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*J Immunol* 1998; 161:2052-2059; ;
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T cells infiltrating the iris/ciliary body of Lewis rats with anterior uveitis (AU) that had been induced by myelin basic protein (MBP) immunization were previously found to share surface markers common to the T cells that cause experimental autoimmune encephalomyelitis (EAE). To determine whether these AU-associated T cells are in fact the same as those that infiltrate the central nervous system to cause EAE, we examined TCR V gene expression in T cells infiltrating the anterior chamber in rats with AU. As with EAE, we found a biased expression of VB8.2 and Vα2 in the iris/ciliary body and, although one would expect an influx of nonspecific inflammatory T cells, these biases were still evident at the peak of AU. An analysis of the TCR VB8.2 and Vα2 sequences derived from the iris/ciliary body demonstrated the presence of the same complementarity determining region 3 motifs found in MBP-specific T cells that are pathogenic for EAE and found in T cells derived from the central nervous system of rats with EAE. Finally, T cells isolated from the iris/ciliary body of rats with AU were found to proliferate in a specific fashion to MBP Ags. Thus, it appears that MBP-specific T cells are pathogenic for AU as well as EAE in the Lewis rat. In addition, the long-term presence of this highly restricted MBP response in the iris/ciliary body indicates that distinct immunoregulatory mechanisms exist in the environment of the eye. This provides an interesting model with which to address questions pertaining to the nature of T cells infiltrating the eye and their regulation during EAE and other systemic diseases. The Journal of Immunology, 1998, 161: 2052–2059.

Uveitis is an intraocular inflammatory disease, and most cases are of unknown etiology. However, ~50% of uveitis cases are known to be associated with underlying systemic diseases such as diabetes, sarcoidosis, rheumatoid arthritis, Vogt-Koyanagi-Harada disease, Behçet’s disease, multiple sclerosis (MS), and others (1–3). In uveitis, inflammatory cells attack the uvea, which consists of the iris, ciliary body, and choroid; these cells appear to be initiated by an autoimmune process. Neighboring tissues such as the retina and vitreous are also often affected. The most common form of uveitis is anterior uveitis (AU), which is characterized by an accumulation of inflammatory cells in the iris and trabecular meshwork, with cells sometimes found within the ciliary body (4, 5). AU has been found to precede, to be concurrent with, or to occur following various systemic diseases (1, 6–9).

An experimental model for AU has been developed in the Lewis rat. Lewis rats that are immunized with myelin basic protein (MBP) develop experimental autoimmune encephalomyelitis (EAE), an inflammatory disease of the central nervous system (CNS) that is characterized by ascending limb paralysis and perivascular lesions in the brain and spinal cord. Recent studies (4, 5, 10) have demonstrated that AU often develops in Lewis rats with EAE, thus providing a model system with which to study the association between AU and a systemic disease. The target autoantigens in EAE and possibly AU consist of the myelinated neurons found within the CNS and the iris, respectively. EAE is often referred to as a model for the human paralytic disease MS. Although AU is not the most common form of eye inflammation associated with MS, the incidence of uveitis in MS is higher than in the general population, varying from 2.7 to 27% depending upon the MS population and the criteria of diagnosis (11). Recently, AU has specifically been identified in a number of MS cases (8, 9, 12).

Encephalitogenic T cells that infiltrate the CNS have been characterized as CD4+ , MHC class II-restricted cells that secrete lymphokines of the Th1 subset (13, 14). T cell lines and clones that recognize the immunodominant MBP epitope at residues 72–89 have been isolated from rats with EAE, and many demonstrate biased expression of the TCR VB8.2 and Vα2 genes (15, 16). In a recent report, phenotyping inflammatory infiltrates isolated from the iris/ciliary body of MBP-immunized rats with AU demonstrated TCR VB8.2 expression on ~30% of total CD4+ T cells (4). In addition, similar to what has been reported in the spinal cord of rats with EAE, the activation marker OX-40 was expressed on 17% of total CD4+ T cells that were isolated from the iris/ciliary body of rats with AU (4).

EAE-associated AU can be induced by immunization with guinea pig MBP as well as with the MBP peptides 71–90 or 87–99 (4, 5). Immunization with adjuvant alone has failed to induce AU, indicating that this disease is triggered by specific Ag (4, 5). In addition, AU can also be induced by passive immunization with
MBP-specific T cells (4, 5). The kinetics of AU appears to differ from that of EAE. The onset of AU as determined by histologic assessment coincided with the onset of EAE at day 11 after MBP immunization (4). However, while clinical symptoms of EAE and inflammation in the spinal cord peaked at days 13 to 14, inflammation in the anterior segment of the eye peaked later at day 18 (EAE recovery). In a separate report, AU was found to appear after recovery from MBP-induced paralysis (5).

