Autoreactive T Cells in Immunopathogenesis of TB-Associated Uveitis

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PURPOSE. Intraocular inflammation in tuberculosis-associated uveitis (TBU) is usually widespread, and responds unpredictably to treatment. Herein, we analyze the intraocular T-cell response in TBU for its surface phenotype, antigenic specificity, and functional characteristics to explain the above observations.

METHODS. We isolated T cells from vitreous humor samples of patients with TBU and non-TB uveitis (controls). These were directly stained for surface markers CD4, CD8, CD45RO, CD45RA, CCR7, as well as intracellular cytokines IFN-γ, TNF-α, and IL-17 and analyzed on flow cytometry. Antigenic specificity was determined by activating with Mycobacterium tuberculosis-specific antigen Early Secreted Antigenic Target-6 (ESAT-6) or retinal crude extract (RCE). Activation-induced cell death (AICD) characteristics of each T-cell population were analyzed by staining for PI-Annexin V, Fas-FasL, phospho-Akt, and phospho-Erk1/2.

RESULTS. Immunophenotyping of vitreous humor samples demonstrated polyfunctional effector and central memory CD4+ T helper cells coexpressing IFN-γ, TNF-α, and IL-17. Both ESAT-6 and RCE (autoreactive) specificity was found in T cells extracted from TBU samples; however, the mycobacterial and autoreactive T-cell populations differed in their sensitivity to AICD. Autoreactive T cells appeared to resist AICD through decreased expression of apoptotic markers, FasL and caspase-3, sustained phosphorylation of Akt, and lowered Erk1/2 activity.

CONCLUSIONS. Autoreactive T cells are present in TBU eyes and are relatively resistant to AICD. An understanding of this epiphenomenon could be crucial in planning treatment of TBU patients, and interpreting response to anti-TB therapy.

Keywords: tuberculosis, uveitis, pathogenesis, autoreactive, antigen-induced cell death
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 genesis of human uveitis. This is especially relevant for TBU, because the local immune response at the site of TB infection has been shown to be distinct from peripheral blood and more representative of the ongoing disease process. Mtb-specific T cells migrate to sites of local infection, where they proliferate and exert effector functions. Phenotypic and cytokine profiling of activated T-cell populations from the disease sites can provide an immunologic snapshot of the disease process. Previous studies have taken advantage of body fluids present in TB-infected tissues, such as bronchoalveolar lavage and pleural effusions, to study the local T-cell response in TB. TB-infected tissues, such as bronchoalveolar lavage and pleural effusions, provide an immunologic snapshot of the disease process. The interface layer of mononuclear cells was collected and washed twice with 2% FBS-PBS. Total CD4+ T cells were isolated from the PBMCs by negative selection procedure through depletion of other cell types using Dynabeads (Invitrogen, Carlsbad, CA, USA). Briefly, antibody cocktail (containing anti-human CD8, CD14, CD16a, CD16b, CD19, CD36, CD56, CD123, and CD235a, all mouse IgG) was added to the PBMCs and incubated at 4°C for 20 minutes. Then Dynabeads were added and incubated at RT for 15 minutes by tilting and rotation. Dynabeads are coated with a monoclonal human IgG1 anti-mouse IgG, which can bind and deplete CD8+ T cells, macrophages, monocytes, neutrophils, dendritic cells, B cells, natural killer T cells, platelets, and red blood cells, but not CD4+ T cells. Thus, untouched (or negatively selected) CD4+ T cells were obtained from the PBMCs.

**Retinal Crude Extract (RCE) Preparation**

Freshly isolated retinal tissue, obtained from a noninfected posttrauma enucleated eye, was lyophilized using liquid nitrogen. The retina used for this preparation had no sign of Mtb infection, as determined by PCR on a section of the tissue, and lack of any history of eye disease before the trauma. These tissues were ground to fine powder using a prechilled mortar and pestle. The total powder obtained was then transferred to individual tubes containing 0.5 mL sample buffer (0.125 M Tris/HCl, pH 6.8; 1% SDS; 4 M urea; 5 M EDTA; 1 mg/mL bromphenol blue (BPB); and freshly added 1 mM phenyl-methanesulphonate fluoride). The tubes were then heated to 65°C for 15 minutes, followed by centrifugation at 10,000g for 2 minutes to obtain the crude protein extract. The contents were then measured for integrity and concentration, by Nanodrop and Bradford assay. We achieved a final quantity of 0.534 μg of RCE, which was dissolved in 0.5 mL PBS and stored at −20°C.

