Linkage of IL-6 with Neutrophil Chemoattractant Expression in Virus-Induced Ocular Inflammation

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PURPOSE. Herpes simplex virus (HSV)-1 infection of the murine cornea is known to stimulate a vigorous interleukin (IL)-6 response, but whether this pleiotropic cytokine is an essential participant in corneal inflammation is unclear. This study was designed to compare the early inflammatory response in IL-6 gene-deficient mice to that in wild-type hosts.

METHODS. Gene knockout and wild-type mice (C57BL/6 background) were infected intracorneally with HSV-1 (strain RE) and observed through clinical examination and immunohistochemistry for the development of corneal opacity. Virus corneal titers were determined by standard plaque assay on Vero cells. Cytokine and chemokine levels in corneal lysates were measured with commercial ELISA kits.

RESULTS. Corneal opacity in IL-6−/− mice was substantially diminished in comparison with IL-6+/+ hosts 24 to 48 hours after intracorneal viral infection, and corneal levels of MIP-2 and MIP-1α were significantly reduced. Local administration of IL-6 at the time of infection restored corneal opacity and chemokine levels to that of wild-type hosts. Antibody neutralization of endogenous IL-6 in IL-6−/− animals reduced corneal opacity scores and MIP-2 levels to that of IL-6−/− mice. Ex vivo studies with excised corneal buttons revealed that uninfected IL-6−/− corneas injected with IL-6 produced MIP-2 and MIP-1α at levels comparable to that seen in IL-6+/+ hosts.

CONCLUSIONS. Collectively, these results suggest that IL-6 promotes corneal inflammation by acting in an autocrine–paracrine fashion to induce resident corneal cells to make MIP-2 and MIP-1α, which in turn recruit neutrophils to the virus infection site. (Invest Ophthalmol Vis Sci. 2002;43:737–743)

Interleukin-6 (IL-6) is a cytokine that is rapidly produced at local tissue sites after disruption of homeostasis due to trauma or infection.1 It is functionally diverse, influencing the growth, differentiation, and activation of cells and their expression of proteins principally in inflammation, immune responses, and hematopoiesis. To evaluate the inflammatory role of IL-6, studies have been conducted in gene-disrupted mice. It has been found that antigen-induced arthritis is absent or substantially reduced in the IL-6−/− mice.2,3 Such mice are also resistant to experimental autoimmune encephalomyelitis.4,5 Administration of exogenous IL-6 restores susceptibility.4 Other studies have shown that less tissue injury is observed in turpentine-6 or carrageenan-treated IL-6−/− hosts7 and that treatment with an anti-IL-6 receptor (IL-6R), mAb is protective in a murine model of colitis.8 Thus, IL-6 can be an important promoter of inflammation.

However, IL-6 can also function as an anti-inflammatory cytokine. For example, Xing et al.9 reported that acute inflammatory responses in animal models of endotoxic lung or endotoxemia were more severe in IL-6−/− mice. Administration of recombinant IL-6 reduced circulating levels of proinflammatory mediators. IL-6 can also produce an anti-inflammatory effect by inducing glucocorticoids and natural antagonists of IL-1α (reviewed in Ref. 10). Additionally, IL-6 may exist as a bystander, neither actively promoting nor inhibiting inflammation.11

Ongoing studies in our laboratory have sought to identify and characterize the mediators that participate in the inflammatory cascade in the herpes simplex virus (HSV)-1-infected murine cornea. In this model, the inflammatory response can progress over a 14- to 21-day period to severe stromal keratitis, causing permanent blindness.12–14 As part of the early warning alarm system, IL-6 appears rapidly after both virus15 and bacterial infection.16–18 Indeed, it is one of the more abundantly produced cytokines and can persist as inflammation progresses.

IL-6 is made by a wide variety of cell types, including those found in ocular tissue. We have shown that IL-1α and TNF-α can induce human corneal fibroblasts and epithelial cells to synthesize and secrete IL-6.19–21 Additionally, studies in excised mouse corneas have revealed that IL-6 mRNA induced by endogenous IL-1α is found in all three resident corneal cell types and that the corneal epithelial layer is the most abundant producer of protein.20 Kanangat et al.21 have reported that HSV-1 infection selectively upregulates IL-6 gene expression in the murine epithelial-like cell line EMT-6.

