MCP-1 Expression in Endotoxin-Induced Uveitis

Nadine Tuaillon,1,2 De Fen Shen,1 Ravi B. Berger,1,3 Bao Lu,4 Barrett J. Rollins,5 and Chi-Chao Chan1

PURPOSE. Monocyte chemoattractant protein (MCP)-1 (CCL-2) is a chemokine with chemoattractant properties for monocytes, memory T cells, natural killer cells, mast cells, and basophils. To delineate the role played by MCP-1 in acute anterior uveitis, a common ocular inflammation, MCP-1−/− mice and wild-type matched control mice were analyzed for the development of endotoxin-induced uveitis (EIU) in response to subcutaneous injection of a sublethal dose of lipopolysaccharide (LPS).

METHODS. EIU was induced in MCP-1−/− and wild-type control mice by a single subcutaneous injection of Salmonella typhimurium LPS endotoxin at day 0. Alternatively, MCP-1−/− mice were injected subcutaneously with LPS plus recombinant MCP-1 at day 0 and with recombinant MCP-1 6 hours later. Mice were killed at day 1 or 3 after injection. Serum levels of IL-1α, IL-1β, IL-6, IFN-γ, TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein (MIP)-1α, MIP-2, regulated on activation normal T-cell expressed and secreted (RANTES), and MCP-1 were determined by ELISA. Eyes were collected and analyzed histologically and by RT-PCR for MCP-1, IFN-γ, IL-6, TNF-α, β-actin, MCP-5, RANTES, KC, inflammatory protein (IP)-10, and toll-like receptor (TLR)-4.

RESULTS. EIU was strongly reduced in MCP-1−/− mice compared with wild-type control mice. The number of ocular inflammatory cells was significantly reduced. Moreover, intracellular IFN-γ transcription was increased. EIU was induced in MCP-1−/− mice by co-administration of recombinant rat MCP-1 and LPS.

CONCLUSIONS. Data indicate that MCP-1 plays a crucial role in the induction of EIU. MCP-1 may be a new therapeutic strategy for acute anterior uveitis. (Invest Ophthalmol Vis Sci. 2002;43: 1493–1498)

Lipopolysaccharide (LPS), a major glycolipid component of the outer membrane of Gram-negative bacteria, induces a generalized proinflammatory response during infection. Systemic injection of a sublethal dose of LPS induces bilateral acute ocular inflammation in susceptible strains of rats and mice.1,2 This endotoxin-induced uveitis (EIU) is an animal model for acute anterior uveitis in the human. In general, EIU peaks 24 hours after LPS injection and subsides within the next 96 hours. EIU is characterized by percolation of proteins from the serum and by infiltration of macrophages and neutrophils into the eye.3 In Lewis rats with EIU, acute inflammation develops mainly in the anterior chamber (iridocyclitis) and inflammatory cells may also infiltrate the vitreous and retina. In the mouse, the inflammation in the anterior chamber is less severe, and a relatively large number of neutrophils and macrophages accumulate in the vitreous, around the retinal vessels at the optic nerve head (posterior vitritis).4–5 Recently, genetic regulation of LPS susceptibility has been linked to the toll-like receptor (TLR)-4 and MD-2 genes.6–10 Numerous data indicate that cytokines play an essential role in the development of EIU. In particular, tumor necrosis factor (TNF)-α, IL-1β, IL-6, interferon-(IFN)-γ, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-2, granulocyte-macrophage colony-stimulating factor (GM-CSF), growth-related oncogene (GRO), and IL-1 receptor antagonist (IL-1RA) expression have been described in the eyes of rabbits, rats, and mice with EIU.11–15 In the human, IL-8, MCP-1, and regulated on activation normal T-cell expressed and secreted (RANTES) appear to be elevated in aqueous samples of patients with active anterior uveitis.16 It is noteworthy that although expressed in the eyes during EIU, TNF-α, IL-1, and IL-6 may not be essential for pathogenesis.17,18

