Interleukin-1 receptor antagonist suppresses Langerhans cell activity and promotes ocular immune privilege

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Interleukin-1 Receptor Antagonist Suppresses Langerhans Cell Activity and Promotes Ocular Immune Privilege

M. Reza Dana,¹ Ruoping Dai,² Suning Zhu,¹ Jun Yamada,¹ and J. Wayne Streilein¹,²

Purpose. To determine whether the capacity of Langerhans cells (LCs) to abrogate ocular immune privilege can be suppressed by the topical application of interleukin-1 receptor antagonist (IL-1ra).

Methods. Cautery was applied to corneas of BALB/c mice on day 0 to induce centripetal migration of LCs. Immune privilege was tested by the ability to induce anterior chamber-associated immune deviation (ACAID) to intracameral injection of soluble antigen 1 to 2 weeks after cautery application. The number of LCs was enumerated by immunofluorescent staining. In other experiments, freshly procured Thy-1-depleted epidermal cells, with or without LC depletion, were injected directly into virgin murine corneas before testing for ACAID. All test animals were randomized for treatment with either topical IL-1ra or placebo in a masked fashion for 1 to 2 weeks after induction of LC migration and before intracameral injection of antigen.

Results. Intracorneal injection of freshly procured LC-depleted epidermal cells into normal eyes failed to abrogate ACAID, whereas LC-containing cell populations uniformly led to loss of immune privilege (P < 0.01). Topical treatment with IL-1ra led to retention of the cauterized eyes’ capacity for ACAID induction (P < 0.01) and to a profound (>80%) suppression of LC migration compared with untreated controls (P < 0.01). Additionally, topical IL-1ra treatment of eyes with intracorneally injected LCs preserved immune privilege and ACAID induction (P < 0.001).

Conclusions. IL-1 mediates mechanisms of immunity in corneal inflammation that subvert the normal eye’s immune privileged state. However, its antagonism with topical administration of IL-1ra preserves ocular immune privilege and ACAID through suppression of LC function. (Invest Ophthalmol Vis Sci. 1998;39:70–77)

Dysregulation of the normal ocular immune privileged state renders the eye susceptible to immunogenic inflammation which may lead to loss of sight.¹ ² Conservation of immune privilege is mediated through the active regulation of both the afferent (antigen processing and sensitizing) and efferent (effector) arms of the immune response.³ Cardinal factors that have been implicated in the maintenance of immune privilege involving the cornea include avascularity that limits the ingress of blood-borne factors and cells into the cornea, absence of corneal lymphatics that prevents the delivery of antigens and antigen-processing cells (APC) to the immunogenic milieu of lymph nodes, rarity of native antigen-presenting (Langerhans) cells, constitutive expression of immunomodulatory cytokines, and the normal expression of Fas ligand that mediates lymphocyte apoptosis.⁴ ⁶

Anterior chamber-associated immune deviation (ACAID) is defined as an antigen-specific systemic response evoked by intracameral injection of soluble antigens.⁷ The stereotypic ACAID response is distinct from conventional immune responses in that it leads to a systemic suppression of antigen-specific, delayed-type hypersensitivity (DTH). Immune privilege is thought to be an evolutionary adaptation designed to limit the intraocular expression of immunogenic inflammation, and depends, in part, upon the induction of ACAID.⁵ ⁷ ⁸ Previously, in reporting our observations that a variety of angiostatic treatments can restore ACAID in eyes with inflammatory corneal neovascularization, we hypothesized that these therapies (e.g., corticosteroids) also downregulate the activity of Langerhans cells (LCs), suppressing antigen processing and presentation by these cells in inflamed corneas.¹ In this series of experiments we were interested in formally testing our hypotheses that corneal LCs mediate abrogation of immune privilege and that this function is dependent, in part, on interleukin-1 (IL-1).