**Antigen-Specific T-Cell Stimulation**

ESAT-6 peptides 1 to 3 (catalog no. NR-34824; BEI Resources, Bethesda, MD, USA) and retinal crude extract (RCE) were used for the specific stimulation of T cells. Briefly, 10 μg/mL of ESAT-6 and RCE, along with 2 μg/mL of CD28, were added to culture media containing 10^6 cells/mL. Cells were incubated at 37°C and 5% CO2 for approximately 12 hours with 10 μg/mL Brefeldin A and/or 2 μmol/mL monensin during the last 8 hours.

**Flow Cytometry**

For cell surface markers, cells were stained in PBS containing 2% fetal bovine serum for 15 minutes, unless mentioned otherwise. For intracellular cytokine staining, cells were stimulated with phorbol 12-myristate acetate (PMA) (50 ng/mL) and ionomycin (1 μg/mL), or with different antigens, the last 8 hours with 10 μg/mL Brefeldin A and/or 2 μmol/mL monensin, at 37°C and 5% CO2 as mentioned above, and then fixed and stained according to manufacturer’s protocols. Antibodies used were as follows: CD3-Alexa Fluor 700, CD4-PacificBlueCy5.5A, IFN-γ Alexa Fluor 488, IL-17-PacificBlueCy5.5A, CCR7-APC-Cy7Fluor780 (eBioscience, San Diego, CA, USA), CD8-
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V500A (Tonbo, San Diego, CA, USA), TNF-α-Alexa Fluor 700(BD), CD45RA-PECy7, CD45RO-PECF594, FAS-PECF594 (BD, San Diego, CA, USA), Fasl-PE (Invitrogen), AnnexinV- APC (Immuno Tools, GmbH, Germany). Cells were acquired and analyzed by BD LSR Fortessa II (BD), using FlowJo (Ashland, OR, USA) three-star or FACSDIVA 6 software (BD Biosciences, San Jose, CA, USA).

Imaging Flow Cytometry

Isolated CD4+ T cells were activated with ESAT-6 (BEI Resources) and retinal crude extract, respectively, in the absence of CD28, for 10 hours under standard cell culture conditions. Then cells were stained for intra/extra cellular proteins, FasL-PE (Invitrogen), LAMP-1 FITC (eBioscience). Samples were acquired and analyzed by using Amnis ImageStream Mark II (Merck Millipore, Seattle, WA, USA) with appropriate controls.

Apoptosis Assays

Cells were stimulated with ESAT-6 10 µg/mL and RCE for approximately 16 hours for PI-Annexin V, 10 hours for FAS-FasL staining at 37°C and 5% CO2, and acquired by BD LSR Fortessa II.

Phospho Protein Staining

CD4+ T cells from VH were activated with ESAT-6 and RCE for different time intervals, such as 0, 15, and 30 minutes. Treated and untreated cells were fixed by adding 16% formaldehyde directly to the medium to obtain a final concentration of 2% formaldehyde. Cells were left in fixative for 20 minutes at RT and pelleted. They were then permeabilized with 500 µL 80% ice-cold methanol at 4°C for at least 20 minutes. Cells were washed twice in staining media (0.05% Triton X-100 in 2% PBS, PBS) and finally resuspended in 50 µL staining media. Cells were stained with phospho-Akt APC or phospho Erk1/2 PE (eBioscience) for 30 minutes at RT. Finally, samples were analyzed by flow cytometry.

Statistics

Statistics were performed using 1-way ANOVA when more than two groups were compared. Paired and unpaired Student’s t-tests were used to analyze between two groups. All statistics were performed using Prism 5.0 (GraphPad, La Jolla, CA, USA) software. Results were expressed as mean ± SEM. P < 0.05 was considered significant.

