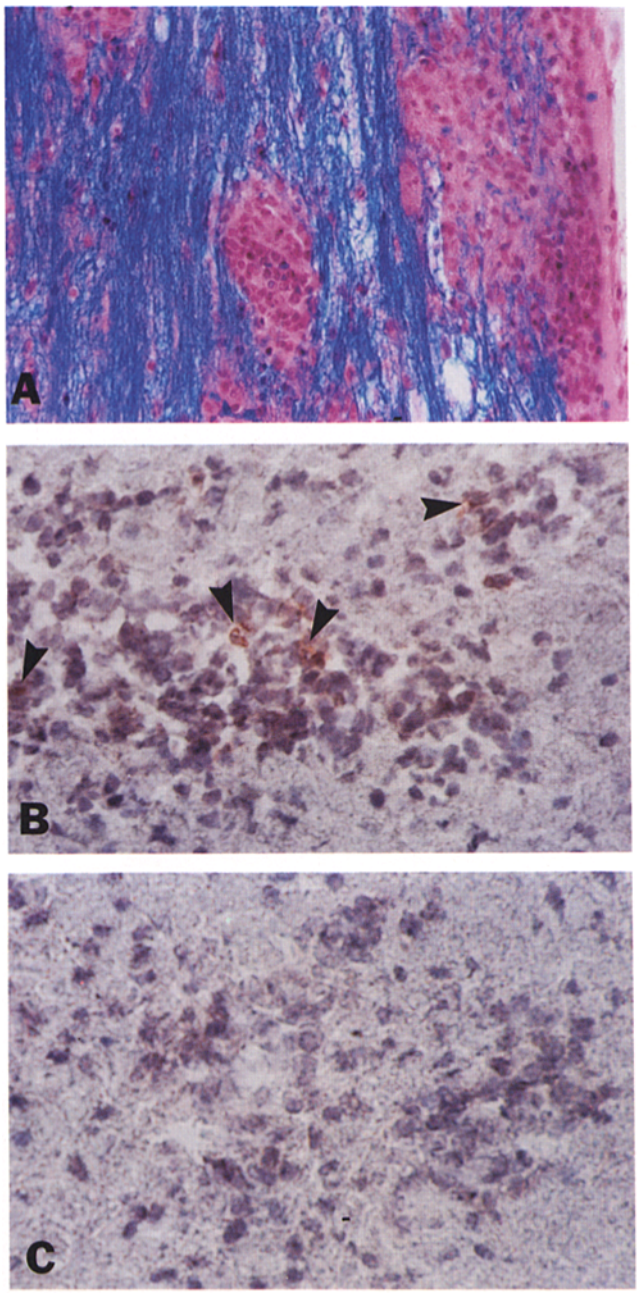


Figure 3. Transgenic and nontransgenic mice were immunized with PLP-peptide 139-151 in CFA. Brains, spinal cords, and lymphoid tissues were obtained at the peak of the disease for histopathological and immunohistochemical analysis. (*A*) Typical perivascular mononuclear cell infiltrate in a paraffin section of the spinal cord of a transgenic mouse immunized with PLP 139-151. Demyelination is indicated by pink staining, whereas intact white matter myelin is stained blue. Luxol fast blue-hematoxylin and eosin. ×218. (*B*) Numerous TCR Vβ 8$^+$ cells (*arrowheads*) in an acute EAE lesion in the brain of a Vβ8 transgenic SJL mouse. Cryostat section, mAb KJ 16-133 immunoperoxidase with hematoxylin. ×340. (*C*) Section adjacent to B stained with anti-TCR Vβ4 antibody. Cryostat section antiVβ4 with hematoxylin. ×340.

of inflammatory lesions (Table 1). In contrast, immunization with the dominant encephalitogenic MBP epitope 89-101 did not result in EAE in the transgenic mice, whereas the nontransgenic control mice developed typical EAE (Table 1). These results show that limitation of the TCR β chain diversity to a single β chain gene results in loss of susceptibility to disease induction by the dominant MBP epitope but not by either of the PLP epitopes.

The difference in susceptibility to EAE suggested that both PLP peptides elicited encephalitogenic T cell responses in the transgenic mice, but that the dominant MBP determinant did not. We examined in vitro proliferation of lymph node T cells in response to the encephalitogenic determinants of MBP and PLP. Lymph node cells from mice immunized with PLP peptide proliferated in response to the immunizing PLP peptide, but not to other control PLP or MBP peptides. However, the proliferative responses of the lymph node cells isolated from the transgenic mice were reduced by a factor of three to four compared with those from nontransgenic controls (Fig. 2, *A–D*). In contrast, little or no proliferative response was detected in lymph node cells isolated from transgenic mice immunized with MBP 89-101, despite the strong proliferative response observed in lymph node cells from nontransgenic littermates (Fig. 2, *E* and *F*). Thus, the transgenic mice appear to be unable to develop a proliferative T cell response to the dominant MBP determinant 89-101. TCR-β transgenic mice are unable to recognize some peptides (18) probably because of limitation in the available TCR repertoire. This may account for the lack of T cell response and the lack of disease in transgenic mice immunized with MBP 89-101.

