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Conversion of Monophasic to Recurrent Autoimmune Disease by Autoreactive T Cell Subsets

Hui Shao, Song Lei, Sheher L. Sun, Henry J. Kaplan, and Deming Sun

Autoimmune uveitis has been elicited in susceptible rodents by several ocular-specific Ags. In most of these animal models the induced uveitis is acute and monophasic. Because recurrent uveitis poses the highest risk for blinding ocular complications in human disease, a spontaneous relapsing animal model would be most helpful in understanding the disease pathogenesis. In our current study we have observed that the adoptive transfer of interphotoreceptor retinoid-binding protein residues 1177–1191-specific T cells to naive Lewis rats induced a chronic relapsing disease, in contrast to the monophasic disease induced by immunization with interphotoreceptor retinoid-binding protein residues 1177–1191 emulsified in CFA. The chronic relapsing uveitis induced by autoreactive T cell subsets is dependent on the number of autoreactive T cells generated as well as their activation status. Our study documented a spontaneous model of recurrent uveitis in the rat, which should assist us in the study of disease pathogenesis and the design of specific therapy. The Journal of Immunology, 2003, 171: 5624–5630.

Uveitis is a common cause of human visual disability and blindness. The recurrent nature of autoimmune uveitis may result in severe clinical complications, such as cystoid macular edema, cataract formation, and glaucoma, even though a single episode of the disease usually does not cause permanent visual loss. Experimental autoimmune uveitis (EAU) can be elicited in rodents following immunization with several different Ags, e.g., retinal-soluble Ag, interphotoreceptor retinal-binding protein (IRBP) (1, 2), melanin-associated Ag (MAA) (3, 4), and myelin proteins (5–7), as well as by the adoptive transfer of uveitogenic T cells between syngeneic rodents (7–10). Uveitogenic T cells that mediate EAU are assumed to be exclusively CD4+ T cells.

The adoptive transfer of autoreactive T cells has a number of advantages over active immunization, including avoidance of the use of adjuvant, mycobacterium, or pertussis toxin. In addition, in several experimental models the autoreactive T cell subsets elicited by an autoantigen differ greatly in their disease-inducing ability and immunoregulatory activity (11–13). In the present study we have shown that the adoptive transfer of T cell subsets specific for residues 1177–1191 of IRBP (peptide R16) into naive Lewis rats induced a chronic relapsing uveitis, rather than the monophasic disease induced by immunization with R16 emulsified in CFA. The model of recurrent uveitis induced by the transfer of autoreactive T cell subsets was determined by both the number of autoreactive T cells injected and their activation state. This experimental model should help greatly in the study of the pathogenesis of recurrent uveitis in humans.

Materials and Methods

Animals

Pathogen-free female Lewis rats (5–6 wk old) were purchased from Harlan Sprague Dawley (Indianapolis, IN) and were housed and maintained at the animal facilities of the University of Louisville.

All animal studies conformed to the Association of Research in Vision and Ophthalmic Research statement on the use of animals in Ophthalmic and Vision Research. Institutional approval was obtained, and institutional guidelines regarding animal experimentation were followed.

Animal model of EAU

The induction of uveitis in Lewis rats using peptide R16 has been previously described (13, 14). Briefly, the rats were immunized s.c. with 200 μl of an emulsion containing 30 μg of R16 and 500 μg of Mycobacterium tuberculosis H37Ra (Difco, Detroit, MI) in CFA (Sigma-Aldrich, St. Louis, MO), distributed over six spots on the tail base and flank.

For induction of uveitis by adoptive transfer of R16-specific T cells (tEAU), naive Lewis rats were injected i.v. either with in vitro restimulated R16-specific T cells prepared from rats with uveitis (induced either using Ag immunization or cell transfer) or with R16-specific T cell lines in 0.5 ml of PBS and were examined daily for clinical signs of uveitis by slit-lamp biomicroscopy. The intensity of uveitis was scored blind on an arbitrary scale of 0–4 (13), with 0 as no disease, 1 as engorged blood vessels in the iris and an abnormal pupil configuration, 2 as a hazy anterior chamber, 3 as a moderately opaque anterior chamber with the pupil still visible, and 4 as an opaque anterior chamber, obscured pupil, and frequently photoproposis.