Murine MCP-1 (CCL-2), originally termed JE, is considered to be the equivalent of human MCP-1, even though it has an extra 49-amino-acid fragment at the C terminus. Murine MCP-1 is a 125-amino-acid (25–30 kDa) member of the C-C subfamily of chemokines.19 It is produced by immune and nonimmune cells in response to various stimuli including TNF-α, IL-1β, IL-4, viruses, and endotoxins. MCP-1 has been shown to have chemoattractant properties for monocytes, memory T cells, natural killer (NK) cells, mast cells, and basophils.20–22 It appears to activate monocytes, induce IL-4 production by T lymphocytes, induce transforming growth factor (TGF)-β and collagen production by fibroblasts, and induce smooth muscle cell proliferation and mast cell activation (reviewed by Gu et al.23). MCP-1 is postulated to be involved in several diseases, including arteriosclerosis, rheumatoid arthritis, and multiple sclerosis.25–27 These data indicate that MCP-1 is a major proinflammatory cytokine. Studies using a murine model of Schistosoma mansoni induce pulmonary granuloma, a murine model of acute septic peritonitis, and studies of murine models of LPS-induced sepsis indicate that MCP-1 can also act as an anti-inflammatory cytokine.25,28–30 Another role for MCP-1 has been described in development of T helper cell (Th)1 and Th2.31 MCP-1-deficient mice (MCP-1−/−) have been generated.32 They develop normally and have normal hematologic profiles, including a normal number of macrophages. Data show that despite the expression of other chemokines in these mice, MCP-1 is essential for monocyte recruitment.32 In addition, a role for MCP-1 in arteriosclerosis and experimental autoimmune encephalomyelitis (EAE) has been demonstrated in MCP-1−/− mice.25,32 MCP-1−/− mice fed a high cholesterol diet have less monocyte accumulation and lipid deposition in atherosclero-

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sisc. Similarly, MCP-1−/− mice appear to be markedly resistant to EAE after active immunization, with drastically impaired recruitment of macrophages to the central nervous system (CNS). MCP-1 is necessary for Th1 immune responses during EAE, and macrophage recruitment to the inflamed CNS is essential for primed T cells to execute a Th1 effector program in EAE.

In the current study, to delineate the role played by MCP-1 in EIU, we analyzed the development of EIU in MCP-1−/− mice and wild-type matched control animals in response to a single subcutaneous injection of a sublethal dose of LPS. Data indicate that MCP-1 played an important role in the induction of EIU.

METHODS

Mice

MCP-1−/− mice and wild-type congenic control animals (129Sv/J x C57Bl/6) have been described previously. Male and female knockout and wild-type mice were bred in parallel and kept in a pathogen-free environment. Mice were 6 to 10 weeks old and were treated according to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Induction of EIU

EIU was induced at day 0 in groups of five to eight mice by a single subcutaneous injection of 0.2 mg Salmonella typhimurium LPS endotoxin (Difco Laboratories, Detroit, MI) in 0.05 mL PBS into the hind footpad. Control mice were injected with 0.05 mL PBS into the hind footpad. Mice were killed at 24 ± 5 hours (day 1) or at 72 ± 5 hours (day 3) after injection.

To further analyze the role played by MCP-1 in EIU, groups of seven MCP-1−/− mice were treated with recombinant rat MCP-1 (rMCP-1; Endogen, Woburn, MA). MCP-1−/− mice were injected in the hind footpad at day 0 with 0.2 mg S. typhimurium LPS endotoxin mixed with 500 ng rMCP-1 in 0.05 mL PBS and 0.2% BSA. Six hours later, mice were injected intraperitoneally with 500 ng rMCP-1 in 0.1 mL PBS and 0.2% BSA. Another group of mice were injected in the hind footpad with 0.05 mL PBS containing 0.2% BSA and 500 ng rMCP-1 followed 6 hours later by intraperitoneal injection of 0.1 mL PBS and 0.2% BSA containing 500 ng rMCP-1. Mice were killed at 24 ± 5 hours (day 1) after injection. The endotoxin level of rMCP-1 is 0.01 ng/µg protein. Each experiment was repeated three to four times, with similar results.