Langerhans cells are a population of constitutively immunogenic dendritic cells that mediate antigen presentation and immune surveillance in the skin and cornea, where they also play a critical role in the afferent limb of allo sensitization.⁹ ¹³ Centripetal migration and upregulation of LC activity have been reported to be associated with a heightened state of immune reactivity in the cornea,⁹ ¹³ ¹⁶ and their accessory function in vitro, measured by their immunostimulatory capacity and expression of costimulatory molecules, can be upregulated by IL-1.¹⁷ ¹⁹ It has been reported that inflammatory in-
sults to the normal cornea, such as light application of heat cautery, cause the centripetal migration of LCs, interfering with induction of ACAID. In an elegant and pioneering series of experiments, Niederkorn and colleagues demonstrated that phagocytosis of particulate matter or killed *Staphylococcus aureus* stimulate corneal epithelial cells to secrete increased amounts of IL-1, which in turn is associated with the centripetal migration of LCs. Because of these observations, antagonism of IL-1 activity serves as an attractive target for therapeutic interventions designed to suppress immunogenic inflammation in the eye.

IL-1, a potent proinflammatory cytokine produced primarily by monocytes and macrophages, but also by resident corneal cells, has a wide range of activities, including mediation of the acute-phase response, chemotaxis and activation of inflammatory and antigen-presenting cells, and stimulation of neovascularization. In the eye, IL-1 activity is correlated with corneal neovascularization, endotoxin-mediated uveitis, corneal collagenase and metalloprotease expression, corneal injury in vitamin-A deficiency, and herpetic stromal keratitis. Recently, it has been correlated with corneal allograft survival. Interleukin-1 receptor antagonist (IL-1ra) is a naturally occurring IL-1 isoform produced by the same cells that synthesize IL-1. It has high-affinity binding to IL-1 receptors, but shows no agonist activity. There is a 77% homology between the human and murine IL-1ra, and systemic administration of recombinant human IL-1ra has been shown to have a profound downregulatory effect on IL-1-mediated activities in both humans and mice.

To test the potential of antagonizing IL-1 activity in corneal inflammatory disease, we have examined the effects of topically administered IL-1ra on LC migration and induction of immunity. In this series of experiments we demonstrate that antagonism of IL-1 activity by application of IL-1ra is successful not only in suppressing LC migration but also in preventing the abrogation of immune privilege in corneal inflammation.

**Materials and Methods**

**Mice and Anesthesia**

Mice (BALB/c (H-2^b_), aged 8–10 weeks) were obtained from the Schepens Eye Research Institute’s animal colony. Animals with dystrophic–degenerative corneal calcific deposits were excluded from study. All animals were treated according to the tenets of the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Each animal was deeply anesthetized with an intramuscular injection of 3 to 4 mg of ketamine and 0.1 mg of xylazine before all surgical procedures.

**Cauterization of the Corneal Surface**

Mice were anesthetized and placed under the operating microscope. Using the tip of a hand-held thermal cautery, two to three (light) or five to six (heavy) light burns were applied to the central 50% of the cornea as previously described to induce centripetal migration of LCs without associated neovascularization. Immediately after surgery, cryothromycin ophthalmic ointment was applied to the ocular surface. Corneas received 1 to 2 weeks of topical IL-1ra or placebo, as specified by the protocol, before LC enumeration or intracameral injection of antigen as detailed below.

**Corneal Injection of Keratinocytes and Langerhans Cells**

IL-1ra-enriched epidermal cells were prepared according to a method previously described. Briefly, the dry-shaved abdominal skin of the BALB/c female mice was removed and floated (epidermal side up) on phosphate-buffered saline containing 0.25% trypsin (Bio Whittaker, Walkersville, MD) at 37°C in 5% CO₂ for 1 hour. The epidermis was then separated from the dermis with forceps and incubated in 0.25% trypsin plus 0.5 mg/ml DNase (Sigma Chemical, St. Louis, MO) for an additional 10 minutes. The epidermis was then desegregated by using a 10-ml syringe, and the single cells recovered were filtered through a 75-µm nylon cell strainer. To deplete Th1+ epidermal dendritic cells, epidermal cells were further incubated with anti-mouse Thy-1 monoclonal antibody (Collaborative Biomedical Products, Bedford, MA) plus complement for 45 minutes. To enrich for IL-1a LCs, the suspension was layered on an equal volume of Accu-prep Lymphocytes (Nycomed Pharma, Oslo, Norway) and centrifuged at 1600 rpm for 20 minutes. The recovered interface cells comprised 10% to 15% Th1+ LCs. To deplete IL-1a+ cells, epidermal cells were treated with anti-mouse IL-1 monoclonal antibody (Collaborative Biomedical Products) plus complement for 45 minutes. Flow cytometric analysis of this method of depletion has demonstrated no IL-1a+ cells, and hapten-derivatized IL-1a-depleted epidermal cells lose their sensitizing capacity when injected subcutaneously into naive mice. IL-1ra-enriched or IL-1a-depleted epidermal cells were resuspended in completed RPMI 1640 (Bio Whittaker) supplemented with 10% fetal calf serum at two desired concentrations: 5 × 10⁵ cells/ml and 5 × 10⁶ cells/ml. A 0.5-µl portion of each of these populations was injected subepithelially using calibrated glass needles 1 or 2 days before intracameral injection of soluble antigen as described below.