Although IL-6 is quickly produced after HSV-1 corneal infection, it is not known whether it is a necessary component of the inflammatory cascade. We, therefore, initiated studies to investigate whether IL-6 may be involved in the modulation of chemokine expression. We focused on macrophage inflammatory protein (MIP)-2 and MIP-1α, because these chemokines are known to rapidly recruit neutrophils into the cornea after HSV-1 infection.22 The experimental approach was to compare the inflammatory response elicited by HSV-1 intracorneal infection in IL-6 gene–deficient mice with that of their wild-type counterparts. In this study, IL-6 was a critical component of the early inflammatory response. Our data indicate that IL-6 enhanced the production of MIP-2 and MIP-1α, chemokines important in the recruitment of neutrophils into the HSV-1-infected cornea.

MATERIALS AND METHODS

Animals

Four-week-old IL-6 gene–deficient mice and matched control mice (C57BL/6 mice) were obtained from Jackson Laboratories (Bar Harbor, ME). All animals were cared for in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and in compliance with federal, state, and local regulations.
Antibodies and Reagents

Rat IgG mAb to mouse IL-6 and murine recombinant IL-1β/H9251 were purchased from Biosource International (Camarillo, CA); recombinant murine (rm)IL-6 from Endogen, Inc. (Woburn, MA); and hamster IgG monoclonal antibody to mouse IL-1β/H9251 from R&D Systems (Minneapolis, MN). Rat RB6-8C5 monoclonal antibody (mAb), a gift from Robert Coffman (DNAX Research Institute, Palo Alto, CA), was prepared as previously described.23 RB6-8C5 mAb reacts with the Ly-6G antigen, which is expressed on neutrophils and other granulocytes at a level that directly correlates to the differentiation and maturation stage of the cell.

Intracorneal and Subconjunctival Inoculations

Intracorneal injection was accomplished by first puncturing the corneal epithelium wall with a 30-gauge disposable needle. A 30-cm 32-gauge stainless steel needle attached to a dispenser (Hamilton, Reno, NV) was then threaded into the corneal stroma and 1.0 mL of solution containing the appropriate dose of HSV-1 strain RE (10^3-10^5 plaque-forming units [PFU]) was injected. In some experiments the 1.0 mL inoculum contained a mixture of HSV-1 (10^5 PFU/mL) admixed with mAb to IL-6 (5 μg/mL) or rmIL-6 (50 ng/mL). These mixtures were prepared immediately before use and directly administered. Pilot studies established that neither addition of IL-6 nor antibody to IL-6 impaired virus infectivity. Subconjunctival antibody injections were performed by using a 2-cm 32-gauge needle and syringe (Hamilton) to penetrate the perivascular region of the conjunctiva and deliver 4 μL into the subconjunctival space. To score corneal opacity, eyes were graded on a scale of 0 to +4 by visual observation, using a dissecting biomicroscope. Eyes were graded as follows: 0, clear cornea; +1, slight corneal haze; +2, moderate corneal opacity; +3, severe corneal opacity with visible iris; +4, severe corneal opacity with iris not visible. Eyes were examined in a coded manner, with the reader unaware of the treatment administered.

Incubation of Corneas Ex Vivo

After intracorneal injection, the corneas were immediately excised, trimmed with a 2-mm trephine, and incubated individually in 200 to 250 μL RPMI-1640 medium in a polypropylene tube at 37°C in 5% CO₂ for 10 hours. The medium, with or without corneas, was then frozen at -70°C.

Chemokine and Cytokine Assays

Samples containing corneas were thawed, minced, and processed for 80 seconds (Tissue Tearer, Biospec Products, Bartlesville, OK), sonicated for 20 seconds, and clarified by centrifugation at 150 g for 10 minutes, thus producing clarified corneal lysates. Samples (clarified corneal lysates or supernatant) were assayed by ELISA for MIP-2, MIP-1α, and IL-6. The MIP-2 kit (assay sensitivity, 1.5 pg/mL), and MIP-1α kit (assay sensitivity, 1.5 pg/mL), were purchased from R&D Systems (Minneapolis, MN). The IL-6 kit (assay sensitivity, 7.0 pg/mL) were purchased from Endogen, Inc.