In recent studies, we have analyzed the TCR V region genes encoding the AgR on T cells that infiltrate the spinal cord of MBP-immunized rats at the onset of EAE (17–19). Consistent with other studies (20, 21), the Vβ8.2 gene was highly expressed in the spinal cord at EAE onset, as were EAE-associated Vβ8.2 complementarity determining region 3 (CDR3) motifs. The biased expression of three Vα genes at EAE onset was also recently demonstrated. In agreement with other studies (15, 16), Vα2 expression was overused, but an increased expression of Vα1 and Vα23 in spinal cord T cells relative to T cells that had been derived from the lymph nodes (LN) of the same animals was also noted (19). Finally, the presence of a Vα CDR3 motif associated with the spinal cord-infiltrating T cell population was detected (19). It has been proposed that the CDR3 loops of the TCR Vα and Vβ chains interact with peptide Ag presented by MHC molecules (22–25). Thus, the presence of conserved CDR3 motifs are likely to be highly significant to T cell recognition and the specificity of the T cells responsible for autoimmune pathogenesis.

Our present study addresses, at the molecular and functional level, the question of whether T cells infiltrating the iris in AU are the same as those that infiltrate the CNS to cause EAE. We demonstrate here that the T cells isolated from the iris/ciliary body of rats with AU present TCR Vα and Vβ gene profiles that are very similar to those of T cells isolated from the spinal cord of rats with EAE. Moreover, the TCR Vα and Vβ CDR3 regions of iris/ciliary body-derived T cells bear motifs that are identical with those described for MBP-specific T cell clones and with those found in TCR sequences derived from the CNS of rats with EAE. Finally, the T cell lines generated from the iris/ciliary body-derived T cells of rats with AU were found to proliferate in a specific response to MBP Ags. The significance of these findings and their importance to immunoregulatory mechanisms are discussed.

Materials and Methods

Animals

Female Lewis rats (6–8 wk of age) were used in groups of three to four animals per experimental timepoint and were obtained from Harlan Sprague-Dawley (Indianapolis, IN). The animals were housed and cared for in the Animal Resource Facility at the Portland Veterans Affairs Medical Center according to institutional and federal guidelines.

Induction of EAE and AU

Active EAE was induced by a s.c. injection in the footpad with 25 μg guinea pig MBP in CFA containing 150 μg Mycobacterium tuberculosis strain H37Ra (Difco Laboratories, Detroit, MI). Animals were monitored daily for clinical signs of EAE and AU. Rats developing EAE were scored using the following scale: 0 = no clinical signs; 1 = limp tai; 2 = hind limb weakness; 3 = paraplegia; and 4 = paraplegia with forelimb weakness, moribund condition. Rats developing AU were evaluated clinically by an independent observer using biomicroscopy. Clinical observations were graded on a scale of 0 to 3 based on the following criteria: 0 = no inflammation; 0.5 = mild dilation of iris vessels and/or flare in the anterior chamber; 1 = cells in the anterior chamber; 2 = infiltrates present in <50% of the surface of the iris, fibrin in the anterior chamber; and 3 = infiltrates present in >50% of the surface of the iris.

Isolation of T lymphocytes

T cells were recovered from the iris/ciliary body under sterile conditions by removal of the eye and microdissection to obtain the anterior segment, as described previously (4). The iris/ciliary body was placed into RPMI 1640 plus 10% FBS containing 200 U/ml collagenase and incubated at 37°C for 2 h. A single-cell suspension was obtained by passage through a nylon filter followed by two washings with RPMI 1640 medium. LN T cells were isolated as described previously (26).

Tissue isolation

For the isolation of whole tissue, the iris/ciliary body was recovered as described above, and the spinal cord was removed by insufflation as described previously (27). Tissue samples were quick-frozen and stored at −80°C before RNA isolation.

