Elevated Levels of Monocyte Chemoattractant Protein-1 in the Aqueous Humor after Phacoemulsification

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Purpose. To elucidate the impact of phacoemulsification on aqueous monocyte chemoattractant protein-1 (MCP-1) levels, and identify its cell origin.

Methods. For clinical study, aqueous humor samples were collected before and after surgery (17.0 ± 4.0 months postoperatively) from 21 cataract cases that underwent phacoemulsification and intraocular lens (IOL) implantation. Aqueous MCP-1 levels were determined using a multiplex immunoassay. For animal experiments, rabbits underwent phacoemulsification (±IOL). Aqueous humor samples were collected from nonoperated eyes and operated eyes, and immunoassays were performed. Eyes were analyzed by reverse transcription-polymerase chain reaction and immunohistochemical studies.

Results. In the clinical study, mean (±SD) aqueous MCP-1 levels were higher postoperatively (1773.5 ± 321.2 pg/mL) than preoperatively (796.9 ± 211.3 pg/mL; P < 0.0001). In animal experiments, mean aqueous MCP-1 levels (pg/mL) were higher in postoperative eyes on day 30 (207.1 ± 62.9) than in nonoperated eyes (31.2 ± 12.5; P = 0.018). IOL implantation did not affect the changes in MCP-1 levels. After phacoemulsification, MCP-1 mRNA expression was increased in the cornea, iris, ciliary body, and capsular bag. Expression of MCP-1 mRNA in the capsular bag, but not the other tissues, increased from day 30 to 90. Immunohistochemical studies showed positive immunoreactivity for MCP-1 in cells of the posterior capsule after phacoemulsification.

Conclusions. Aqueous MCP-1 levels were elevated in both human and animal eyes after phacoemulsification. Proliferated lens epithelial cells on the capsule might be the major cell origin for prolonged MCP-1 production after phacoemulsification. (http://www.umin.ac.jp/ number, UMIN000005788.) (Invest Ophthalmol Vis Sci. 2012;53:7951–7960) DOI: 10.1167/iovs.12-10231

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i�ration, and that the cell origin for MCP-1 production may be proliferated lens epithelial cells on the capsule.

**MATERIALS AND METHODS**

**Clinical Study**

Patients and Sample Collection. The protocol was approved by the Institutional Review Board at Kumamoto University in compliance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients. Patients who underwent phacoemulsification and intraocular-lens (IOL) implantation were recruited. Patients with systemic diseases other than hypertension or hyperlipidemia, ocular diseases other than cataracts, a history of ocular surgeries, or intraocular pressure (IOP) of more than 21 mm Hg were excluded from the study. IOP was measured using a noncontact tonometer. None of the patients were under topical or systemic anti-inflammatory drugs, including corticosteroids. Preoperative aqueous humor was collected at the beginning of the phacoemulsification surgery before any incisional procedures. The second collection of aqueous humor was conducted between 1 and 2 years after phacoemulsification. A total of 100 to 150 μL of aqueous humor was gently withdrawn and stored at −80°C as described previously.13

Multiplex Analysis. The concentrations of MCP-1, interleukin (IL)-8, tumor necrosis factor (TNF)-α, platelet-derived growth factor (PDGF)-AA, and vascular endothelial growth factor (VEGF) in the aqueous humor samples were determined using multiplex immunoasays, as described previously.13

**Animal Experiment**

Experiments were conducted according to the guidelines of the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and approved by the Animal Use Committee of Kumamoto University. A total of 42 female Japanese White rabbits (2.0–2.4 kg, 12–14 weeks old) were used. Twenty-four animals underwent only phacoemulsification, six animals underwent phacoemulsification and IOL implantation, and 12 animals were examined without surgery as controls. Animals who had undergone surgery were killed on days 30 and 90 after phacoemulsification (n = 12 each) and the other animals (n = 12) were killed untreated for the control study. Among the 12 animals in each group, six animals were used to evaluate IOP, aqueous humor, and blood serum; three animals were used for the reverse transcriptase polymerase chain reaction (RT-PCR) experiments; and the remaining three animals were used for immunohistochemical studies. For comparison of the MCP-1 levels in the aqueous humor after phacoemulsification between aphakic and pseudophakic eyes, additional animals (n = 6) underwent phacoemulsification with IOL implantation. Only the right eye was used for the analyses.

Phacoemulsification Protocol. The animals were anesthetized with an intramuscular injection of ketamine hydrochloride (Ketalar; 25 mg/kg body weight; Daiichi Sankyo, Tokyo, Japan), and xylazine hydrochloride (Celactal; 10 mg/kg body weight; Bayer Leverkusen, Germany), and prepared for surgery by pupil dilation with tropicamide (Mydrin-P; Santen, Osaka, Japan) in the right eye. The left eye remained untreated. The right eye was washed with topical xylene to remove the paraffin. After endogenous peroxidase was endogenous peroxidase was inhibited with blocking buffer containing 2% BSA for 1 hour at 4°C. The sample was immediately stored at −80°C. Aqueous humor was withdrawn gently. After centrifugation at 7830 g for 10 minutes at 4°C, the supernatant serum was collected and stored in aliquots at −80°C.

