Blockade of Interleukin-6 Signaling Suppresses Not Only Th17 but Also Interphotoreceptor Retinoid Binding Protein–Specific Th1 by Promoting Regulatory T Cells in Experimental Autoimmune Uveoretinitis

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PURPOSE. Both Th17 and Th1 cells contribute to experimental autoimmune uveoretinitis (EAU). Interleukin-6 (IL-6) blockade inhibits Th17 differentiation in EAU and potently suppresses ocular inflammation, although its effect on Th1 cells is unknown. To clarify the mechanism of IL-6 blockade, the authors investigated T helper cells with particular focus on Th1 and regulatory T cells (Treg) in EAU of IL-6 gene knockout (KO) mice.

METHODS. EAU was induced in wild-type (WT) mice and in mice lacking IL-6 (IL-6KO), IL-17 (IL-17KO), and IFN-γ (GKO) on a C57BL/6 background. Clinical scores of EAU, cytokine levels in supernatants from ocular tissue homogenates, and T helper cell differentiation in lymph nodes in each mouse were examined. To study the roles of Treg cells, EAU was induced in IL-6KO mice treated with anti-CD25 monoclonal antibody (mAb) to deplete Treg cells in vivo.

RESULTS. Inflammation was comparable between WT, IL-17KO, and GKO mice but was absent in IL-6KO mice. Th17 and interphotoreceptor retinoid binding protein (IRBP)-specific Th1 cells were increased in GKO and IL-17KO mice, respectively, whereas both populations were reduced in IL-6KO mice. Th1-dominant EAU in IL-17KO mice was suppressed by anti–IL-6R mAb treatment. Treg cell depletion in vivo induced EAU in IL-6KO mice.

CONCLUSIONS. After the induction of EAU, IL-6 deficiency resulted in the inhibition of the IRBP-specific Th1 response and enhanced the generation of IRBP-specific Treg cells. Furthermore, Treg was needed to inhibit Th1 responses and ocular inflammation in IL-6KO mice. Protective effects of IL-6 signaling blockade in EAU involve not only Th17 cell inhibition but also IRBP-specific Treg cell promotion.

Experimental autoimmune uveitis (EAU) is a rodent model of human uveoretinitis, and recent studies have revealed that highly proinflammatory interleukin (IL-17)-producing CD4+ T helper cells (Th17) play a pivotal role in the development of EAU, human uveitis,1,2 and other experimental autoimmune diseases.3-5

Th17 cells are a newly identified subset of helper T cells distinct from Th1 or Th2 cells, and both IL-6 and TGF-β are required for their differentiation. On the other hand, TGF-β alone promotes naïve T cells to differentiate into regulatory T cells (Treg), which are considered immunosuppressive helper T cells.6-8 Thus Th17 and Treg cells are distinct subsets of helper T cells, and IL-6 signaling promotes Th17 cells and inhibits Treg cell differentiation.9 From these studies, IL-6 signaling may represent a target for anti-inflammatory therapy. In fact, several studies have already reported that the anti–IL-6R monoclonal antibody (mAb) suppresses autoimmune disease models, including arthritis,10 encephalomyelitis,11 and uveitis,12 by inhibiting Th17 cell development.

In our own previous studies, we studied the effect of anti–IL-6R mAb in EAU and found that antigen-specific IFN-γ-producing CD4+ T helper cells (Th1) were also suppressed.13 Before the discovery of the Th17 cell subset, Th1 cells had been considered to play a key role in EAU induction.14,15 However, the loss of IFN-γ did not prevent EAU induction.16,17 and the loss of IL-17 did not prevent EAU completely.18 To explain these observations, studies have demonstrated that both Th1 and Th17 cells are redundant for the induction of EAU and that they substitute for each other.18,19 Taken together, these published studies indicate that both Th1 and Th17 cells should be suppressed to completely suppress the inflammation of EAU and that the anti-inflammatory mechanism of IL-6 signaling blockade cannot be fully explained by mere Th17 cell inhibition. Th1 cells are understood to require IL-12 and IFN-γ for their differentiation from naïve T cells and are not understood to require IL-6; rather, IL-6 is considered to suppress Th1 cell differentiation.20,21 Therefore, the role of the IL-6 signaling blockade in the inhibition of Th1 responses in vivo remains to be explained clearly.