Histopathology

Murine right eyes were enucleated and used for histopathology. Eyes were immersed in 4% glutaraldehyde for 30 minutes, fixed in 10% buffered formalin for at least 24 hours, and then embedded in methacrylate. Four- to 6-µm vertical sections were cut through the pupillary optic nerve axis and stained with hematoxylin and eosin (H&E). Infiltrating inflammatory cells in the anterior chamber and posterior vitreous were counted and identified histologically in a masked fashion by an ocular pathologist (CCC).

Enzyme-Linked Immunosorbent Assay

Serum samples were collected and pooled from each time point. IL-1α, IL-1β, IL-6, IFN-γ, TNF-α, GM-CSF, MIP-1α, MIP-2, RANTES, and MCP-1 expression was determined by ELISA using commercially available kits (BioSource International, Camarillo, CA; R&D Systems, Minneapolis, MN). These cytokines were tested because previous data indicate that MCP-1 played an important role in the induction of EIU. Similar results.

Table 1. Oligonucleotide Sequences

<table>
<thead>
<tr>
<th>Oligonucleotide</th>
<th>Oligonucleotide Sequence (5′–3′)</th>
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<tr>
<td>MCP-1</td>
<td>Sense: ACCTGGAAGCCAGCTCTCTCTGTC</td>
</tr>
<tr>
<td></td>
<td>Antisense: TTGCTCTGTCGAAAGACCT</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Sense: CTCCTGCTGTTTGCCTGGTTTGCCT</td>
</tr>
<tr>
<td></td>
<td>Antisense: GCATTTGCTTCCAGATATCG</td>
</tr>
<tr>
<td>IL-6</td>
<td>Sense: TTGCTCTGTCGAAAGACCT</td>
</tr>
<tr>
<td></td>
<td>Antisense: TTGATCTCTGTCGAAAGACCT</td>
</tr>
<tr>
<td>TNF-α</td>
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</tr>
<tr>
<td></td>
<td>Antisense: TTGATCTCTGTCGAAAGACCT</td>
</tr>
<tr>
<td>β-Actin</td>
<td>Sense: CTTGCTAGAGGCTAGAGAGGAGGT</td>
</tr>
<tr>
<td></td>
<td>Antisense: GTGCTAGAGGCTAGAGAGGAGGT</td>
</tr>
<tr>
<td>MCP-5</td>
<td>Sense: AGCTTCCATTGGAAGCTTCTTGG</td>
</tr>
<tr>
<td></td>
<td>Antisense: CTCTTCTTCTGGAAGAGCAC</td>
</tr>
<tr>
<td>RANTES</td>
<td>Sense: CCTCAACATCATCCTCTACCTGGA</td>
</tr>
<tr>
<td></td>
<td>Antisense: TCTCTTCTTCTGGAAGAGCAC</td>
</tr>
<tr>
<td>KC</td>
<td>Sense: AACGAGGAAGAGAGACAGACTGCT</td>
</tr>
<tr>
<td></td>
<td>Antisense: GAGGAGGAGAGAGAGACAGACTGCT</td>
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<td>IP-10</td>
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<td></td>
<td>Antisense: GAGGAGGAGAGAGAGACAGACTGCT</td>
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<tr>
<td>TLR-4</td>
<td>Sense: AGCAGAGGAGAGAGAGACAGACTGCT</td>
</tr>
<tr>
<td></td>
<td>Antisense: GAGTGAAGGAGAGAGACAGACTGCT</td>
</tr>
</tbody>
</table>

Reverse Transcription–Polymerase Chain Reaction

Mice left eyes were collected and pooled for RNA preparation, as described by Chomczynski and Sacchi. Briefly, eyes were homogenized in solution D (guanidium isothiocyanate 4 M, sodium citrate 25 mM, sarcosyl 0.5%, and β-mercaptoethanol 0.1 M). RNA was extracted by phenol-chloroform and treated with DNase I. Ten micrograms of RNA was used in the reverse transcription reaction, with commercially available reverse transcriptase (Superscript II; Life Technologies, Grand Island, NY) and random hexamers (Promega, Madison, WI). The 10-µL PCR amplification of 0.5 µg single-strand cDNA was performed by 40 cycles of 45 seconds’ denaturation (94°C), 1.5 minutes’ annealing (54–58°C), and 2 minutes’ elongation (72°C) using 0.5 U gold polymerase (AmpliTag Gold; Perkin-Elmer Corp., Hayward, CA). The final cycle was completed by 7 minutes’ elongation at 72°C. Three picomoles of the 32P end-labeled sense primer and of the non-labeled antisense oligonucleotides were used as appropriate. Primer sequences are indicated in Table 1. PCR products were size fractionated using 15% polyacrylamide TBE gels (Bio-Rad, Richmond, CA). Gels were analyzed by autoradiography.