Lymphocyte proliferation assay

T cells that had been freshly obtained from the inflamed eyes were pooled and resuspended in RPMI 1640 medium containing 10% FBS and plated at a density of 5 × 10^5/ml. Irradiated rat thymocytes at a density of 5 × 10^5 cells/ml and 100 μg/ml of MBP were added. After stimulation for 3 days, cells were centrifuged and resuspended in RPMI 1640/10% FBS containing human rIL-2 (Boehringer Mannheim, Indianapolis, IN) for 7 days. For the proliferation assay, T cells were plated in RPMI 1640/10% FBS at a density of 1 × 10^5 cells/well in the presence of 1 × 10^5 irradiated thymocytes/well. Con A, 10 μg of MBP or MBP peptides, or RPMI 1640 medium as a control were also added to each well. Wells were done in duplicate. Cultures were incubated for 72 h at 37°C and 5% CO2 and then pulsed with 1 μCi of tritiated thymidine for an additional 16 h. Cells were harvested onto glass fiber filters, and thymidine uptake was assessed by liquid scintillation counting. Stimulation indices (SIs) of ≥2 were considered positive, whereas SIs of <2 were negative. Since duplicate wells were used, statistical tests were not applied to the results.

RT-PCR analysis of TCR V gene expression

For the sequencing of the Vβ8.2 chain, cDNA was first amplified with a 5′ Vβ8-specific primer, Vβ8ascII, and a 3′ C region primer, RCβ-E (29), for 35 cycles. PCR products were diluted to 1/1000 or to 1/1000, and 2 μl was used in a second amplification with an internal primer that was specific for Vβ8.2 and the Cβ region primer RCβ-I for 32 cycles. A total of 0.5 μl of the amplified product was ligated into the pCR II vector and used to transform OneShot competent cells (Invitrogen, San Diego, CA). Carbenicillin-resistant colonies were screened directly by boiling in 30 μl of water for 5 min and using 10 μl of the supernatant in an amplification reaction with RVβ8.2 and RCβ-I. PCR products of the expected sizes were detected by separation in a 2% agarose gel. Plasmid DNA was isolated using an alkaline lysis/polyethylene glycol precipitation procedure. Cloned TCRβ8.2 genes were sequenced on an ABI automated sequencer (Applied Biosystems, Foster City, CA) that was operated at the Portland Veterans Affairs Medical Center Core Sequencing Facility, using RCβ-I as the sequencing primer.

The sequencing of the Vα2 chain was performed in a similar manner using the rat Vα2 region primer RVα2 EcoO (5′-GAGCAATTCCATGCGT CAGCAGGTCAACAAAC3′), and the Cα region primer Ca2-E (19). Transformed bacterial colonies were screened by PCR using internal primers Rvα2 and RCα-E (19) and were sequenced using RCα-E. The TCR residue numbering system of Kabat et al. (30) was used.

Results

Induction of EAE and AU

Lewis rats immunized with MBP/CFA developed classical monophasic EAE. The onset of both EAE and AU was observed on days 10 to 11 postimmunization. AU was mild and restricted to
the anterior segment, with maximum severity observed on days 17 to 18. EAE peaked on days 13 to 14, and rats were in recovery from EAE by day 18.

**TCR Vα and Vβ gene expression of iris/ciliary body- and spinal cord-infiltrating T cells**

We examined the TCR V gene usage of the T cells infiltrating the iris/ciliary body at an early timepoint (day 15 postimmunization: AU score = 1.5; EAE score = 2.25) and at the peak of AU (day 18: AU score = 2.5; EAE score = 0). For day 15, RNA was obtained from a total yield of $1.3 \times 10^6$ T cells, isolated, and pooled from the iris/ciliary body of 20 rats (40 eyes). Since V gene profiles from isolated T cells and tissue were fully comparable and fewer animals were required when using iris/ciliary body tissue, RNA from day 18 iris/ciliary body tissue was used for RT-PCR analysis, as was RNA from day 14 and day 18 spinal cord tissue. Vβ analysis of day 15 iris/ciliary body T cells demonstrated a pronounced bias (38%) for Vβ8.2 expression (Fig. 1A). This level of Vβ8.2 expression was at least comparable with what we have observed previously in T cells isolated from the spinal cord at EAE onset (day 12 after immunization with guinea pig MBP) (17, 31).

Unlike Vβ8.2 expression in the spinal cord at the peak of EAE (13%, day 14, Fig. 1A), Vβ8.2 expression in the iris/ciliary body was still significantly elevated at day 18, which was the peak of AU (28%, Fig. 1B) (31). Vβ8.2 expression in the spinal cord at day 18 was more elevated than at day 14, which is consistent with what we have seen previously in late recovery from EAE (31).