In the present study, we focused on Treg cells, which are promoted by the IL-6 signaling blockade, and analyzed the roles of the IL-6 signaling blockade. We found that the IL-6 signaling blockade not only inhibited Th17 cell differentiation...
but also promoted antigen-specific Treg cells, which, in turn, suppressed the inflammatory effects of antigen-specific Th1 cells. Thus, the inhibitory effect of the IL-6 blockade in the development of EAU is associated with suppression of the induction of both Th1 and Th17 cells and their dominant proinflammatory effects in this disease.

**Materials and Methods**

**Mice**

Wild-type (WT) C57BL/6 mice were purchased from Charles River Laboratories (Yokohama, Japan). C57BL/6-background IL-6−/− (IL-6KO), IL-17A−/− (IL-17KO) mice were kindly provided by Yoichiro Iwakura (Laboratory of Molecular Pathogenesis, Center for Experimental Medicine, Institute of Medical Science, University of Tokyo, Tokyo, Japan), and IFN-γ−/− (GKO) mice were described previously. All mice were maintained in specific pathogen-free conditions at The National Institute of Biomedical Innovation, Osaka, Japan. Female mice (6–8 weeks of age) were used in all experiments. All animals were treated humanely, and all experiments conformed to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

**EAU Induction**

All mice were immunized with 100 μg human interphotoreceptor retinoid binding protein (IRBP) epitope contained in residue 1–20 sequences (GPTHLFQPSLVLDMAKVLLD) in 0.2 mL emulsion of complete Freund’s adjuvant (CFA) supplemented with Mycobacterium tuberculosis H37Ra to 2.5 mg/mL. In addition, 500 ng pertussis toxin was inoculated intraperitoneally.

**Clinical and Histopathologic Evaluation**

Ophthalmic examinations were carried out after immunizations. Tropiamide (0.5%) was applied to the eyes to induce mydriasis, and the fundus of the eye was examined using a slit lamp microscope. Every 48 hours from 11 days to 29 days after immunization, animals were clinically assessed in a masked fashion by experienced ophthalmologists who examined them for the presence of dilation, white focal lesions, and white linear lesions affecting blood vessels, retinal hemorrhaging, and retinal detachment. Clinical scores between 0 and 4 were assigned according to severity, as described previously. Then modifications. Eyes were enucleated from each mouse at peak of EAU (17–21 days after immunization) and were embedded in optical cutting temperature compound (Tissue-Tek; Sakura Finetechnical Co. Ltd., Tokyo, Japan) or paraffin. Sections approximately 8- to 10-μm thick were stained by standard hematoxylin and eosin.

**Preparation of Supernatants from Ocular Tissue Homogenates and Cytokine ELISAs**

Eyes were enucleated after kill, and conjunctival tissue was removed. Remaining eye tissues including cornea, vitreous body, retina, choroids, and sclera were homogenized using a sample preparation device (BioMasher; Nippi Inc., Tokyo, Japan). Supernatants were collected after centrifugation at 14,300g for 1 minute, and levels of IFN-γ and IL-17 were measured by ELISA kits (R&D Systems, Minneapolis, MN) according to the manufacturer’s instructions.

**Intracellular Cytokine Staining Assays**

Draining cervical lymph node cells were collected from three to six mice on indicated days after immunization with IRBP. For intracellular cytokine detection, cells were stimulated for 4 hours with 50 ng/mL phorbol 12-myristate 13-acetate (PMA) and 750 ng/mL ionomycin in the presence of 10 μg/mL Brefeldin A (BD Biosciences, San Jose, CA). Cell surface antigens were stained with anti–CD4 antibody (Biolegend, San Diego, CA). For the detection of FoxP3 Treg cells, cells were stained using a FoxP3 staining kit (eBioscience, San Diego, CA) according to the manufacturer’s instructions. Antibodies anti–IFN-γ (Biolegend) and IL-17 (BD Bioscience) were used simultaneously for detecting Th1 and Th17 cells, respectively. Stained cells were analyzed by flow cytometry (FACScanto; BD Biosciences). Each fluorescence-activated cell sorting (FACS) profile was obtained using cells from one mouse.