RESULTS

Clinical Profile of TBU Patients and Controls

The clinical details of TBU patients and non-TBU controls are summarized in the Table. Overall, vitreous samples were collected from 48 TBU patients and 23 controls, of which 22 and 13, respectively, yielded adequate T-cell counts for individual experiments. The most common clinical presentations of TBU in our cohort were retinal vasculitis (n = 15, 68.2%), and multifocal serpiginoid choroiditis (n = 3, 13.6%), respectively (Figs. 1A, 1B). All but two of the retinal vasculitis patients had focal chorioretinitis lesions overlying blood vessels. Fluorescein angiography of the retinal vasculature demonstrated breakdown of the inner blood-retinal barrier in these patients (Figs. 1C, 1D). The controls consisted of a variety of noninfectious uveitis conditions, such as seronegative spondyloarthritides, intermediate uveitis, sarcoidosis, and juvenile idiopathic arthritis. Half (n = 11) of the TBU samples and none of the controls tested positive for Mtb on quantitative real-time PCR (based on cutoff value of mpb64:human RNase P ratio, described above). Seven of 22 TBU patients had radiographic evidence of healed or active pulmonary and/or extrapolmonary TB.

Intraocular T-Cell Response in TBU is Highly Proinflammatory and Involves Effector and Central Memory T Cells

To compare the overall cytokine profile between TBU and controls, we evaluated levels of IFN-γ, TNF-α, IL-17, IL-23, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, IL-15, IL-21, and IL-22 in vitreous samples by cytokine multiplexing. We found that all the above cytokines, except IL-10, IL-6, IL-15, IL-21, and IL-22, were significantly more elevated in TBU as compared with controls (Fig. 1E, Supplementary Fig. S1). IL-10 and IL-6 levels were also higher in TBU, although not statistically significant. Our data demonstrated that TBU has an overall greater proinflammatory cytokine milieu in vitreous fluids, as compared with non-TBU inflammation.

We next analyzed the predominant cellular source of proinflammatory cytokines in TBU. We found that CD4+ cells were the predominant phenotype in all TBU samples (Figs. 1F, 1G). The mean CD4+/CD8+ ratio in TBU samples was 6.52 ± 6.69. Our results for TBU matched earlier reports for ocular and systemic sarcoidosis in which high CD4+/CD8+ ratio was found in vitreous fluid and bronchoalveolar lavage and was of significant diagnostic value. Of note, the non-TBU controls used for this experiment did not include sarcoidosis.

Next, we examined the intracellular cytokine profile of CD4+ cells, with a polychromatic flow cytometry panel for IFN-
c, IL-17, TNF-α, and IL-10 (Fig. 2A). We found a significant proportion of polyfunctional cells, including triple-positive cells for IFN-γ, IL-17, and TNF-α, as well as various dual-positive (IFN-γ–IL-17, IFN-γ–TNF-α, and IL-17–TNF-α) phenotypes (Fig. 2A). There was no difference between the retinal vasculitis samples (most common TBU subtype) and those from other clinical presentations of TBU (see Supplementary Fig. S2). There was also no difference in the cytokine response between Mtb PCR-positive and PCR-negative samples (see Supplementary Fig. S3). We found that the CD4+ population in TBU predominantly was composed of effector (TEM, CD45RO+), CCR7−, and central memory (TCM, CD45RO+, CCR7+) phenotypes, with greater preponderance of TEM than TCM cells. The polyfunctional phenotypes were distributed across both TEM and TCM subsets, although the cytokine response was significantly stronger among TCM cells (Fig. 2B, 2C).

Antigenic Specificity to Both ESAT-6 and Retinal Antigens Is Seen in TBU

To further validate our hypothesis that intraocular T-cell response is directed against active Mtb infection, we studied cytokine response to peptides from Mtb-secreted protein ESAT-6 (Fig. 3A). We found polyfunctional responses to ESAT-6 peptides in all TBU samples. No detectable cytokine response to ESAT-6 was found in non-TBU controls, most likely due to the absence of Mtb-specific cells (see Supplementary Fig. S4A). More importantly, the cytokine response to ESAT-6 was significantly less or undetectable in corresponding blood samples of the TBU patients, suggesting that the Mtb-specific response was restricted to the site of infection (see Supplementary Fig. S4B).