In related ACAID experiments in which the role of IL-1ra was examined, corneas received 1 week of topical IL-1ra or placebo, as specified below, before the intracameral injection of soluble antigen.

**Application of IL-1ra**

One drop (40 µl) of each topical preparation was applied to the eyes of BALB/c mice three times daily as specified by the specific experimental protocol. The study medication was composed of 20 mg/ml human recombinant IL-1ra in 0.2% sodium hyaluronate in phosphate-buffered saline (supplied by Amsco, Boulder, CO). Placebo-treated animals received the vehicle 0.2% sodium hyaluronate only.

**ACAID Induction and Delayed-Type Hypersensitivity Assessment**

At specific time points subsequent to corneal cautery or intracameral injection of cells as described above, anesthetized BALB/c mice were administered 50 µg of soluble antigen ovalbumin (Sigma), per 3-µl volume of Hanks’ balance salt solution, into the anterior chamber of one of their eyes as previously described. Seven days later, they received an immunizing 100-µg dose of ovalbumin antigen (emulsified in complete Freund’s adjuvant) for a total volume of 100 µl injected subcutaneously into the nape of the neck. Seven days later, the mice received intradermal inoculations of antigen (200 µg/10 µl) into their ear pinna. The ear swelling response at 24 and 48 hours, as a measure of delayed-type hypersensitivity (DTH), was assessed using a micrometer. The investigator
FIGURE 1. Various concentrations of congenic epidermal cells, consisting of keratinocytes (kerat) or keratinocytes and Langerhans cells (LCs), were injected into the normal cornea of BALB/c mice. Subsequently, animals received intracameral inoculations followed by immunization and ear challenge, and measurements for delayed-type hypersensitivity were made 24 and 48 hours later. Results at 24 hours (results at 48 hours were similar) indicated that only eyes with LCs were incapable of supporting ACAID induction.

FIGURE 1. Various concentrations of congenic epidermal cells, consisting of keratinocytes (kerat) or keratinocytes and Langerhans cells (LCs), were injected into the normal cornea of BALB/c mice. Subsequently, animals received intracameral inoculations followed by immunization and ear challenge, and measurements for delayed-type hypersensitivity were made 24 and 48 hours later. Results at 24 hours (results at 48 hours were similar) indicated that only eyes with LCs were incapable of supporting ACAID induction.

was masked as to which group of animals the ear measurements were being taken from.

Langerhans Cell Enumeration

The LCs were assessed by an immunofluorescence assay performed on whole corneal epithelial mounts as previously described. Briefly, each eye was enucleated, and the anterior segment was dissected under an operating microscope. The corneas were placed in 20 mM ethylenediaminetetraacetic acid buffer and incubated for 30 minutes at 37°C. The epithelium were removed in toto and washed in phosphate-buffered saline at room temperature. The corneas were fixed with 95% ethanol, washed, and incubated with 1:20 diluted primary anti-murine Ia antibody for 45 minutes at 37°C. The tissue was then washed again in phosphate-buffered saline and incubated with a fluorescein isothiocyanate-labeled goat anti-mouse secondary antibody for 30 minutes at 37°C. Negative controls either bypassed this step or were incubated with antibody specific for an unrelated major histocompatibility complex epitope. Sections were then mounted on slides and examined under a fluorescence microscope using a square ocular grid to enumerate the LCs.