Statistical Analysis

Data were analyzed by parametric analysis of variance (ANOVA) with Bonferroni correction (StatView, ver. 5.0; SAS, Cary, NC). Each mouse was treated as one statistical event. Probabilities inferior to 0.05 were considered statistically significant.

RESULTS

Decreased Ocular Inflammation in MCP-1−/− Mice with EIU

After LPS injection, conjunctival chemosis (edema), erythema (redness), and ocular discharge developed in the mice. Although both types of mice had these symptoms, the clinical response was reproducibly more intense in wild-type control than in MCP-1−/− mice. Histopathologically, EIU is characterized by the infiltration of inflammatory cells in the eye, mainly in the anterior chamber. On average, 31 ± 5 inflammatory cells per ocular section (mainly neutrophils, but also macrophages) were detected in the anterior chamber of wild-type congenic control mice (n = 27) on day 1 after LPS injection (Fig. 1, Table 2). This number was significantly reduced in MCP-1−/− mice.

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(P < 0.0001). On average, 6 ± 1 inflammatory cells per ocular section (mainly neutrophils, with only rare macrophages) were detected in the anterior chamber of MCP-1−/− mice (n = 29) on day 1 after LPS injection (Fig. 1, Table 2). During EIU, inflammatory cells are also detected in the posterior vitreous of the eye—in particular, around the optic nerve head. On average, 47 ± 8 inflammatory cells per ocular section were detected in the whole eye (anterior chamber and posterior vitreous) of wild-type congenic control mice (n = 27) on day 1 after LPS injection (Fig. 1, Table 2). The number of inflammatory cells was also significantly reduced in MCP-1−/− mice (P = 0.01). On average, 26 ± 4 inflammatory cells per ocular section were detected in the whole eye of MCP-1−/− mice (n = 29) on day 1 after LPS injection (Fig. 1, Table 2).

**Increased IFN-γ and Decreased IL-6 Expression in the Serum of MCP-1−/− Mice with EIU**

At day 1 after immunization, wild-type mice expressed approximately 4.2 ng/mL serum of soluble MCP-1 (Fig. 2). MCP-1 was not detected by ELISA before immunization in these mice (data not shown) or in MCP-1−/− mice. Markedly high levels of IL-6 were detected in the serum of wild-type control mice at day 1 (3.4 ng/mL). The level of serum IL-6 was significantly reduced in MCP-1−/− mice (2.2 ng/mL; P = 0.001). IFN-γ was expressed at low levels in the serum of wild-type mice (232 pg/mL), but its expression was significantly increased in the serum of MCP-1−/− mice (850 pg/mL; P = 0.01). In addition, RANTES was expressed at high levels (approximately 3.9 ng/mL) in the serum of both wild-type control and MCP-1−/− mice. Serum levels of MIP-1α and MIP-2 were slightly increased after injection of LPS in both wild-type control and MCP-1−/− mice. After LPS injection, IL-1α, IL-1β, GM-CSF, and TNF-α serum levels remained below the detection sensitivities of the assays in both wild-type control and MCP-1−/− mice (Fig. 2). Data indicate that MCP-1 mice respond to LPS and that cytokine production is induced normally, indicating that reduced inflammation is not due to a defect in the LPS receptor or in the signal transduction cascade after LPS-to-TLR4-MD2 binding. All the cytokines and chemokines tested were below detection levels in control mice injected with PBS.