Inflammation in the eye was confirmed by histopathology. Many inflammatory cells were seen in both anterior and posterior chambers together with a disorganized retinal architecture, retinal detachment, and photoreceptor cell damage.

R16-specific T cell lines

R16-specific T cell lines were isolated from R16-immunized Lewis rats, using the methods of generating Ag-specific T cells as previously described (15–18). T cells were isolated 10 days postimmunization (p.i.) from lymph node cells or spleen cells by passage through a nylon wool column. The cells (1 × 10⁶) were first stimulated with 20 μg/ml of R16 in 2 ml of
medium in a six-well plate (Costar, Cambridge, MA) with 2 \times 10^7 irradiated syngeneic spleen cells as APCs. After 2 days the activated lymphoblasts were isolated by gradient centrifugation in Lymphoprep (Robbins Scientific, Mountain View, CA) and cultured in RPMI 1640 medium supplemented with 15% IL-2-containing medium (supernatant from Con A-stimulated rat spleen cells). These T cell lines were maintained by periodic restimulation for 48 h (about once every 10 days) with Ag in the presence of irradiated syngeneic APCs. The lines were used after three or four stimulation/restimulation cycles.

Cell proliferation assay
R16-specific T cells (3 \times 10^6 cells/well) in a total volume of 200 \mu l were cultured at 37°C for 48 h in 96-well microtiter plates with medium or R16 and irradiated syngeneic spleen APCs (2 \times 10^6), and [3H]thymidine incorporation during the last 8 h was assessed using a microplate scintillation counter (Packard Instruments, Meriden, CT). The proliferative response was expressed as the mean counts per minute ± SD of triplicate determinations.

Isolation of cells from inflamed eyes
After perfusion of the anesthetized rat with PBS on the indicated day after immunization or injection of T cells, the eyes were collected, and a cell suspension was prepared by digestion for 10 min at 37°C with collagenase (1 mg/ml) and DNase (100 \mu g/ml) in RPMI 1640, followed by gradient centrifugation on 25% Percoll and subsequent Ficoll separation; in some experiments, cells separated only by Percoll were used, as indicated in the text. The cells were washed and resuspended in staining buffer (PBS containing 3% FCS and 0.1% sodium azide) for Ab staining. The cells obtained using the full separation procedure consisted mainly of inflammation-recruited immune cells as well as a minor population of intraocular resident macrophages and dendritic cells.

Immunofluorescence flow cytometry
Aliquots of 2 \times 10^5 cells were double-stained with combinations of FITC- or PE-conjugated mAbs against rat \alpha beta TCR (R73), NK cells (NKR-P1a), macrophages (ED1), dendritic cells (OX-62), or bone-marrow-derived cells (CD45). All Abs were purchased from BD Bioscience (La Jolla, CA). Data collection and analysis were performed on a FACS Calibur flow cytometer using CellQuest software.

Pathological examination
For histology, whole eyes were collected, immersed for 1 h in 4% phosphate-buffered glutaraldehyde, then transferred to 10% phosphate-buffered formaldehyde until processed. The fixed and dehydrated tissue was embedded in methylacrylate, and 5-\mu m sections were cut through the pupillary-optic nerve plane and stained with H&E. The presence or the absence of disease was evaluated blind by examining six sections cut at different levels for each eye. The severity of EAU was scored on a scale of 0 (no disease) to 4 (maximum disease) in half-point increments, as described previously (13).

Statistical analysis
The data are expressed as the mean ± SD. Each experiment was repeated at least three times. Student’s t test was used to analyze the results.

Results
Monophasic uveitis is induced by immunization with R16 peptide
Lewis rats immunized with R16 developed acute and monophasic uveitis, showing overt clinical symptoms at 8–9 days p.i. Maximum disease was observed in animals immunized with ≥30 \mu g of peptide/rat. The clinical signs observed by slit-lamp biomicroscopy included engorged iris blood vessels, abnormal pupil configuration, and hazy anterior chamber. The disease persisted for 7–10 days. No spontaneous recurrence was observed. Fig. 1 illustrates the histopathology of the inflamed eye in Lewis rats at the peak (12 days p.i.) of the monophasic disease. Inflammatory cell infiltrates were present in both anterior and posterior chambers (Fig. 1C), the vitreous, and the retina (Fig. 1D). Damage to the photoreceptor layer, retinal folding, and retinal vasculitis were also observed (Fig. 1D).