Statistical Analyses

Ear swelling (DTH) measurements and LC enumerations were evaluated statistically by using the two-tailed Student’s t-test. A probability of <0.05 was deemed to be statistically significant. All experiments were repeated to ensure reliability of results. Representative data are exhibited below.

RESULTS

Corneal Langerhans Are Necessary for Impairment of Ocular Immune Privilege and Subversion of ACAID

It has previously been demonstrated that centrally migrating LCs can mediate immune reactivity; however, experimental insults capable of stimulating LC migration could theoretically affect the ocular microenvironment (through upregulation of cytokines by resident cells) sufficiently to disturb the eye’s capacity to retain immune privilege. We hypothesized that intracorneal injection of LC-containing (but not LC-depleted) epidermal cells can suppress immune privilege. Therefore, LC-enriched or LC-depleted epidermal cells were injected into the normal corneas of normal naive mice who were subsequently challenged with soluble antigen to assay for ACAID induction as described above.

Experimental results (Fig. 1) indicated that intracorneal injection of LC-depleted cells was incapable of subverting ACAID, with ear swelling responses consistent with those found in ACAID controls. However, injection of LC-enriched cells into the normal cornea neutralized the eye’s capacity to induce antigen-specific ACAID with DTH measures significantly elevated compared with ACAID controls (P < 0.01) or those observed in LC-depleted cells (P < 0.01). Interestingly, the one log-unit difference in concentration of injected LCs was associated with a marginally significant difference in DTH response at 24 hours (Fig. 1, P = 0.03) but not at 48 hours (P = 0.15).

Interleukin-1 Receptor Antagonist Can Suppress Corneal Langerhans Cell Migration

It has been suggested that the loss of immune privilege (ACAID) observed in cauterized eyes is correlated with the centripetal migration of LCs into the cornea. Because IL-1 has the potential to mediate LC migration, we tested whether its neutralization by topical IL-1ra could suppress corneal LC migratory capacity. To quantify the centripetal migration of LCs into the central cornea after different degrees of corneal thermal cauterization and to assess the efficacy of topical IL-1ra in arresting that migration, groups of animals (N = 10) received light or heavy cauterization as described above on day 0. Test animals received topical IL-1ra, and control animals...
Topical IL-1ra Preserves Ocular Immune Privilege after Corneal Cauterization

Because IL-1ra was shown to effectively suppress LC migration and LCs mediate abrogation of immune privilege, we examined the possibility that topical IL-1ra could retain the eye's capacity for ACAID induction after corneal cautery. Groups of animals received light or heavy cautery on day 0. Each group \(N = 20\) was subdivided into eyes that received topical IL-1ra or placebo for 1 to 2 weeks before intracameral injection of antigen on days 7 or 14. ACAID controls received injections of antigen in a noncauterized eye. In each case, including positive controls receiving no anterior chamber injections, mice were subcutaneously immunized 7 days after their anterior chamber injections, followed by ear challenges 1 week later (Table 1).

Cauterization prevented the induction of ACAID after intracameral injection of antigen at 1 and 2 weeks (Fig. 3) subsequent to the corneal injury. However, application of IL-1ra was capable of preserving the mechanisms of ACAID induction, after corneal cautery, compared with cauterized, untreated controls \(P < 0.01\); DTH responses in IL-1ra-treated animals were consistent with those in animals with normal eyes \(P = 0.91\).

Neutralization of Ocular Immune Privilege by Langerhans Cells is Interleukin-1 Dependent

The above results suggested that corneal LCs were associated with the loss of ocular immune privilege and that IL-1ra antag-

Table 1. Protocol for Testing the Treatment Effect of Topical IL-1ra on the Capacity of the Eye to Sustain Anterior Chamber–Associated Immune Deviation