![Figure 1](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933592/)  
**Figure 1.** IL-6−/− mice displayed less severe corneal opacity than IL-6+/+ mice 48 hours after HSV-1 infection. Hosts were infected intracorneally with the indicated concentrations of HSV-1 and individually scored for corneal disease. Data are the mean ± SE of five corneas per group.

![Figure 2](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933592/)  
**Figure 2.** Photomicrographs of cross sections of corneas from IL-6+/+ (left) and IL-6−/− (right) mice, removed 48 hours after infection with 10^5 PFU HSV-1 and stained with an mAb RB6-8C5. Note the swelling and extensive leukocyte infiltrate in the IL-6+/+ cornea. Magnification, ×400.
Immunohistochemistry

Immunohistochemical staining was performed using a slight modification of the procedure of Hendricks et al.²⁴ Infected eyes were enucleated and embedded in optimal cutting temperature compound (Tissue Tek; Sakura Finetek, Torrance, CA) and 6-μm sections were cut at −20°C. The sections were fixed in cold acetone for 10 minutes and then blocked with normal goat serum. The primary antibody, RB6-8C5 (5 μg/mL) was applied to the tissue for 1 hour at room temperature. The sections were then washed and stained using the streptavidin-biotin complex immunoperoxidase staining procedure, according to the manufacturer’s protocol (Zymed Laboratories, South San Francisco, CA). The slides were washed in distilled water and counterstained in Harris hematoxylin for 3 minutes. The slides were then examined under a light microscope, and pictures were taken (BX50 camera; Olympus Optical Co., Tokyo, Japan).

Neutrophil Isolation and Stimulation

Bone marrow (BM) was flushed from the femur and tibia with media (RPMI-1640 with 5% newborn calf serum) using a syringe and 25-gauge needle. The BM cells were centrifuged (1200 rpm for 5 minutes), washed twice, layered over a gradient (Histopaque 1119 and 1077; Sigma, St. Louis, MO), and centrifuged at 700g for 30 minutes. The enriched neutrophil layer was removed, washed twice in medium and treated with red blood cell lysis buffer (Sigma). Contaminating monocytes were depleted by adherence (30 minutes at 37°C) to a polystyrene tissue culture plate²⁵ (Corning Glass Co., Corning, NY). Neutrophil purity was consistently more than 99%, as assessed by staining (HEMA 3; Biochemical Sciences Inc., Swedesboro, NJ) of cytospin slides (Shandon, Pittsburgh, PA).

For stimulation 1 × 10⁶ neutrophils in 0.5 mL medium were placed in triplicate in 24-well tissue culture plates (Corning Glass Co.). The wells were precoated with 0.5 mL newborn calf serum per well for 1 hour at 37°C and then washed three times with PBS. Stimulations were performed by the addition of rmIL-6 to wells at a final concentration of 5 or 50 ng/mL. rmIL-1α was used at 1 or 10 ng/mL. Phorbol 12-myristate, 13 acetate (PMA; 30 ng/mL) served as the positive control and medium only as the negative control. After incubation for 8 hours at 37°C in 5% CO₂ supernatants were removed, clarified by centrifugation, and assayed for chemokine content by ELISA.

**FIGURE 3.** Effect of IL-6 treatment on (A) corneal opacity and (B) MIP-2 and (C) MIP-1α levels in HSV-1–infected IL-6−/− corneas. IL-6 was mixed with 10⁴ PFU HSV-1 and inoculated intracorneally into IL-6−/− mice. Additional IL-6−/− and IL-6+/+ groups were treated with virus only. At 48 hours after infection, corneal opacity was scored. Corneal lysates were then prepared and assayed for chemokines by ELISA. Data are the mean ± SE of five corneas per group.

**FIGURE 4.** Antibody neutralization of IL-6 suppressed (A) corneal opacity and (B) MIP-2 levels in IL-6−/− mice. Wild-type mice were infected intracorneally with 10⁵ PFU HSV-1, admixed with neutralizing mAb to IL-6 (5 μg/μL). Additional antibody (4 μL) was administered subconjunctivally at 12, 24, and 36 hours after infection. Other IL-6−/− and IL-6+/− hosts received control rat IgG. Corneal opacity was recorded at 48 hours, and corneal lysates were assayed for MIP-2.
Statistical Analysis

The Mann-Whitney test was used to determine significant differences in the corneal opacity scores between treated and control groups. Student’s t-test was used to evaluate mediator responses between treated and control cells. The level of confidence at which the results were judged significant was $P < 0.05$.