**Cell Cultures**

Cells were cultured in RPMI 1640 (Wako, Osaka, Japan) supplemented with 10% fetal bovine serum (HyClone, Irvine, CA), 2-mercaptoethanol (Nacalai Tesque, Kyoto, Japan), penicillin G, and streptomycin for 72 hours.

**5.6-Carboxyfluorescein Succinimidyl Ester and Enzyme-Linked Immunosorbent Assays**

Draining cervical lymph node cells were collected 10 days after immunization. Cells were labeled in 3 μM carboxyfluorescein succinimidyl ester (CFSE; Molecular Probes, Eugene, OR) and were cultured with IRBP (100 μg/mL) for 3 days, harvested, and stained with antibodies against CD4, IFN-γ, IL-17, and Foxp3 for the detection of Th1 and Th17 Treg cells or with antibodies against GITR, Foxp3, and CTLA-4 (Biolegend) for the detection of Foxp3 Treg cells and were analyzed using flow cytometry (FACS Canto; BD Biosciences). For these FACS analyses we used a Foxp3 staining kit with which we could detect both intracellular antigens, including cytokines, Foxp3, and CTLA-4, and extracellular antigens, including CD4 and CTLA-4 (which is expressed intracellularly and is also cell-surface expressed). In addition, IFN-γ and IL-17 in the cell culture supernatant were measured by ELISA kits (R&D Systems).

**Treatment with Anti–IL-6R Antibody**

Neutralizing anti–IL-6R mAb (clone MR16–1), which is a rat IgG1 antibody against murine IL-6 receptor, was provided by Chugai Pharmaceutical Co. (Gotemba, Japan) and Oriental Yeast Co. Ltd. (Tokyo, Japan). Anti–IL-6R mAb (8 mg) or purified rat nonimmune isotype control IgG (MP Biomedicals, Solon, OH) was injected intraperitoneally on day 1 after the induction of EAU in IL-17KO and GKO mice.

**Regulatory T Cell Depletion In Vivo**

IL-6KO mice were administered a total of three intraperitoneal injections (100 μg/injection) of either anti–CD25 mAb (clone PC61; BD Pharmingen, San Jose, CA) or purified rat nonimmune isotype control IgG (MP Biomedicals) at 48-hour intervals, as described previously. EAU was induced 7 days after the completion of treatment.

**Results**

**IL-6 Gene Knockout Inhibits the Development of EAU**

A previous study by Yoshimura et al. has shown that IL-6KO mice displayed weak inflammation after EAU induction whereas WT mice displayed severe inflammation. In agreement with this observation, we obtained comparable data in the present study. Histologic examination showed that a number of inflammatory cells infiltrated the eyes of WT mice and that the retinal structure was destroyed; IL-6KO mice showed almost no inflammation (Fig. 1A). In addition, IFN-γ and IL-17 cytokines in supernatants from ocular tissue homogenates were detected after the induction of EAU in WT mice but not in IL-6KO mice (Fig. 1B).

**IL-6 Gene Knockout Inhibits the Development of Th17 and IRBP-Specific Th1 Cells In Vivo**

Because IL-6 is essential in Th17 cell differentiation in vitro, we evaluated in vivo helper T cell differentiation in WT and IL-6KO mice by FACS. On days 0, 10, and 20 after immunization, cervical lymph node cells were collected. Th17 cells in WT
mice increased markedly on day 10 and decreased on day 20. Compared with WT mice, the development of Th17 cells in IL-6KO mice was significantly \((P < 0.05)\) impaired throughout the course of EAU (Figs. 2A, 2B). In contrast, Th1 cells in both WT and IL-6KO mice increased on day 10 (Figs. 2A, 2B). As we expected, the development of Th17 cells was also impaired, but the development of Th1 cells was not impaired in vivo with the abrogation of IL-6 signaling. However, these results were obtained from whole CD4\(^+\) cells in vivo. To analyze IRBP-responsive T cells, we cultured lymph node cells labeled with CFSE dye. IRBP-specific CD4\(^+\) T cells were investigated by FACS by means of gating on CFSE\(^{low}\) cells (Fig. 2C). In addition, cell supernatants cocultured with IRBP (10 and 100 \(\mu\)g/ml) were investigated by ELISA. The proportion of IRBP-specific Th17 cells decreased in IL-6KO mice, and IL-17 protein levels in cell culture supernatants significantly decreased in IL-6KO mice compared with WT mice. Interestingly, IFN-\(\gamma\) and IRBP-specific Th1 cells in IL-6KO mice also decreased compared with WT mice (Figs. 2C-E). From these data, we conclude that endogenous IL-6 is required for the development of both Th17 and IRBP-specific Th1 cells in vivo in EAU.