Recurrent uveitis is induced by transfer of R16-specific T cell subsets
In initial experiments uveitogenic T cells were prepared from the draining lymph nodes and spleens 10–14 days after active immunization with R16 and were stimulated for 3 days with R16 in the presence of syngeneic APC. The Ficoll-isolated T cell blasts (3 \times 10^6/rat) were then injected i.v. into naive Lewis rats. Over the following 80 days the majority of the recipient rats developed acute uveitis with several recurrences. Each recurrent episode lasted 1–7 days and was followed by varying periods of remission. Fig. 2 shows a typical experiment in which six recipient rats received 3 \times 10^6 R16-specific T cells and showed a similar, but not identical, pattern of relapsing EAU with neither the time nor the duration of the relapse predictable. Interestingly, the right and left...
eyes of a single recipient showed a different pattern of relapse (data not shown), analogous to that frequently observed in human disease.

Because R16-specific T cells directly prepared from immunized rats are very heterogeneous (data not shown), we investigated whether immortalized R16-specific T cell lines had similar uveitogenic activity. The generation of uveitogenic T cell lines largely followed the experimental procedures used to isolate myelin-reactive encephalitogenic T cells (17, 19). Fig. 3 shows the results of a proliferation assay for one representative R16-specific T cell line. All the cell lines responded to R16, but not to unrelated Ags, such as protein-purified derivative or MAA. When these T cell lines (3 × 10⁶) were used for adoptive transfer, the disease-inducing capability of the individual lines differed significantly. As shown in Table I, the incidence and onset of disease (days p.i.) were recorded. NA, not applicable.

![Figure 2](image)

**FIGURE 2.** Recurrent EAU induced by adoptive transfer of R16-specific T cells. T cells isolated from the draining lymph nodes and spleens of R16-immunized animals were enriched by passage through nylon wool and restimulated in vitro with R16 (20 µg/ml) presented by irradiated syngeneic spleen APCs. After 3 days, activated T cell blasts were separated on a Ficoll gradient and injected (3 × 10⁶ cells, i.v.) into naive Lewis rats. Clinical signs were observed by slit-lamp biomicroscopy and scored as described in Materials and Methods. This experiment was repeated 20 times.

![Figure 3](image)

**FIGURE 3.** Antigenic specificity of a typical R16-specific T cell line. T cells (3 × 10⁶/well) were incubated for 48 h in 96-well, flat-bottom plates in the presence of 2 × 10⁵ irradiated syngeneic splenic APC and 10 µg/ml of R16, protein-purified derivative (PPD), or MAA. [³H]thymidine incorporation during the last 8 h was assessed using a microplate scintillation counter. The proliferative response is expressed as the mean counts per minute ± SD of triplicate determinations. The experiment was repeated three times with similar results.

![Table I](image)

**Table I. Relapsing uveitis induced by R16-specific T cell lines**

<table>
<thead>
<tr>
<th>T Cell Line</th>
<th>Incidence</th>
<th>Disease Onset (days p.i.)</th>
<th>Disease Score</th>
<th>Relapse</th>
</tr>
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<tr>
<td>IRBP-1</td>
<td>6/6</td>
<td>5</td>
<td>2–3</td>
<td>No</td>
</tr>
<tr>
<td>IRBP-2</td>
<td>0/6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>IRBP-3</td>
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<td>3</td>
<td>3–4</td>
<td>Yes</td>
</tr>
<tr>
<td>IRBP-6</td>
<td>0/6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>IRBP-21</td>
<td>6/6</td>
<td>3</td>
<td>3–4</td>
<td>Yes</td>
</tr>
<tr>
<td>IRBP-22</td>
<td>6/6</td>
<td>5</td>
<td>2–3</td>
<td>No</td>
</tr>
</tbody>
</table>

* Cells (3 × 10⁶) of each T cell line were injected i.v. into naive Lewis rats (six animals per group), then the animals were observed daily by slit-lamp biomicroscopy. The incidence and onset of disease (days p.i.) were recorded. NA, not applicable.
* Peak score during the acute phase of disease.
* Relapse of uveitis (more than two uveitis attacks in all animals).
in Table I, lines 3 and 21 consistently induced recurrent uveitis, while lines 1 and 22 only induced monophasic disease similar to active immunization. Lines 2 and 6 proliferated in response to the immunizing peptide, but were not uveitogenic.