RESULTS

HSV-1–Induced Corneal Opacity in IL-6$^{-/-}$ Mice

When HSV-1 is inoculated intracorneally a rapid inflammatory response is elicited, which is evident by 24 hours and peaks at 48 hours after infection.22 We investigated whether disruption of the IL-6 gene would influence this initial response. It was found that IL-6$^{-/-}$ animals challenged with virus over a 100-fold dose range consistently showed significantly less corneal cloudiness than did IL-6$^{+/+}$ mice, as determined by microscopic observation during the first 2 days postinfection. Figure 1 shows representative results from one of five independent experiments. This striking disparity was confirmed histologically: IL-6$^{-/-}$ corneas were less swollen and contained many fewer neutrophils positively stained with RB6-8C5 mAb than did corneas from IL-6$^{+/+}$ hosts (Fig. 2). The difference in inflammation was transient; the opacity scores of the two groups were no longer significantly different 4 days after infection. The distinct disparity in corneal responsiveness observed during the first 2 days could not be attributed to a difference in HSV-1 replication as the titers of infectious virus in the wild-type mice ($1.0 \times 10^5 \pm 0.4 \times 10^5$) were not significantly different ($P > 0.7$) from that observed in the ocular tissue of knockout hosts ($1.2 \times 10^5 \pm 0.5 \times 10^5$). Similar virus titer results were obtained in two additional independent experiments.

Effect of IL-6 Administration on Corneal Opacity and Chemokine Expression

To evaluate whether exogenous IL-6 could restore heightened corneal opacity, reconstitution experiments were performed in IL-6$^{-/-}$ mice. It was found that a single inoculation of IL-6 administered locally, together with the virus challenge inoculum restored corneal opacity to the levels seen in IL-6$^{-/-}$ mice at 24 and 48 hours after infection (Fig. 3A; only 48-hour results from a representative experiment are shown). No corneal cloudiness was observed in animals given 50 ng IL-6 in the absence of HSV-1. Administration of IL-6 together with the virus significantly raised the levels of chemokines MIP-2 (Fig. 3B) and MIP-1α (Fig. 3C) relative to that seen in control mice treated with virus only. Furthermore, the amounts of each mediator were comparable to the levels found in the corneas of the IL-6$^{-/-}$ hosts and thus correlated with increased mean corneal opacity scores.
Effect of IL-6 Neutralizing Antibody on Corneal Opacity and MIP-2 Response in HSV-1–Infected IL-6+/−/− Hosts

We next determined whether antibody neutralization of endogenous IL-6 would influence HSV-1 induced corneal opacity in IL-6+/−/− mice. IL-6 antibody was introduced intracorneally at a concentration of 2.5 g/L when admixed with the challenge virus. In preliminary studies, it was determined that a concentration of anti-IL-6 antibody lower than 2.5 g/L was not sufficient to neutralize the effect of IL-6 (data not shown). Additional antibody was administered subconjunctivally at 12-hour intervals, and corneas were examined at 48 hours after infection. Figure 4A shows results from a representative experiment in which corneal opacity scores in IL-6+/−/− hosts after anti-IL-6 antibody treatment were significantly reduced compared with IgG-treated control animals and indeed were comparable to that seen in IL-6+/−/− mice. In addition, corneal MIP-2 concentrations were also significantly reduced (p<0.3) to levels observed in IL-6+/−/− mice (Fig. 4B).

Induction of MIP-2 and MIP-1α in Infected and Uninfected Corneal Tissue

We postulated that HSV-1 infection induces resident corneal cells to synthesize and secrete IL-6. This hypothesis was investigated using excised corneas to avoid production of mediators by infiltrating leukocytes. Figure 5 shows that after HSV-1 infection, corneal tissue from IL-6+/−/− hosts had high levels of IL-6, whereas none was seen in virus-infected IL-6+/−/− corneas. Significantly, MIP-2 levels in infected IL-6+/−/− corneas were 10-fold higher than that seen in infected corneas without a functional IL-6 gene. This suggests that IL-6 induces resident corneal cells to make a neutrophil chemoattractant. Support for this prediction comes from experiments in which antibody neutralization of IL-6 in HSV-1-infected IL-6+/−/− corneas abrogated production of MIP-2 and MIP-1α (Fig. 6).