**Increased Intraocular IFN-γ Transcription in MCP-1−/− Mice with EIU**

MCP-1 mRNA was detected in the eyes of wild-type control mice at days 1 and 3 after LPS injection. It was not detected before the injection and was never detected in MCP-1−/− mice (Fig. 3). mRNA of other cytokines and chemokines, including TNF-α, MCP-5, RANTES, and KC were detected at similar levels in the eyes of both wild-type control and MCP-1−/− mice at days 1 and 3 after LPS injection. Levels of intraocular expression of IFN-γ mRNA were strikingly different between MCP-1−/− and wild-type mice. Indeed, IFN-γ mRNA was below detection level in wild-type mice but was easily detected in MCP-1−/− mice. It is noteworthy that intraocular IFN-γ mRNA

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**Table 2. Number of Inflammatory Cells Present in the Anterior Chamber and Whole Eye of Wild-Type Control or MCP-1−/− Mice at Days 1 and 3 after PBS or LPS Injection**

<table>
<thead>
<tr>
<th></th>
<th>Wild-Type Control</th>
<th></th>
<th>MCP-1−/− Mice</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anterior Chamber</td>
<td>Whole Eye</td>
<td>Anterior Chamber</td>
<td>Whole Eye</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>LPS</td>
<td>PBS</td>
<td>LPS</td>
</tr>
<tr>
<td>Day 1</td>
<td>0 (n = 10)</td>
<td>31 ± 5 (n = 27)</td>
<td>0 (n = 10)</td>
<td>47 ± 8 (n = 27)</td>
</tr>
<tr>
<td>Day 3</td>
<td>ND</td>
<td>26 ± 6 (n = 18)</td>
<td>ND</td>
<td>50 ± 11 (n = 18)</td>
</tr>
</tbody>
</table>

Data are the number (mean ± SE) of inflammatory cells per section in four independent experiments.
was usually not detected by RT-PCR in various susceptible murine strains with EIU (Tuillon N, unpublished data, 2001). Similarly, IFN-γ inducible protein (inflammatory protein-10) mRNA appeared to be expressed in the eyes of both wild-type control and MCP-1−/− mice, but the band intensity was reproducibly lower in wild-type mice. IL-6 was detected at day 1 after injection in the eyes of both wild-type control and MCP-1−/− mice. The band intensity was reproducibly lower in MCP-1−/− mice, whereas the intensity of the β-actin band remained constant. The band intensity for TLR4 was similar in all mice, before and after LPS injection (Fig. 3). This indicates that the reduced response to LPS injection in MCP-1−/− mice was not due to reduced TLR4 ocular transcription. Our data indicate that among the cytokines tested, only IFN-γ ocular transcription was significantly different between wild-type and MCP-1−/− mice with EIU.

**rRMCP-1 Reconstitution of MCP-1−/− Mice**

The coinjection of rRMCP-1 and LPS into MCP-1−/− mice resulted in an increase in the number of inflammatory cells in the anterior chamber and in the posterior vitreous. The number of inflammatory cells in the anterior chamber, although increased, remained lower than in wild-type control mice injected with LPS (P < 0.0001). On average, 11 ± 2 inflammatory cells were detected in the anterior chamber of MCP-1−/− mice (n = 21) on day 1 after LPS and rRMCP-1 coinjection. The number of inflammatory cells in the whole eye, however, was equivalent to the number of inflammatory cells present in wild-type control mice injected with LPS. On average, 48 ± 9 inflammatory cells were detected in the whole eye of MCP-1−/− mice (n = 21) on day 1 after LPS and rRMCP-1 coinjection. The inflammatory response in MCP-1−/− mice injected with LPS and rRMCP-1 involved more macrophages than neutrophils. Control mice that received rRMCP-1 and PBS did not show any ocular inflammation (data not shown). IFN-γ transcripts were still detected in the eyes of mice reconstituted with MCP-1, but the level of transcription was lower than in MCP-1 mice that received LPS only (Fig. 4). These data indicate that the injection of rRMCP-1 in MCP-1−/− mice restores susceptibility to EIU.