Non-Vβ8$^+$ T cells, which constitute <5% of the total T cell pool in the transgenic mice (8), could be responsible for the induction of EAE with the encephalitogenic PLP determinants. The proliferative responses of lymph node cells from transgenic and nontransgenic littermate mice immunized with PLP 139-151 were examined in the presence of anti-Vβ8 (KJ16) mAb. The anti-Vβ8 mAb blocked the PLP 139-151 specific proliferative response of lymph node cells from transgenic mice, but not the response of lymph node cells from nontransgenic mice. Antibodies to other TCR Vβ chains (Vβ 4, 6, and 11) did not inhibit the proliferation of transgenic lymph node cells in response to PLP 139-151 (Fig. 2, *G* and *H*). By immunohistochemistry, the vast majority of the T cells in the lymphoid tissue from the transgenic mice expressed Vβ 8 (~95–99%) with rare, scattered cells expressing some of the other TCR Vβ (Vβ4 and Vβ6). In contrast, lymphoid tissues from the nontransgenic littermates were totally devoid of Vβ8-bearing cells and expressed larger numbers of TCR Vβ4, Vβ6, and other TCR Vβs (data not shown). Immunocytochemical staining of the inflammatory lesions in the CNS of the transgenic mice demonstrated the presence of Vβ8$^+$ cells and virtually no other Vβ-bearing T cells (Fig. 3, *B* and *C*). Consistent with previous results (19), the T cells constituted ~30% of the total inflammatory cell population in the EAE lesions, which corresponded to the number of Vβ8$^+$ cells detected in the EAE lesions of the transgenic mice (Fig. 3 *B*). In contrast, in the nontransgenic control mice (which lack Vβ8), accumulation of T cells expressing various TCR Vβs (Vβ 2, 4, 6, 7, and 14) was seen in the infiltrates, but no TCR Vβ8-bearing cells were detected (data not shown).

Analyses of TCR usage by MBP-specific T cell clones in mice, rats, and humans have suggested a restricted TCR Vβ usage (4–6, 20, 21). Both mouse and rat MBP-specific encephalitogenic T cell clones use the same Vβ gene segment (Vβ8.2). The "V-region disease hypothesis" (22) proposed that TCR Vβ8.2 in association with a specific TCR Vα may recognize a ligand in the CNS and induce EAE. SJL mice do not express a Vβ8.2 gene segment (17), but introduction of a Vβ8.2 transgene into the SJL T cell repertoire provided us with a unique opportunity to test the role of this V gene in the induction of EAE. Overexpression of a Vβ8.2 transgene in SJL mice did not permit an immune response to MBP 89-101 (Fig. 2 *F*) or development of EAE (Table 1). The T cell response to MBP 89-101 is largely mediated by Vβ17a- and Vβ4-bearing cells (23, 24). Limitation of the TCR β chain repertoire to a single rearranged β chain does not permit development of an immune response to this encephalitogenic MBP epitope. In contrast, the severe limitation on TCR β chain diversity does not prevent a T cell response to encephalitogenic PLP epitopes or the induction of EAE in a susceptible mouse strain. T cells using the novel rearranged TCR β chain are therefore able to recognize the encephalitogenic PLP epitopes and induce EAE. Although the autoantigen(s) involved in MS has not been identified, PLP could be involved in pathogenesis of MS. Our data would suggest that T cell responses to PLP epitopes may differ from those to MBP epitopes and that this finding should be considered in the design of TCR-based therapies for MS.

We thank M. B. Lees, J. M. Greer, A. Abbas, and L. Glimcher for careful reading of the manuscript; Mr. Deepak Kaul and Mr. David Fruman for technical assistance; and Kerry Kelleher for DNA sequencing.

This work was supported by grants from the National Multiple Sclerosis Society, N.Y. (RG 2751-A-2, RG 2582-A-1), the National Institutes of Health (NS-30843, NS-29352, NS-26773), the American Heart Association, the American Cancer Society, the Howard Hughes Medical Institute, and the Genetics Institute (M. Collins, M. J. Whitters). I. J. Rimm is a Claudia Adams Barr Investigator.

Address correspondence to Dr. Mary Collins, Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140.

Received for publication 12 January 1994 and in revised form 28 February 1994.

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