EAU following adoptive transfer had a much early onset, varying from 3–5 days, than active immunization. As seen in Table I recipients of lines 3 and 21 had an earlier onset of disease (day 3) than recipients of lines 1 and 22 (day 5). The clinical severity of uveitis after the adoptive transfer of T cells after 3 days in vitro stimulation is similar to that of actively immunized rats (see Fig. 2).

Recurrent uveitis after the adoptive transfer of uveitogenic T cells is dose dependent

To determine whether recurrent uveitis was dose dependent, we injected different numbers (0.5, 1, or $3 \times 10^6$) of a uveitogenic T cell line (IRBP-3) into groups of naive Lewis rats. The results showed that transfer of 1 or $3 \times 10^6$ T cells consistently induced acute uveitis in all recipient rats, whereas $0.5 \times 10^6$ T cells induced disease in only 50%. Furthermore, only rats receiving $3 \times 10^6$ autoreactive T cells consistently showed relapsing disease, whereas $0.5 \times 10^6$ T cells induced only monophasic disease. Those animals who received $1 \times 10^6$ cells developed either monophasic or recurrent disease (Table II).

Adoptive transfer of uveitis is dependent on the activation status of R16-specific T cell lines

Based on our previous observations in EAE that autoreactive T cell lines are only encephalitogenic within 3 days after each in vitro restimulation, we tested whether the uveitogenic activity of R16-specific T cell lines was similarly restricted by the activation status of the T cells. An R16-specific T cell line (IRBP-3) was stimulated in vitro for 2 days with an optimal dose (10 µg/ml) of R16 and APCs. The activated T cell blasts were then harvested and cultured in IL-2-containing medium for an additional 0, 3, or 5 days before being collected and injected into naive recipient rats ($3 \times 10^6$ cells/rat). As shown in Table 2B, when cells were used immediately after in vitro restimulation (day 0) all recipients developed uveitis, whereas T cells injected 3 or 5 days after restimulation induced EAU in only some or none, respectively. Interestingly, only T cells used immediately after restimulation induced recurrent EAU.

<table>
<thead>
<tr>
<th>A</th>
<th>No. of T Cells ($\times 10^6$)</th>
<th>Incidence</th>
<th>Onset (days p.i.)</th>
<th>Disease Score</th>
<th>Relapse</th>
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<tbody>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>6/6</td>
<td>4</td>
<td>3–4</td>
<td>±</td>
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</tr>
<tr>
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<td>4/6</td>
<td>5</td>
<td>2</td>
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<table>
<thead>
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<th>B</th>
<th>Days of Resting after Stimulation</th>
<th>Incidence</th>
<th>Onset (days p.i.)</th>
<th>Disease Score</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6/6</td>
<td>3</td>
<td>3–4</td>
<td>Yes</td>
<td></td>
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<tr>
<td>3</td>
<td>4/6</td>
<td>5</td>
<td>2–3</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0/6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

* Table II. The relapsing nature of adoptively transferred EAU is associated with the number (A) and activation status (B) of the autoreactive T cells transferred.

* A. IRBP line 3 T cells were restimulated for 2 days, then the indicated number of cells was injected i.v. into naive Lewis rats (six animals per group), and the animals were observed daily by slit-lamp biomicroscopy. B. As in A, but using $3 \times 10^6$ cells restimulated for 2 days, followed by resting for the indicated number of days. The incidence and onset of disease (days p.i.) were recorded.

* Days after restimulation in vitro.

* Peak score during the acute phase of disease.

* Relapse of uveitis (more than two uveitis attacks in all animals).

FIGURE 4. Pathology of relapsing EAU. Recurrent EAU was induced, and the eyes were examined histologically at varying time points. A and B, The eye during acute disease (day 6 p.i.); C and D, relapse (second relapse, day 30 p.i.). A and C, Anterior segment; B and D, retina. Note the inflammatory cell infiltration (arrows), and damage of the photoreceptor cell layer (+). Mild, chronic inflammation remains to be seen in the remission, even though there were no clinical signs of inflammation upon resolution of disease.