Additionally we found that administration of exogenous IL-6 to uninfected IL-6−/−/− corneal tissue at a 10- to 50-ng dose stimulated a 24- to 45-fold increase in MIP-2 (Fig. 7A) and an 8- to 23-fold increase in MIP-1α (Fig. 7B). These amounts were comparable to that stimulated by IL-6 in uninfected wild-type corneas.

Effect of IL-6 on MIP-2 and MIP-1α Induction in Neutrophils

The IL-6 produced by resident corneal cells could also induce neutrophils recruited to the HSV-1 infection site to produce chemokines. Accordingly, we tested whether IL-6 stimulates MIP-2 or MIP-1α synthesis in these cells. Figure 8 depicts representative data from one of four independent experiments. Five or 50 ng/mL IL-6 added to bone marrow–derived neutrophils did not enhance production of MIP-2 or MIP-1α above background levels (a less than twofold increase). In contrast, IL-1α stimulated a two- to sixfold increase in MIP-1α. MIP-2 production was also enhanced by IL-1α in a dose-dependent manner, although the amounts generated were substantially lower (18- to 31-fold) than MIP-1α. Neutrophils stimulated with...
There are several mechanisms by which HSV-1 infection could induce IL-6. One is that virus infection may directly activate IL-6 gene expression in corneal cells.\(^{21}\) Alternatively, virus infection may induce IL-1\(\alpha\), which in turn induces IL-6. This latter possibility is supported by earlier studies that showed that synthesis of IL-6 stimulated by mechanical trauma in excised corneal buttons was abrogated by antibody to IL-1\(\alpha\) but not antibodies to IL-1\(\beta\) or TNF-\(\alpha\).\(^{20}\)

Our present data provide evidence that IL-6 promoted induction of neutrophil chemoattractants. Initial evidence for this conclusion comes from in vivo studies that show that IL-6 administered to infected corneas of IL-6\(^{-/-}\) mice elevates MIP-2 and MIP-1\(\alpha\) to wild-type levels and that antibody neutralization of IL-6 locally in wild-type corneas reduces MIP-2 to IL-6\(^{-/-}\) levels. It is worth noting that our follow-up ex vivo studies demonstrated that uninfected as well as infected resident cells in corneal tissue exposed to IL-6 produced MIP-2 and MIP-1\(\alpha\). Thus, IL-6 induction of chemokines does not require that the corneal cells be infected. Collectively, a likely scenario based on our findings is that HSV-1 corneal infection initiates an inflammatory cascade in which IL-1\(\alpha\) induces IL-6 and then these two cytokines through autocrine-paracrine action stimulate resident corneal cells to produce neutrophil chemoattractants. An earlier report showing that IL-1\(\alpha\) inoculated into the mouse cornea results in the production of MIP-2\(^{22}\) is compatible with this conclusion.

In contrast to resident corneal cells, exposure of purified mouse neutrophils to recombinant IL-6 caused little or no elevation of MIP-2 or MIP-1\(\alpha\). However, IL-1\(\alpha\) induced substantial levels of MIP-1\(\alpha\) and more modest but significant amounts of MIP-2. This suggests that resident cells in the cornea are the principal targets of IL-6, whereas IL-1\(\alpha\) acts on both resident corneal cells and infiltrating leukocytes. Whether IL-6 can induce infected corneal cells or infiltrating neutrophils to make and secrete other proinflammatory mediators remains to be determined. Additionally, IL-6 may also influence the effector responses of neutrophils.\(^{27}\)

It has been reported that IL-10 is produced constitutively in the mouse cornea and acts to antagonize development of virus-induced inflammation.\(^{28}\) It may be speculated that IL-6 enhances corneal disease because it suppresses endogenous IL-10 expression. However, in three independent experiments we found that administration of IL-6 to IL-6\(^{-/-}\) mice did not alter IL-10 corneal levels (Fenton and Lausch, unpublished observations, 2001). In contrast, antibody neutralization of endogenous IL-10 significantly enhanced production of IL-6, MIP-2, and MIP-1\(\alpha\).\(^{28}\) We conclude that HSV-1 infection of IL-6-deficient mice did not result in upregulation of the anti-inflammatory cytokine IL-10 as was seen in Candida albicans infection.\(^{29}\)