Because molecular mimicry between mycobacterial and retinal antigens has been proposed as a possible mechanism for TBU,10 we also evaluated the cytokine response of intraocular T cells to RCE. Surprisingly, we found a strong polyfunctional cytokine response to RCE as well (Fig. 3A). To rule out the possibility of a common T-cell population getting activated by both ESAT-6 and RCE, we checked Basic Local Alignment Search Tool (BLAST) alignment between sequences of ESAT-6 and a set of retinal antigens commonly implicated in experimental and human uveitis: arrestin, retinal S-antigen, interphotoreceptor binding protein (IRBP), and cellular retinaldehyde-binding protein (CRALBP). We did not find any sequence homology between ESAT-6 and retinal antigens. Also, no cytokine response was seen on stimulation with a skin...
crude extract, which ruled out false-positive response to RCE (Fig. 3A). For each of the samples, the cytokine secretion was significantly higher in response to RCE, as compared with ESAT-6 (Fig. 3B). Taken together, it appeared that there might exist two distinct T-cell populations in TBU, with antigenic specificity for Mtb (ESAT-6) and retinal antigens (RCE), respectively.

Retinal Antigen-Specific Cells Are Resistant to AICD

Next, we studied the impact of the autoreactive T-cell response on tissue immune homeostasis in TBU. AICD mediated by Fas-FasL interaction plays a major role in contraction of activated T-cell clones after antigenic stimulation. Such interactions are particularly required in situations that involve repeated antigenic stimulation as in autoimmunity or chronic infection. AICD is known to be impaired in various autoimmune diseases, resulting in persistence of autoreactive T-cell populations. The two-pronged immune response in TBU samples provided a unique opportunity to compare AICD between microbe-specific and autoreactive T cells, extracted from the same anatomic space. First, we compared sensitivity to apoptosis between ESAT-6 and RCE-stimulated cells by staining with Annexin V and propidium iodide (PI). We found that both early (PI⁻) and late (PI⁺) apoptotic cells were lower after RCE stimulation as compared with ESAT-6 (Figs. 4A–D). Then, we found that FasL expression was significantly lower in RCE-specific T cells compared with ESAT-6–specific cells (Figs. 4E, 4F). The FasL expression trend was also confirmed on studying degranulation of FasL by imaging flow cytometry (Amnis, Fig. 4G). Finally, the late apoptotic marker, cleaved Caspase-3, was found to be lower in a RCE-specific than ESAT-6–specific population (Figs. 4H, 4I). Taken together, these results demonstrate the potential of autoreactive T cells to persist in TBU eyes that may have a role in prolonging the ocular inflammatory response.

Retinal Antigen-Specific T Cells Showed Lowered Erk1/2 and Increased Akt Phosphorylation

Last, we tried to dissect the mechanisms by which autoreactive T cells might resist AICD. Because Th17 cells are known to be resistant to AICD as compared with Th1 cells, we compared the Th17 abundance in the autoreactive and Mtb-specific T-cell populations. As expected, we found that both Th17 and Th1/17 subsets were significantly more abundant among the autoreactive T cells (Fig. 3B). Next, we explored the signaling pathways underlying the AICD resistance in...
these autoreactive T cells. Our previous work on CD4+ T cells from the peripheral blood of rheumatoid arthritis patients demonstrated that an inherently low MAPK activity, particularly ERK1/2, protects Th17 cells from AICD. We could validate those results in TBU, because we found that ERK1/2 activity was significantly lower in the autoreactive T cells compared with the ESAT-6–specific population (Figs. 5A, 5B). This was further substantiated by demonstrating increased phosphorylation of survival protein, Akt, in the autoreactive T-cell population compared with the Mtb-specific ones (Figs. 5C, 5D). Taken together, lowered ERK1/2 activity and increased Akt phosphorylation appeared to protect autoreactive T cells against AICD.