**Vα expression of T cells**

Expression of T cells infiltrating the iris/ciliary body and spinal cord were also examined at the two different timepoints. Both the day 15 (Fig. 2A) and the day 18 (Fig. 2B) iris/ciliary body did not present a clear-cut bias for the expression of a single Vα gene, but there appeared to be elevated levels of Vα1, Vα2, Vα10, and Vα11 expression. Since the expression of Vα1, Vα10, and Vα11 was also elevated in the periphery, i.e., in the LN (Vα1, Vα10, and Vα11) (19) and in splenic T cells (Vα1 and Vα10, Fig. 2B), an overexpression of these Vαs may not be specifically related to the induction of AU. Vα2 overexpression, on the other hand, appeared to be specific to the iris/ciliary body and spinal cord during disease (Fig. 2A and B (19)). Thus, for the subsequent sequencing analysis of the Vα CDR3 regions described below, we focused on the Vα2 genes that are expressed in the T cells infiltrating the iris/ciliary body in rats with AU.
EAE-specific Vβ8.2 CDR3 motifs are associated with iris/ciliary body-infiltrating T cells

The T cells infiltrating the iris/ciliary body in rats with AU appeared to possess a phenotype that was similar to that of the MBP-specific, pathogenic T cells that cause EAE. T cells from the iris/ciliary body were found to be surface positive for CD4 and Vβ8.2 (4), and we found that these cells also had increased specific expression of Vα2. Next, we examined the CDR3 regions of these T cells at the sequence level to look for similarities to MBP-specific T cells. Figure 3, A and B, presents the Vβ8.2-associated CDR3 sequences obtained from the iris/ciliary body on days 14 (peak of EAE) and 18 (peak of AU) after MBP immunization, respectively. With the exception of two sequences from the day 18 group, all of the Vβ8.2 sequences from the iris/ciliary body (11 sequences from day 14 and 9 sequences from day 18) contained one of two previously described Vβ CDR3 motifs (Asp<sub>96</sub>Ser<sub>97</sub> or X<sub>96</sub>Ser<sub>97</sub>) associated with EAE (29, 32).

The Asp<sub>96</sub>Ser<sub>97</sub> and X<sub>96</sub>Ser<sub>97</sub> motifs have been detected previously in a number of MBP-specific, Vβ8.2<sup>+</sup> rat T cell clones that can passively transfer EAE (29, 32). We have also found that both of these motifs are abundant in Vβ8.2<sup>+</sup> sequences from spinal cord-infiltrating T cells isolated at the onset of EAE (17). In addition, although the EAE motifs are limited to amino acid positions 96 and 97, there appears to be a preferential use of certain Jβ segments that also contribute to the CDR3 loop (17). Interestingly, use of the same Jβ gene segments (Jβ1.3 and Jβ2.7) was also biased in iris/ciliary body T cells from rats with AU (Fig. 3). As a control, we obtained the Vβ8.2 sequences of LN T cells from the same rats at days 14 and 18. As seen in Figure 4, A and B, only 7 sequences were found to contain either the Asp<sub>96</sub>Ser<sub>97</sub> or the X<sub>96</sub>Ser<sub>97</sub> motif out of a total of 24 sequences obtained for both days. Jβ gene usage was also much less restricted in the LN sequences.

An EAE-specific Va2 CDR3 motif is associated with iris/ciliary body-infiltrating T cells

As Vα2 expression appeared to be specifically elevated in the iris/ciliary body-infiltrating T cells, we examined the Va2-associated CDR3 sequences obtained on days 14 and 18 (Fig. 5, A and B, respectively). As we found with the Vβ8.2 sequences above, most of the Va2 sequences from the iris/ciliary body contained a CDR3 motif that we previously described to be associated with Vα sequences from spinal cord T cells at EAE onset (19). We have also found that the N<sup>3</sup> motif is present in MBP-specific, encephalitogenic T cell clones (19). In contrast, the N<sup>3</sup> motif was not found in any of the 20 control Va2 sequences obtained from LN T cells at days 14 and 18 (Fig. 6, A and B, respectively). In our previous study of Va2 expression in EAE, two different Va2 genes, C14Va2 and 510Va2, were found to be equally expressed in the spinal cord-infiltrating T cell population (19). Similar results were found for the Va2 sequences from the LN T cell population of rats with AU (Fig. 6, A and B). Interestingly, this was not the case for Va2 sequences from the iris/ciliary body (Fig. 5, A and B), where we observed a notable preference for C14Va2 gene expression over that of the 510Va2 gene. However, in a separate experiment, Va2<sup>+</sup> sequences from T cells infiltrating the iris/ciliary body of rats with AU demonstrated the presence of 510Va2 sequences bearing the N<sup>3</sup> CDR3 motif (data not shown).