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We then studied whether the number and/or pattern of eye-infiltrating cells differed between the acute (day 6 p.i.) and the relapsing (second relapse, day 30 p.i.) phase of EAU induced by the transfer of $3 \times 10^6$ IRBP-3 T cells. Histological examination (Fig. 4) of the eyes did not show a significant difference between the two phases of the disease, except that the damage to the photoreceptor layer was more severe (Fig. 4D), and mild cellular infiltration...
never resolved in recurrent disease (not shown). Thus, in monophasic EAU there were no clinical signs or histologic evidence of inflammation upon resolution of the disease, whereas in recurrent EAU, although there were no clinical signs of inflammation upon resolution of disease, there was mild chronic inflammation on histologic examination.

Cytograms of the cells obtained from the peak of inflamed eyes after adoptive transfer (Fig. 5, 1B, day 6) were similar to those after active immunization (Fig. 5, 1A, day 10). Both types of uveitis were characterized by a major infiltration of polymorphonuclear leukocytes (Fig. 5, 1A and 1B), which were removed by Ficoll separation (C). Parenchymal cells (CD45 negative) are much smaller in size (Fig. 5, 1) and thus can be readily distinguished from inflammatory cells in cytograms. The only difference between actively induced (Fig. 5, 1A) and passively induced (Fig. 5, 1B and 1C) EAU was that more parenchymal cells showed increased granularity and higher side scatter profile in recurrent disease (Fig. 5, 1B and 1C). When Percoll-prepared cells were double-stained with a panel of mAbs specific for rat T cells (αγTcR), macrophages (CD11b/c, ED1), dendritic cells (OX-62), NK/NKT cells (NKR-P1a), and hemopoietic (nonparenchymal) cells (CD45+) and analyzed by flow cytometry, recurrent EAU (day 30) was found to be associated with increased infiltration of NK cells and a decrease in macrophages/dendritic cells (Fig. 5, 2D–2F) compared with acute EAU (day 6, Fig. 5, 2A–2C). It was also noted that the NKR-P1a+TCR+ (NKT) cell profile became more heterogeneous when examined by FACS analysis (Fig. 5, 2D) during the relapsing phase of the disease.

R16-specific T cells persist in recurrent uveitis

In parallel with the chronic cellular infiltration observed in recurrent EAU, R16-specific T cells were consistently detected in the spleens of recipient rats for 3–6 mo after the injection of a single dose of 3 × 106 cells. This contrasted sharply with rats actively immunized with R16, in which R16-specific T cells were undetectable following the acute phase of the disease (>30 days p.i.; Fig. 6A). Limiting dilution assays showed that the frequency of R16-specific T cells in the periphery ranged from 1/5,000 to 1/10,000 in animals at the peak of a relapse, whereas animals with monophasic disease after active immunization had many fewer autoreactive T cells (data not shown). Importantly, after in vitro restimulation, splenic T cells from rats that had received 3 × 106 R16-specific IRBP-3 T cell line cells 60 days previously proliferated in response to R16 (Fig. 6A) and were uveitogenic when adoptively transferred into naive recipients (Fig. 6B).

Discussion

In this study we showed that Lewis rats adoptively transferred with uveitogenic R16-specific T cells developed chronic relapsing uveitis, which contrasted with the monophasic disease induced by active immunization with peptide R16. No significant difference in clinical disease was seen between these two types of autoimmune uveitis, except that the onset of the adoptively transferred disease was much earlier (3–4 days after cell injection), and histologic evidence of inflammatory cell inflammation persisted even after clinical resolution of inflammation.

Animals were either actively immunized with R16 or adoptively transferred with R16-specific T cells and closely monitored for >80 consecutive days. Surprisingly, most of the animals with uveitis induced by the adoptive transfer of T cells experienced several recurrent episodes of EAU, whereas relapses were not seen in actively induced uveitis, i.e., the disease was monophasic.

To explain the chronic relapsing nature of EAU observed after adoptive transfer, we considered the possibility that adoptive transfer provided a larger number of highly activated autoreactive T cells than active immunization. This idea is supported by the previous observations that although BALB/c mice and Fischer 344 rats are resistant to the active induction of autoimmune encephalomyelitis (EAE), they are susceptible to adoptively transferred EAE (20–22). It is likely that these so-called resistant strains generate fewer autoreactive T cells on Ag immunization than autoimmune-prone strains and that the injection of sufficient autoreactive T cells renders recipients susceptible. Thus, we injected different numbers of R16-specific T cells into naive recipient Lewis rats. Interestingly, the recipient rats receiving 3 × 106 R16-specific T cells consistently developed chronic relapsing uveitis, which was associated with early disease onset, whereas rats receiving lower numbers (0.5 × 106) of IRBP-specific T cells showed only monophasic disease and later disease onset.