**DISCUSSION**

Our study is the most extensive investigation to date into the intraocular adaptive immune response in any form of human uveitis. We obtained direct phenotypic and functional analyses of the intraocular T cells despite relatively low cellular yields from such samples, and thus avoided the inherent limitations of in vitro expansion. It helped us gain unique insight into the patho-mechanisms involved in development of TBU. Our hypothesis, derived from the results, is given on the flowchart in Figure 6. Briefly, as in other forms of extrapulmonary TB, Mtb spreads to the eye from site of pulmonary infection. Whenever Mtb is able to initiate a local innate immune response in the eye, Mtb-specific memory T cells that had formed during initial pulmonary infection gain access into the eye and become activated by their cognate antigen into highly proinflammatory phenotypes. Mtb-induced inflammation possibly breaks down the blood-retinal barrier (BRB), which allows peripheral autoreactive cells to reach the eye and become activated by their cognate self-antigens (which are also significantly more abundant in the eye than Mtb antigens). The autoreactive T cells are relatively resistant to antigen-induced cell death, and can be expected to have a role in prolonging the ocular inflammatory response. However, as discussed below, our model is based on several assumptions, and alternative pathways might exist that lead to outcomes similar to our results.

Retinal antigen-specific T-lymphocytes have been demonstrated in the peripheral blood in several types of uveitis, such as Behcet’s disease, Vogt-Koyanagi-Harada syndrome, and birdshot chorioretinopathy (BSCR). Retinal and choroidal-reactive T cells were also found in the vitreous of a patient with BSCR. However, it remained unclear if these autoreactive T cells have a role in etiopathogenesis of uveitis, or...
represent an epiphenomenon of autoimmunization due to breakdown of the BRB. That the retinal antigen-specific response was seen in 6 of the 15 vitreous samples that were tested by RCE activation suggests that autoreactive T cells could indeed be an epiphenomenon due to breakdown of the BRB. Animal studies have also shown that autoreactive T cells from the peripheral circulation reach the eye entirely by chance. There can be several sources for the presence of these autoreactive T cells in the peripheral circulation, and subsequently the eye. Retinal antigen-specific cells that escape thymic elimination can persist in the circulation in healthy individuals. More recently, commensal microbiota in the gut have been discovered to be a source of retinal antigens that can prime autoreactive T cells to trigger an autoimmune response in the eye. Another possibility, based on recent studies in Citrobacter rodentium intestinal infection in mice, could be apoptosis of infected host cells that enables presentation of self-antigens, leading to generation of autoreactive T cells. Thus, there exist several mechanisms by which Mycobacterium tuberculosis (Mt) and retinal antigen-driven immune responses coexist in TB-associated uveitis eyes, although the sequence of events leading to this unique milieu needs further investigation.

The presence of two distinct intraocular T-cell populations in TB-associated uveitis (TBU), one specific for Mt and another for retinal antigens, could be supported by the absence of homology between ESAT-6 and four retinal antigens commonly implicated in experimental and human uveitis. Needless to say, this approach is not foolproof, as there might exist other retinal antigens that share the same sequence as ESAT-6. We therefore intended to select the Mt-specific CD4+ T cells by staining with ESAT-6 peptide-loaded tetramers and demonstrate their lack of responsiveness to RCE. However, the number of CD4+ cells was too low in ocular samples to conduct cell-sorting experiments. Further evidence of the presence of two distinct populations of T cells could be obtained from other data in our study. First, as shown in Figure 3A, a larger T-cell population was activated by RCE, compared with ESAT-6, in the same tested sample, suggesting that there exist additional cells in the sample that are responsive to RCE. Second, the overall cytokine response was significantly more in response to RCE than ESAT-6 even in individual patients (Fig. 3B). This could be accounted for not only by greater abundance of retinal antigens in the eye as compared with Mt antigens, but also by differences in affinity of autoreactive and microbe-specific T-
FIGURE 5. Retinal antigen-specific T cells showed lowered Erk1/2 and increased Akt phosphorylation. (A, C) Cells from VH of TBU patients were stimulated with ESAT-6 and RCE for 10 minutes, then cells were fixed in 2% formaldehyde and permeabilized by 80% ice-cold methanol and stained for pErk1/2 and pAkt. (B) MFI of Erk1/2 ($n = 6$). (C) pAkt overlay. (D) IMFI of pAkt ($n = 4$). **$P < 0.01$. 