**IL-17KO and GKO Mice Displayed Inflammation Similar to That of WT Mice**

Because both Th1 and Th17 cells are considered to play important roles in the development of EAU,\(^{18,19}\) we investigated whether mice lacking IFN-\(\gamma\) or IL-17 develop EAU, and we investigated T cell differentiation in EAU. Consequently, in agreement with previous reports, GKO mice showed severe inflammation comparable to that in WT mice (Fig. 3A).\(^{16,17}\) IL-17KO mice displayed slightly weaker inflammation compared to that in WT mice; however, this difference did not attain statistical significance. Histologic examination revealed the infiltration of inflammatory cells and the destruction of retinal structure in IL-17KO and GKO mice, as was observed in WT mice (Fig. 3B).

**IRBP-Specific Th1 or Th17 Cells Can Induce EAU**

We used FACS to investigate T cell differentiation in IL-17KO and GKO mice compared with WT mice to examine Th1 and Th17 cell differentiation. IRBP-specific Th17 cells on day 10 after immunization markedly increased in GKO mice compared with WT mice (Figs. 3C, 3D). In contrast, IRBP-specific Th1 cells moderately increased in IL-17KO mice compared with WT mice by FACS analysis (Figs. 3C, 3D). Taken together, we consider that Th1 cells are dominant in IL-17KO mice and Th17 cells in GKO mice, as has been previously reported.\(^{18}\)

**Anti–IL-6R Antibody Suppressed Inflammation of EAU in GKO and IL-17KO Mice**

Treatment with anti–IL-6R mAb in GKO and IL-17KO mice was performed to examine the role of IL-6 signaling in the development of EAU in these two mouse strains. Inflammation could be suppressed by anti–IL-6R mAb treatment in GKO mice, as was expected (Fig. 3E). Interestingly, treatment with anti–IL-6R mAb also suppressed EAU in IL-17KO mice (Fig. 3F). Given the dominant inflammatory effects of Th1 cells in the development of EAU in IL-17KO mice, anti–IL-6R mAb suppresses Th1-induced inflammatory responses in the EAU model. Based on our data, we considered that IL-6 signaling blockade inhibits both Th17 and IRBP-specific Th1 cell effects in EAU model. Thus far, there have been few studies on the relationship of IL-6 and Th1 cells in vitro and in vivo; rather, IL-6 is considered to inhibit Th1 cell differentiation.\(^{20,21}\) Therefore, we next investigated the mechanisms of IRBP-specific Th1 cell inhibition in IL-6 signaling blockade.

**Treg Cell Increases**

Treg cells increased in the late phase of EAU in both WT and IL-6KO mice. IRBP-specific Treg cells increased in IL-6KO mice in the effector phase of EAU.

TGF-\(\beta\) without IL-6 promotes Treg cell differentiation, and Treg cells are reported to be immunosuppressive T cells.\(^{7}\) Therefore, we hypothesized that Treg cells may play an important role in ameliorating inflammation by IL-6 signaling blockade and thus examined whether Treg cells increase with IL-6 signaling blockade. However, Treg cells in vivo on day 0 and on day 10 after immunization showed equivalent levels in both WT and IL-6KO mice (Fig. 4A) and increased on day 20 after immunization. We further investigated IRBP-specific Treg cells by coculture with IRBP. IRBP-specific Treg cells in IL-6KO mice were significantly increased compared with WT mice on day 10 (Figs. 4B, 4C). In GKO and IL-17KO mice, the IRBP-specific Treg cell population showed no significant differences compared with WT mice (Fig. 3C). To detect Treg markers other than Foxp3, we also used antibodies against GITR and CTLA-4. The expression of these two Treg markers was increased in Foxp3\(^+\) cells of both WT and IL-6KO mice, and the frequency of cells expressing these markers was higher in IL-6KO mice than in WT mice (Fig. 4D).