We also tested the hypothesis that a weaker autoimmune attack induced monophasic disease, whereas a stronger autoimmune attack resulted in relapsing disease, by injecting recipient rats with R16-specific T cells of varying activation status. The rationale for this experiment is that Ag-specific T-cell lines require periodic in vitro restimulation and expansion in IL-2-containing medium, and cells harvested at different times after in vitro restimulation have different activation status. R16-specific T-cell lines were restimulated in vitro with an optimal dose of Ag and APC and were then maintained in IL-2-containing medium, and cells harvested at different times after in vitro restimulation have different activation status. R16-specific T-cell lines were restimulated in vitro with an optimal dose of Ag and APC and were then maintained in IL-2-containing medium for 0, 3, or 5 days before being used for disease induction. Only T cells used immediately after activation (0 days in IL-2 medium) induced chronic relapsing uveitis. After 3 days of maintenance, T cells remained uveitogenic, but only induced monophasic disease, whereas those maintained for 5 days lost uveitogenic activity. It is interesting to note that we have seen similar results in rat uveitis induced by T cells specific for myelin basic protein, which induced both uveitis and encephalomyelitis. In those experiments the encephalitogenic activity was strictly restricted to highly activated T cells (i.e., those maintained for 0 day poststimulation), whereas the same T cells were still uveitogenic 2 days later (D. Sun, S. L. Sun, H. J. Kaplan, and H. Shao, manuscript in preparation). Our results imply that the number of autoreactive T cells and their activation status will determine whether EAU is monophasic or relapsing.

Our study of a panel of R16-specific T cells showed that R16-specific T-cell lines vary greatly in their ability to induce monophasic or relapsing uveitis. This observation matches our previous studies of autoreactive T cells induced by myelin proteins (12, 17, 18). It is likely that the pathogenic capability of autoreactive T-cell subsets is determined by multiple factors, including the ability of autoreactive T cells to access Ag, enter their target organ, and interact with parenchymal cells of the tissue.

We have noted that the NKR-P1a+TCR+ (NKT) cell profile became more heterogeneous during the relapsing phase of the disease. In a previous report we have shown that NK/NKT cells are the major infiltrating cells of the inflamed eye actively induced by immunization with peptide R16; however, functional tests on eye-derived NK/NKT cells showed increased suppressive and decreased cytolytic activities (23). It remains to be determined whether the infiltration of an excessive number of NK/NKT cell subsets will be associated with increased tissue damage and chronic disease progression.

We have observed that parenchymal cells showed increased granularity and a higher side scatter profile in relapsing disease compared with active immunization (Fig. 5, 1B and 1C), suggesting that local parenchymal cells were activated in recurrent disease in contrast to the monophasic disease seen after active immunization. Such an observation agrees with previous reports that parenchymal cells of the autoimmune organ are not simply the victims...
of an autoimmune attack and that their functional alteration is closely linked to the course of the disease (24–30).

Most cases of human uveitis are of unknown etiology and thus are considered to be autoimmune in etiology. The clinical course of intraocular inflammation (i.e., uveitis) in these patients is frequently unpredictable, but is often characterized by recurrent episodes that affect first one eye and then the other. Additionally, although there may be minimal evidence of intraocular inflammation following resolution of an acute episode, the patient’s vision is frequently decreased as a result of cystoid macular edema, which suggests that a low grade, chronic subclinical inflammatory reaction is present, but undetectable. This EAU exhibits resolution of the acute episode with spontaneous recurrences and evidence of chronic, subclinical intraocular inflammation. It should provide important insights into the immunological mechanisms responsible for both the resolution of an acute episode and the subsequent relapse, similar to the human disease.

In summary, we have shown that R16-specific T cells can induce either monophasic or chronic recurrent EAU depending on the autoreactive load, i.e., the number of autoreactive T cells and/or their activation status. The creation of a relapsing model of autoimmune uveitis, i.e., the number of autoreactive T cells for both the resolution of an acute episode and the subsequent relapse, similar to the human disease.

References

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