IL-6\(^{-/-}\) mice have been observed to produce a lower antibody response or a reduced cytotoxic T-lymphocyte response to certain selected viral pathogens\(^{30}\) but not others.\(^{31}\) We found that although HSV-1 ocular titers in IL-6\(^{-/-}\) mice were similar to those of IL-6\(^{+/+}\) hosts at 48 hours after infection 8 of 15 (53%) showed development of fatal encephalitis, whereas only 1 of 15 (7%) IL-6\(^{+/+}\) mice died. These results are in agreement with the report of LeBlanc et al.\(^{32}\) Neutrophils and mononuclear cells are known to help limit HSV-1 growth and spread to the central nervous system after ocular infection.\(^{23,33}\) Their diminished early recruitment due to reduced MIP-2 and MIP-1\(\alpha\) production would be expected to increase IL-6\(^{-/-}\) host susceptibility to HSV-1. Our results may also help to explain the impaired neutrophil recruitment and increased susceptibility seen in IL-6\(^{-/-}\) mice infected with Listeria monocytogenes\(^{34}\) and C. albicans.\(^{29}\) In addition, or alternatively, the stronger inflammatory response in the IL-6\(^{-/-}\) cornea may generate a cytokine milieu that favors a greater, and thus more protective, T helper cell-1 response.\(^{35,36}\)

**FIGURE 8.** Neutrophils exposed to IL-1\(\alpha\) but not IL-6 produce (top) MIP-2 and (bottom) MIP-1\(\alpha\). Bone marrow-derived neutrophils (10\(^6\)/well) were prepared and stimulated in triplicate, with the indicated concentrations of IL-6 and IL-1\(\alpha\) for 8 hours. Supernatants were then assayed for chemokines by ELISA. *Significantly higher than the medium control (\(P < 0.001\)).

30 ng/mL PMA produced on average 209 pg/mL MIP-2 and 2198 pg/mL MIP-1\(\alpha\). Incubation of neutrophils with both IL-6 and IL-1\(\alpha\) did not elevate chemokine production above that seen with IL-1\(\alpha\) alone.

IL-6 failed to stimulate neutrophils purified from the bone marrow of IL-6\(^{-/-}\) mice to produce MIP-2 or MIP-1\(\alpha\) when tested as described. However, IL-1\(\alpha\) at 10 ng/mL induced a six- and ninefold increase in MIP-2 and MIP-1\(\alpha\), respectively, over background levels. The inability of IL-6 to induce chemokine production by neutrophils was also observed when the incubation period was extended from 10 to 18 hours.

**DISCUSSION**

In this study, evidence showed IL-6 played a prominent role in initiating corneal inflammation after HSV-1 infection. Mice with a disrupted IL-6 gene displayed substantially reduced corneal opacity 24 to 48 hours after intracorneal infection in comparison with their wild-type counterparts, as judged both clinically and histologically. A single 50-ng dose of IL-6 administered locally at the time of infection restored corneal disease to wild-type levels. Furthermore, antibody neutralization of endogenous IL-6 in IL-6\(^{-/-}\) hosts reduced corneal inflammation to that observed in IL-6\(^{+/+}\) animals. The recent report that IL-6 abolishes immune privilege in eyes with endotoxin-induced uveitis\(^{26}\) also supports the view that IL-6 is proinflammatory in ocular tissue.
In summary, our findings showed IL-6 to be an important participant in the cytokine cascade triggered by HSV-1 corneal infection. By inducing neutrophil chemoattractants IL-6 amplified the inflammatory response. Our data are in agreement with the report of Smith et al.,³⁷ wherein IL-6 was associated with MIP-1α expression in a bleomycin-induced lung injury model. Also, Romano et al.,³⁵ observed that IL-6–/– mice exhibit reduced chemokine production and defective leukocyte recruitment in subcutaneous air pouches injected with inflammatory stimuli. This defect could be reversed by IL-6 administration. In follow-up studies IL-6 itself did not induce human endothelial cells, which have no IL-6R, to make chemokine, but IL-6–soluble (s)IL-6R complexes were active. Collectively, these studies and ours indicate that chemokine production can be induced in distinctly different cell types by IL-6 per se, or by IL-6–sIL-6R complexes. This suggests that IL-6 in one form or another may promote chemokine expression in a variety of tissues. Thus, IL-6 represents a potential therapeutic target for suppressing ocular inflammation.

References