**Enhanced Inflammation in Treg Cell-Depleted IL-6KO Mice Compared with IL-6KO Control Mice**

We considered that early priming of IRBP-specific Treg cells in IL-6KO mice plays a key role in inhibiting inflammation. Therefore, we hypothesized that the depletion of Treg cells in IL-6KO mice might predispose to inflammation after the induction of EAU. Treg cell-depleted mice were generated by preinjection (intraperitoneal) of anti–IL-2R (anti–CD25) mAb 1 week before EAU induction, as described previously.\(^{25}\) As a negative control, purified rat IgG was used. In agreement with our hypothesis, after the induction of EAU, inflammation was induced in Treg cell-depleted mice compared with control
mice, as determined by analysis of EAU clinical scores (Fig. 5A). We confirmed Treg cells were significantly \((P < 0.01)\) impaired in vivo in this model compared with control mice, as determined by FACS analysis of Foxp3 expression (Figs. 5B, 5C).

**Increased IRBP-Specific Th1 and Th17 Differentiation in Treg Cell-Depleted IL-6KO Mice**

To examine the population of Th1 and Th17 cells in Treg cell-depleted mice, lymph node cells on day 10 after immunization were analyzed. Th1 and Th17 cells in vivo were not significantly changed between Treg cell-depleted and control mice (Fig. 5B), but both IRBP-specific Th1 \((P < 0.01)\) and Th17 cells \((P < 0.01)\) increased significantly in Treg cell-depleted mice compared with control mice (Figs. 5D, 5E). We also confirmed that IRBP-specific Treg cells were significantly \((P < 0.01)\) decreased in Treg cell-depleted mice compared with control mice (Figs. 5D, 5E). Taken together, these results suggest that Treg cell depletion by anti-CD25 mAb restored
inflammatory CD4 T cell profiles and ocular inflammation in IL-6KO mice. Therefore, the promotion of IRBP-specific Treg cell generation is critical for inhibiting EAU in IL-6KO mice.

**DISCUSSION**

In the present study, we demonstrated that genetic ablation of IL-6 signaling completely inhibited the development of EAU. In IL-6KO mice, Th17 cell differentiation and IRBP-specific Th1 response were impaired. Ablation of IL-6 signaling in EAU resulted in the promotion of IRBP-specific Treg cells, and the deletion of these Treg cells led to the restored IRBP-specific Th1 response. Our findings suggest that IRBP-specific Treg cell promotion is one of the key mechanisms of the IL-6 signaling blockade for the inhibition of inflammation in EAU.

Previous studies have demonstrated that IL-6 can inhibit Th1 cell differentiation in vitro. However, in our previous study, we demonstrated that treatment with anti–IL-6R mAb in the EAU mouse model inhibits the IRBP-specific Th1 response in vivo. In agreement with this observation, in the present study we analyzed IL-6KO mice and revealed that IRBP-specific Th1 cells are significantly decreased in IL-6KO mice compared with WT mice. Our present study confirmed that inhibition of the Th1 response by anti–IL-6R mAb treatment is not caused by the potential nonspecific effects of this antibody but by its effect on IL-6 signaling itself. In addition, we found that the administration of anti–IL-6R mAb could suppress Th1-dominant EAU in IL-17KO mice. Collectively, IL-6 is likely to be implicated in proper Th1 responses in vivo, especially in IRBP-specific Th1 responses in autoimmune disease; IL-6 may work differently on Th1 cells in vivo and in vitro.

Treg cells are immunosuppressive helper T cells and are effective at ameliorating EAU. As reported previously, our data showed that Treg cells are increased in the late phase of EAU (day 20) in vivo. There were no differences in the frequency of total Treg cells in IL-6KO, GKO, and IL-17KO mice compared with WT mice. In contrast, IRBP-specific Treg cells in IL-6KO mice were significantly increased on day 10, implying that the increase in IRBP-specific Treg cells at an early stage is one of the key immunosuppressive mechanisms of IL-6 signaling blockade.