MBP-specific proliferation of T cells from the iris/ciliary body

A total of 1 × 10<sup>7</sup> T cells were isolated and pooled from the iris/ciliary body tissue of 30 rats at the peak of AU, and 5 × 10<sup>6</sup> T cells were placed into culture. After an initial 3-day stimulation with MBP Ag and APCs followed by a resting period, T cells were tested for the ability to proliferate to MBP and MBP peptides. As demonstrated in Figure 7, T cells isolated from the iris/ciliary body responded specifically to whole MBP and to the dominant encephalitogenic MBP peptide 72–89. However, no response was observed to MBP peptides 55–69 (SI = 1.43x) and 87–99 (SI < 0.45x). As expected, strong proliferative responses were observed in the presence of Con A (SI = 60.1x, data not shown).

A. Day 14

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B. Day 18

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FIGURE 3. Amino acid sequences of the Vβ8.2<sup>+</sup> CDR3 region of T cells infiltrating the iris/ciliary body of Lewis rats with AU. Sequences are shown from day 14 (A) vs day 18 (B) iris/ciliary body tissue after MBP immunization and are subgrouped according to the presence of the EAE-associated D<sub>96</sub>S<sub>97</sub> motif, the X<sub>96</sub>S<sub>97</sub> motif, or no motif.
Discussion

Our analysis of the T cells infiltrating the anterior segment of the eye in rats with MBP-induced AU demonstrates that this population is very similar to the T cells infiltrating the CNS in MBP-induced EAE. Not only did the T cells obtained from the iris/ciliary body demonstrate the same biases in V gene expression and the presence of EAE-associated TCR α- and β-chain CDR3 motifs, but they also proliferated in a specific fashion to MBP Ags. The myelination of sensory fibers in the iris that originate from the trigeminal nerve has been documented in an electron microscopic study by Huhtala (33). Thus, in the current work, we present data supporting a target-directed (i.e., MBP-specific) mechanism in this experimental model of uveitis.

It is not clear whether the myelinated nerves of the iris are more closely representative of peripheral nerves or whether they share more similarity with myelination in the CNS. MBP is expressed as different protein isoforms in both the CNS and peripheral nerves (34, 35). However, the different isoforms are present in varying amounts in the CNS vs the periphery. For example, the 18.5-kDa form of MBP constitutes 2 to 16% of myelin protein in peripheral nerves, but is the induced EAE. Not only did the T cells obtained from the iris/ciliary body demonstrate the same biases in V gene expression and the presence of EAE-associated TCR α- and β-chain CDR3 motifs, but they also proliferated in a specific fashion to MBP Ags. The myelination of sensory fibers in the iris that originate from the trigeminal nerve has been documented in an electron microscopic study by Huhtala (33). Thus, in the current work, we present data supporting a target-directed (i.e., MBP-specific) mechanism in this experimental model of uveitis.

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immunization with several retinal Ags, including interphotoreceptor retinoid-binding protein and S-Ag (38, 39). Interestingly, biased Vβ8+ gene expression has also been correlated with autoimmune pathology in this model (40, 41). However, the CDR3 sequences associated with the Vβ8.2 response to S-Ag did not contain EAU/AU-associated CDR3 motifs (42). Thus, although Vβ8.2 may be used in several autoimmune responses, the conserved CDR3 sequences that are specific to the T cells inducing AU and EAE suggest that these are Ag-directed responses.

Given the similarities described in the T cells infiltrating the iris/ciliary body and the CNS as well as similarities in pathology, it appears that AU and EAE share a common effector mechanism. In EAE, there is a breakdown of the blood-brain barrier and a cellular infiltrate accompanied by perivascular lesions in the white matter. AU is also characterized by cellular infiltration and perivascular lesions, with a disruption of the blood-iris barrier. As we have shown here and in previous work (31), T cells isolated from the inflamed eyes of Lewis rats with AU. T cells were obtained and pooled at the peak of AU, stimulated with MBP, and expanded with IL-2. T cells were then tested for proliferative responses to Con A, MBP, MBP peptides 55–69, 72–89, and 87–99; or media alone in duplicate wells. Iris/ciliary body T cells responded only to whole MBP and the immunodominant peptide 72–89. SI = cpm of T cells plus Ag/cpm of T cells alone. The background incorporation for wells with T cells but no Ag was 1052 cpm.