**Discussion**

In the mouse, four different members of the MCP subfamily of chemokines have been identified: MCP-1, MARC/MCP-3, MCP-5, and eotaxin. Among these chemokines, MCP-1 is uniquely essential for monocyte recruitment during inflammation and atherosclerosis. MCP-1 is expressed in the human during acute anterior uveitis. Its expression also has been described in rabbit and rat EIU models. Experiments in the rabbit LPS-induced uveitis model indicate that intravitreal injection of LPS plus anti-MCP-1 IgG results in a reduction in the number of infiltrating mononuclear cells. Similarly, intravitreal injection of LPS plus anti-IL-8 IgG results in a reduction in the number of infiltrating neutrophils.

In the present study, we analyzed the development of EIU in wild-type control animals and MCP-1−/− mice in response to a subcutaneous injection of a sublethal dose of LPS. Data show that the disease was significantly reduced in MCP-1−/− mice compared with wild-type control mice. In MCP-1−/− mice, the clinical manifestations of ocular inflammation were significantly reduced, with less swelling and less discharge. More important, the number of inflammatory cells determined by histology was significantly reduced (Fig. 1, Table 2). It is noteworthy that in MCP-1−/− mice, the inflammatory response was...
constituted almost exclusively of neutrophils. In the absence of MCP-1, macrophages were no longer recruited into the eye. Among the cytokines tested, serum IL-6 was significantly reduced in MCP1−/− mice, whereas IFN-γ was significantly increased (Fig. 2). IL-6 is a multifunctional cytokine that plays important roles in host defense, acute phase reactions, immune responses, and hematopoiesis. Its production is upregulated by various factors, including LPS and cytokines.43 IL-6 is a crucial cytokine in neonatal sepsis 44 and in biphasic ocular inflammatory response to LPS in C3H/HeN mice.15 Previous data from a murine model of intravitreal LPS injection indicate that IL-6 may not be essential in EUU pathogenesis.18

Among the cytokines tested, IFN-γ appears to be transcribed at higher levels in the eyes of MCP1−/− mice than in those of wild-type mice. Although the RT-PCR methods used are not fully quantitative, IFN-γ mRNA was below detection level in the eyes of wild-type mice injected with LPS but was easily detectable in the eyes of MCP1−/− mice (Fig. 3). Similar intensities were observed, however, for the β-actin band in the two murine types. IFN-γ is produced by macrophages in some but not all murine strains in response to LPS.45 IFN-γ mRNA is usually not detected in the eyes of mice with EUU (Tuallion N, unpublished data, 2001). It appeared, however, to be induced in MCP1−/− mice. Parenthetically, MCP1−/− mice were less susceptible to EUU than their wild-type counterparts. This suggests that LPS-induced IFN-γ may have a protective effect in EUU, in opposition to its deleterious effect in septic shock.46,47 It is noteworthy that the two models (EUU and septic shock) differ in the inflammatory response to endotoxin-induced uveitis in the rat.48

Conjection of LPS and rMCP-1 in MCP1−/− mice resulted in increased inflammation. The number of inflammatory cells in the eye was similar to the number found in wild-type mice injected with LPS. These data indicate that rMCP-1 restored inflammation in the eyes of MCP1−/− mice. In that case, however, the inflammatory response involved mainly macrophages. In normal mice, MCP-1 was produced locally in response to LPS by cells present within the anterior chamber and the posterior vitreous. Exogenous MCP-1 may, localize in the eye of MCP1−/− mice, however, because the penetration of the blood–ocular barrier induced by subcutaneous LPS injection caused macrophages to be recruited into the eye.

Our data clearly indicate that MCP-1 plays an essential role in the development of EIU in the mouse. In the absence of MCP-1, ocular inflammation was significantly reduced. The protection against the deleterious effect of LPS in the eyes of MCP1−/− mice may be in part mediated by overexpression of IFN-γ. Residual disease was probably due to the expression of other chemokines, including MCP-5, RANTES, and KC. Our data indicate that MCP-1 may be a new therapeutic target for acute anterior uveitis, a common ocular inflammation in humans, because previous data indicate that this chemokine is also expressed at high level in the eyes of patients with active anterior uveitis.

References

17. Rosenbaum JT, Han YB, Park JM, Kennedy M, Planck SR. Tumor necrosis factor-alpha is not essential in endotoxin induced eye