To further examine whether Treg cells in IL-6KO mice are critical for the inhibition of EAU, we tried to deplete their Treg cells in vivo. IL-2 is essential in the maintenance of Treg cells and is effective at ameliorating EAU. As reported previously, our data showed that Treg cells are increased in the late phase of EAU (day 20) in vivo. There were no differences in the frequency of total Treg cells in IL-6KO, GKO, and IL-17KO mice compared with WT mice. In contrast, IRBP-specific Treg cells in IL-6KO mice were significantly increased on day 10, implying that the increase in IRBP-specific Treg cells at an early stage is one of the key immunosuppressive mechanisms of IL-6 signaling blockade.

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**FIGURE 3.** Induction of EAU in IL-17KO and GKO mice and inhibition of EAU development by IL-6 blockade therapy. (A) Data show the average ± SD of clinical scores of WT, IL-17KO, and GKO mice. Each group included seven to eight mice. No significant changes were seen between these three groups. N.S., not significant. (B) In IL-17KO and GKO mice, a number of inflammatory cells infiltrated the eye, and the retinal structure was destroyed. Scale bar, 100 μm. (C) Intracellular cytokine staining of three groups. Lymph node cells were CFSE labeled and cocultured with IRBP, as described. Values in boldface are representative data obtained from one mouse per group; all groups include at least three mice. (D) The frequency of IRBP-specific Th17, Th1, and Foxp3 Treg cells. Th17 cells in GKO mice increased greatly, and Th1 cells in IL-17KO mice increased moderately. Treg cells showed no significant change. N.D., not detected. Data show the average ± SD of at least four mice. Welch’s t-test for Th17 cells and Treg cells and Student’s t-test for Th1 cells. *P < 0.05; **P < 0.01. (E, F) Anti–IL6R mAb injection (8 mg) on day 1 after EAU induction ameliorated EAU in both GKO (E) and IL-17KO (F) mice. Mann-Whitney U test; *P < 0.05.
these mice play an important role in the inhibition of EAU. However, although anti–CD25 mAb treatment is widely used for Treg cell depletion,9,25 most—but, importantly, not all—CD4+Foxp3+ cells are also CD25+.31 Thus it should be noted that there exists some degree of limitation in the total depletion of Treg cells by this standard methodology.

Interestingly, the frequency of Th1 and Th17 cells in draining lymph nodes was not significantly different between Treg cell-depleted and -nondepleted IL-6KO mice; however, IRBP-specific Th1 and Th17 cells were increased in Treg cell-depleted mice. In accordance with our finding, Treg cells are considered to suppress Th1 cells directly.6,30,34 In addition, it was reported previously that Treg cell depletion in vivo drives the reappearance of Th17 cells in IL-6 signaling blockade mice.2 Thus, it is reasonable to speculate that the blockade of IL-6 signaling in mice with EAU leads to the promotion of IRBP-specific Treg cell generation, which, in turn, suppresses IRBP-specific Th1 and Th17 response. Furthermore, because the IL-6 signaling blockade can abolish Th17 cell differentiation directly,12 this Treg promotion should be of particular importance in the suppression of IRBP-specific Th1 cells.

We attempted to investigate the mechanisms involved in Treg cell suppression of IRBP-specific Th1 cells in vivo. Although we were able to obtain Treg cells from lymph nodes, we were not able to obtain Treg cells from the eye. In addition, because IRBP-specific Treg cells could be detected only by coculture with IRBP and CFSE, as described. CD4+ cells were gated. Values in boldface are representative data obtained from one mouse per group; all groups include six mice.

(C) Frequency of IRBP-specific Treg cells in IL-6KO mice was significantly higher than that of WT mice. Data show the average ± SD of six mice. Student’s t-test; *P < 0.05. (D) Lymph node cells on day 10 were labeled by CFSE and cocultured with IRBP and CFSElow; CD4+ cells were gated. Values in boldface are representative data obtained from one mouse per group; all groups include at least three mice.

In summary, our study suggest that IL-6 is a key cytokine that determines the fate of IRBP-responsive CD4 T cells, inhibiting the generation of immunosuppressive IRBP-responsive Treg cells and promoting IRBP-specific Th17 and Th1 cells. This is likely the reason IL-6 signaling blockade completely
suppresses the development of EAU in which Th1 and Th17 cells are implicated. Anti-IL-6R mAb therapy may thus be effective in either Th1- or Th17-dominant diseases such as human uveitis and may also be useful for the treatment of inflammatory disease refractory to current therapies.

References