<table>
<thead>
<tr>
<th>Group</th>
<th>Cauterization (Day 0)</th>
<th>IL-1ra TX* (Days 0–7†)</th>
<th>AC Injection (Day 7)</th>
<th>Subcutaneous* Immunization (Day 14)</th>
<th>Ear Challenge (Day 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Low cauterization</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>2. High cauterization</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3. Low cauterization</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4. High cauterization</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5. ACAID control</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>6. Positive control</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* Abbreviations used: IL-1ra, interleukin-1 receptor antagonist; Tx, treatment; AC, anterior chamber; ACAID, anterior chamber-associated immune deviation.
† In companion experiments, treatment with IL-1ra was continued for 2 weeks, with intracameral injections of antigen performed at day 14, and subcutaneous immunizations and antigenic challenges at days 21 and 28, respectively.
onism of IL-1 activity suppressed LC migration and contributed to the preservation of ACAID induction. However, it remained unclear whether the critical ACAID-inhibiting role of LCs, once present in the cornea, was IL-1 dependent or not. High concentrations of LC-enriched (or LC-depleted) epidermal cells were injected into the corneas of normal BALB/c murine eyes. Each group (N = 10) was subdivided into groups receiving topical IL-1ra or placebo for 1 week before intracameral injection of antigen on day 7. As before, ACAID controls received injections of antigen in normal eyes, and positive controls received no anterior chamber injections. Animals were subcutaneously immunized 7 days after their anterior chamber injections followed by ear challenges 1 week later.

Intracorneally injected LCs were capable of subverting immune privilege as measured by ACAID induction. However, when eyes with intracorneal LCs were treated with IL-1ra, the ACAID response was preserved (Fig. 4); antigen-specific ear swelling responses in the IL-1ra-treated animals were significantly suppressed compared with those of mice whose eyes received placebo alone (P < 0.001) and were instead consistent with the DTH responses in ACAID controls (P = 0.54). These results suggested that suppression of IL-1-induced LC activities was essential in preserving immune privilege.

**DISCUSSION**

The maintenance of ACAID and immune privilege in the anterior segment of the eye requires the active participation of a unique spectrum of immunomodulatory cytokines derived from the cornea and the iris–ciliary body, such as transforming growth factor-β, that suppress immunogenic inflammation and complement activation. The delicate balance between immune privilege and immune reactivity can be subverted by a number of pathologic states and cytokines, including interleukin-12 and interferon-γ, that preferentially activate immunogenic inflammation at the expense of ACAID.

There has been significant indirect evidence relating loss of immune privilege in a setting of corneal inflammation to increased LC activity. However, proof of causation has been lacking, because it has been difficult to determine the relative contribution of multiple local factors to the retention or loss of immune privilege. For example, although corneal cauterization has been used as a model to induce LC activity without associated neovascularization, the attendant corneal injury, disruption of the epithelial barrier, lysis of resident cells, and transient edema can all affect corneal physiology. In addition, the tissue injury noted in experimental models of corneal inflammation has made it difficult to directly relate activation of LCs to a given cytokine.

The series of experiments performed in this study were designed to evaluate the role of IL-1 in mediating LC activity in corneal inflammation and to assess whether suppression of IL-1 by its receptor antagonist (IL-1ra) can succeed in reversing the deleterious effects of LC activity on ACAID. Our results indicated that the presence of LCs in the cornea led to a loss of immune privilege and that this loss was mediated, at least in part, by the proinflammatory cytokine IL-1. In cauterized corneas, the migration of LCs, which is associated with loss of ACAID, was suppressed by the topical administration of IL-1ra. In addition, IL-1ra treatment of corneas, injected with LCs, preserved ACAID induction. This suggested that IL-1 had an important role in promoting immunogenic inflammation and
neutralizing the normally immunosuppressive ocular microenvironment. Therefore, these data suggested that the presence of LCs alone in the cornea was necessary, but insufficient, for perturbing immune privilege, and that stimulation of these cells by IL-1 was critical in enhancing their immunoinflammatory function to a sufficient level for the cells to subvert ACAID.