Immunopathogenesis of tuberculosis-associated uveitis – possible mechanisms

1. Intraocular infection by *Mycobacterium tuberculosis* from pulmonary focus
2. Retinal antigen specific auto-reactive T-cells, that escaped thymus
3. Surrogate retinal antigen-specific T-cells generated by gut microbiome
4. Disruption of blood-retinal barrier
5. Adaptative immune response to *M. tuberculosis*
6. Chance encounter of auto-reactive T-cells with cognate antigen in eye
7. Activation and proliferation of autoreactive T-cells (ocular autoimmunity)
8. Autoreactive T-cells resistant to antigen-induced cell death
9. Prolonged intraocular inflammation/recurrent inflammation after anti-TB therapy

FIGURE 6. Flowchart illustrating possible sequence of events in immunopathogenesis of tuberculosis-associated uveitis. *Mtb* spreads to the eye from site of pulmonary infection. Whenever *Mtb* is able to initiate a local innate immune response in the eye, *Mtb*-specific memory T cells that had formed during initial pulmonary infection gain access into the eye and get activated by their cognate antigen into highly proinflammatory phenotypes. *Mtb*-induced inflammation possibly breaks down the BRB, which allows peripheral autoreactive cells to reach the eye and get activated by their cognate self-antigens (which are also significantly more abundant in the eye than *Mtb* antigens). The autoreactive T cells are relatively resistant to antigen-induced cell death, and can be expected to have a role in prolonging the ocular inflammatory response. Please refer to discussion in main text for alternative hypotheses.
cell receptors toward their cognate antigens. Finally, EAST-6 and RCE produced two distinct AICD responses, which again suggests two dissimilar CD4+ T-cell populations in TBU. Intriguingly, the non-TBU (control) samples did not show any responsiveness to RCE (Supplementary Fig. S3A). As discussed above, the control samples were composed primarily of CD8+ cells that need different conditions for activation, and could not be compared with the CD4+ results. As shown in Figure 1G, the CD4+ numbers in non-TBU samples were too low for any useful analysis.

Because the exact sequence of events in TBU is not known, it is important to explore alternative hypotheses to explain the results of our study. First, the possibility of cross-reactivity between ESAT-6 and RCE and therefore produce different dose-dependent cytokine responses. As mentioned above, this needs to be ruled out by cell-sorting experiments. Second, instead of autoreactive T cells entering the eye, due to breakdown of the BRB, it is possible that retinal antigens are released into the circulation where they activate peripheral T cells that subsequently reach the eye. Although we could not find any evidence of RCE-induced activation in the paired peripheral blood samples of TBU patients (Supplementary Fig. S4), it is possible that dilution of RCE-specific cells in peripheral blood precluded their detection in our experiments.

We also could not identify any antigen-presenting cells (APCs) in the vitreous samples, although several cell types in the eye can potentially act as APCs. These include choroidal macrophages, RPE, and retinal microglia, located near blood vessels. Because these cells cannot move from their primary location into the VH, they were not detected in our clinical samples. In addition, we found very low IL-10 production in the samples tested in our study, possibly because the T regulatory (Treg) response had not completely evolved at the time of sample collection. Previous studies on human uveitis have demonstrated a lowered Treg response in the peripheral circulation in active EAU as well as TBU. The role of autoimmunity in TB pathogenesis has generated significant interest of late. The paucibacillary nature of TB granulomas, presence of autoantibodies in TB patients, response to anti-TB therapy in uveitis, and inflammatory polyarthritis (Poncet’s disease) even in the absence of mycobacteria, and striking histopathologic similarities between TB and sarcoidosis, are some of the arguments favoring autoimmune mechanisms in TB pathogenesis. Our study provides definite evidence of the presence of autoimmune response, in TB of the eye. Whether the autoimmune response in the eye is driven by external factors, such as chance encounter with circulating autoreactive T cells due to breakdown of the BRB, or internal factors, such as apoptosis of infected host cells (in the retina), remains open to speculation, and should be addressed in future studies.

Nonetheless, the demonstration of autoimmune response within the eye in an infectious condition such as TBU remains significant. Such a response, can potentially trigger widespread and prolonged inflammation in the eye despite the paucibacillary infection. An understanding of this epiphenomenon would be crucial in planning treatment of TBU patients, and interpreting response to anti-TB therapy. Our observations in TBU also have the potential to be extrapolated to other forms of infectious and noninfectious uveitis that also disrupt the BRB and therefore may generate an autoimmune response. In that scenario, the results of this study would have an overarching impact on the approach to diagnosis and management of all forms of uveitis.

References