FIGURE 6. Control sequences for Figure 5, in which Vα2+ CDR3 region sequences were derived from the LNs of the same animals on day 14 (A) and day 18 (B) postimmunization. No Vα2 sequences from the LN were found to contain the EAE-associated N3 CDR3 motif (19).

FIGURE 7. MBP specificity of T cells isolated from the inflamed eyes of Lewis rats with AU. T cells were obtained and pooled at the peak of AU, stimulated with MBP, and expanded with IL-2. T cells were then tested for proliferative responses to Con A, MBP, MBP peptides 55–69, 72–89, and 87–99; or media alone in duplicate wells. Iris/ciliary body T cells responded only to whole MBP and the immunodominant peptide 72–89. SI = cpm of T cells plus Ag/cpm of T cells alone. The background incorporation for wells with T cells but no Ag was 1052 cpm.

As in the EAE model, it is likely that the TCR Vα and Vβ CDR3 motifs detected in the AU sequence contribute to Ag recognition. Another model of uveitis, experimental autoimmune neuritis, which affects the uveal tract, retina, and pineal gland, is inducible by major MBP form in the CNS (36). TCR V gene usage in experimental autoimmune neuritis (EAN) induced by peripheral myelin Ags was investigated in a recent study by Weilbach et al. (37). The induction of EAN with whole peripheral nerve myelin but was not detected after induction with the myelin protein P2 (which constitutes 45–65% of total peripheral myelin protein) or P2 peptides. Of the three Vβ8.2 sequences obtained after disease induction with peripheral nerve myelin, two contained EAE-associated CDR3 motifs (37). The constitution of the various myelin proteins in the nerves of the iris is not known and could conceivably contain higher levels of certain CNS proteins than is found in peripheral nerves. Thus, differences in the presentation of one MBP isoform over others may account for the site-specific differences in MBP-induced disease. In addition, the varying levels of the targeted autoantigen (i.e., MBP) expressed in the CNS, iris, or peripheral nerves could also play a role in disease severity.

As in the EAE model, it is likely that the TCR Vα and Vβ CDR3 motifs detected in the AU sequence contribute to Ag recognition. Another model of uveitis, experimental autoimmune neuritis, which affects the uveal tract, retina, and pineal gland, is inducible by...
a role in the highly selective presentation of Ag at this site. In addition, dendritic cells isolated from rat iris tissue were able to stimulate unprimed T lymphocytes in vitro, and this stimulatory capability was markedly enhanced after culture for 48 h with granulocyte-macrophage CSF (45).

In a previous study, we observed a marked reduction in biased Vβ8.2 gene expression by the peak of EAE and attributed this reduction to the influx of nonspecific inflammatory cells (31). In AU, we found that Vβ8.2 expression remained high, even at the peak of AU. An examination of the sequence data suggests that EAE-associated CDR3 motifs may be present at a higher frequency in T cells from the iris/ciliary body than from the CNS (17, 19). These observations are consistent with certain aspects of immune regulation that are associated with the eye. The phenomenon of anterior chamber-induced immune deviation is a specialized response in which a selective suppression of delayed hypersensitivity occurs, but in which humoral and cytotoxic T cell responsiveness to intraocular Ag presentation remain intact (46, 47).

Thus, extremely damaging inflammatory reactions are avoided at this highly sensitive tissue site, which may account for the extended Vβ8.2 bias and the sequence restrictions observed later in AU. The mechanisms involved in anterior chamber-induced immune deviation are not fully understood but may involve the action of antiinflammatory cytokines and soluble mediators specific to the microenvironment of the anterior chamber (48). In this environment, it is also possible that T cells specifically activated in the iris do not undergo Fas-Fas ligand-induced apoptosis at the same rate as those activated in the CNS (49).

Since EAE is a model for MS, it seems highly relevant that AU has been associated with a number of MS cases. Several more recent reports have described symptoms of AU in patients with preexisting MS or in individuals who later developed MS (8, 9, 12). The Lewis rat model of EAE and associated AU provides an opportunity to investigate the occurrence of inflammatory eye disorders that accompany systemic diseases in general. Our observations of restricted TCR usage and Ag specificity in AU suggest that, at least in this model of uveitis, pathogenic T cells may be specifically targeted for treatment.

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