What are the mechanisms by which IL-1-mediated LC function can abrogate immune privilege? A wide body of evidence from our laboratory and from other investigators suggests that the regulation of LC function by IL-1 is multidimensional. The accessory function of LCs and dendritic cells to sensitize T cells can be significantly augmented by IL-1 in addition to granulocyte-macrophage colony-stimulating factor. In addition, IL-1 itself significantly upregulates production of granulocyte-macrophage colony-stimulating factor by corneal epithelial and stromal cells, which in turn potentiates the LC's antigen-presenting cell (APC) function. Moreover, as pleuripotent cells that also partake in pro-inflammatory activities, LCs themselves are capable of significantly producing IL-1β, suggesting an autocrine feedback loop that, once activated, in turn profoundly potentiates their accessory function. Preliminary experiments in our laboratory also suggest that topical application of IL-1ra to inflamed corneas can variably, but significantly, downregulate the expression of CD-44 and ICAM-1 by corneal LCs. Hence, these data indicate that the observed IL-1ra regulation of LC APC function is mediated not only by downregulating LC migration (possibly in part by regulating CD-44 expression), but also at least in part by suppressing granulocyte-macrophage colony-stimulating factor and costimulatory molecule (e.g., ICAM-1) expression.

As discussed above, it is important to appreciate that LCs, as IL-1-secreting cells, are capable of functioning as mediators of inflammation in addition to being antigen-presenting cells. We have noted that application of a variety of inflammatory stimuli to the cornea leads to migration of limbal LCs into the cornea as early as 2 hours after these insults, and recent experiments (unpublished data) in our laboratory suggest that this migration is associated with a profound upregulation in IL-1β product levels in the cornea and with the expression of CD-44 and ICAM-1 by resident corneal and iris-ciliary body cells. Moreover, application of IL-1ra appears to reverse expression of CD-44, ICAM-1, and IL-1β. Additionally, we have accumulated data which suggest that IL-1 can interfere with the ACAID-inducing signal either when injected in vivo intracameraly with soluble antigen or in vitro when added to peritoneal exudate cells cocultured with antigen and transforming growth factor β (unpublished data). These observations are consistent with a wide body of evidence suggesting there is an antagonistic functional relationship between IL-1 and the immunomodulatory effects of transforming growth factor β and α-melanocyte-stimulating hormone, two critical mediators of immune privilege in the eye.

Therefore, in this context, our experiments cannot rule out the possibility that suppression of LC activity with IL-1ra and restoration of ocular immune privilege, is in part a result of downregulation of IL-1 paracrine effects on other cells (including possibly the APCs of the iris-ciliary body) and direct interference with the immunosuppressive milieu of the anterior segment to which the cornea normally contributes.

Consideration of the pro-inflammatory aspect of LC function is likely relevant to previous experiments that noted that diseased corneas containing LCs are incapable of supporting ACAID but offered no explanation for how the LCs come in contact with intracameraly injected antigens. While none of these experiments prove, or refute, that LCs perform their APC function in the anterior chamber (as opposed to being performed on the ocular surface by backflow of antigen through the needle track after intracameral injection), it should be considered that LCs may enhance immunity not only in their accessory role as APC but also as pro-inflammatory cells that perturb the net immunosuppressive microenvironment of the anterior chamber. Hence, in the aggregate, the restoration of ocular immune privilege by IL-1ra regulation of LC activity...
most likely includes downregulation of both the accessory and inflammatory aspects of LC function.

Recently, there has been significant interest in the expression of Fas ligand by ocular tissues, and the role that Fas--Fas ligand-mediated apoptosis may likely have on the promotion of ocular immune privilege. It is noteworthy that there is a significant functional role for interleukin-1β-converting enzyme in mediating Fas-mediated apoptosis, but the function of IL-1β per se in apoptosis remains controversial, because it has been shown to be capable of both induction and suppression of Fas-mediated cell death. The applicability to the eye of regulating Fas-mediated apoptosis, by suppressing IL-1 activity through administration of IL-1ra, remains a speculative, though interesting, possibility that deserves further investigation.

In summary, we have shown using an in vivo model that antagonism of IL-1 activity by the topical administration of IL-1ra offers an effective means of suppressing LC-mediated immunity in the anterior segment of the eye. We have recently reported that the topical application of IL-1ra in the murine corneal allograft model leads to a significant suppression of allograft rejection. We postulate, based on the results of the experiments reported here, that the promotion of allograft survival results, at least in part, from suppression of the Langerhans cells' sensitizing capacity. The potential applicability of IL-1ra to a wide range of ocular surface and corneal inflammatory and immune conditions merits further study.

References