Detection of MCP-1 mRNA Expression. We used RT-PCR to determine the expression levels of MCP-1 mRNA in the anterior segments of eyes. After the rabbits were killed, the cornea, iris, ciliary body, and capsular bag were extracted. These tissues were immediately frozen in liquid nitrogen and stored at −80°C after extraction. Total mRNA was isolated from these samples using a NucleoSpin RNA II kit (MACHEREY-NAGEL, Düren, Germany) column. The cDNA was amplified using reverse transcription reagent kit (Prime Script RT Master Mix; Takara, Osaka, Japan), and the transcribed cDNA was amplified using a PCR enzyme kit (Platinum Taq DNA Polymerase High Fidelity; Invitrogen, Carlsbad, CA). The primers were designed to amplify rabbit MCP-1 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH). MCP-1, sense primer: 5′-AGCATGAAGGGTCTGGCAAC-3′; antisense primer: 5′-CAGGTTCACCTGCGGTT-3′; GAPDH: sense primer: 5′-GATCATTGACCGCTCC-3′; antisense primer: 5′-GATCTGGCTCTGGAAAGTG-3′. PCR was performed with 35 cycles of 94°C for 1 minute, 55°C for 2 minutes, and 72°C for 2 minutes. A 1-μL aliquot of PCR product was subjected to electrophoresis on a 2.0% agarose gel in the presence of ethidium bromide. Densitometry analysis of RT-PCR bands was performed using a Java-based image processing software (Image J; National Institutes of Health [NIH], Bethesda, MD).

Immunohistochemistry for MCP-1 and α-Smooth Muscle Actin (α-SMA). The eyes were enucleated and the whole globe was fixed in Super Fix (KY-500; Kurabo, Osaka, Japan) for 48 hours at 4°C, the eyes were cut coronally just behind the equator, the anterior section was cut vertically, embedded in paraffin, and 5-μm thick vertical sections were prepared. The paraffin sections were treated with xylene to remove the paraffin. After endogenous peroxidase was blocked with 3% H2O2 in methanol, the sections were treated with 10% normal rabbit (for MCP-1 evaluation) or goat (for α-SMA
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>21 (15 women, 6 men)</td>
</tr>
<tr>
<td>Age, y</td>
<td>77.5 ± 7.4</td>
</tr>
<tr>
<td>Preoperative IOP, mm Hg</td>
<td>12.1 ± 2.8</td>
</tr>
<tr>
<td>Postoperative IOP, mm Hg</td>
<td>10.2 ± 3.1</td>
</tr>
<tr>
<td>Vertical C/D ratio</td>
<td>0.45 ± 0.1</td>
</tr>
<tr>
<td>Duration from phacoemulsification to sample collection, mo</td>
<td>17.0 ± 4.0</td>
</tr>
</tbody>
</table>

Results

Clinical Study: Cytokine Levels in Aqueous Humor Samples Obtained from Patients before and after Phacoemulsification

The clinical background of the included patients is summarized in Table 1. Included were 21 nonglaucomatous patients whose mean (±SD) age was 77.5 ± 7.4 years. The five cytokines/growth factors (i.e., MCP-1, IL-8, TNF-α, PDGF-AA, and VEGF) were detectable before and after phacoemulsification in all 21 cases. The mean (±SD) preoperative levels of MCP-1, IL-8, TNF-α, PDGF-AA, and VEGF were 796.9 ± 211.3, 3.8 ± 1.1, 0.9 ± 0.3, 34.0 ± 19.3, and 86.7 ± 38.7 pg/mL, respectively. After a mean follow-up period of 17.0 ± 4.0 months, the postoperative levels of MCP-1 and IL-8 were significantly higher than the preoperative levels, exhibiting the statistical significance (1773.5 ± 321.2 pg/mL of postoperative MCP-1, P < 0.0001; 11.6 ± 5.6 pg/mL of postoperative IL-8, P < 0.0001). In addition, there were significantly higher concentrations of TNF-α levels (1.2 ± 0.1 pg/mL, P = 0.002) in postoperative aqueous humor, but no significant changes in postoperative PDGF-AA (38.9 ± 10.1 pg/mL, P = 0.152) or VEGF (95.0 ± 40.3 pg/mL, P = 0.240) levels. The postoperative levels of MCP-1 and IL-8 in all 21 patients were higher than the preoperative levels (Fig. 1). The mean concentration of MCP-1 in the aqueous humor was higher than that of any other growth factor/cytokine detected. MCP-1 and IL-8 concentrations were significantly correlated both preoperatively and postoperatively (Table 2). The mean (±SD) IOP was decreased from preoperative levels of 12.1 ± 2.8 mm Hg to postoperative levels of 10.2 ± 3.1 mm Hg (P = 0.0004). Our statistical analysis also showed significant relationship in percent changes between concentration of MCP-1 and IOP from baseline levels (P = 0.041, Fig. 2).

Animal Experiments: MCP-1 Levels in Aqueous Humor Obtained from Rabbit Eyes with or without Phacoemulsification

The ELISA experiments showed that the mean (±SE) MCP-1 level in aqueous humor samples obtained from control rabbit eyes (nonoperated eyes) was 31.2 ± 12.5 pg/mL, which was much lower than human MCP-1 levels in aqueous humor measured using a multiplex immunoassay. After phacoemulsification, mean (±SE) MCP-1 levels in the rabbit aqueous humor on days 30 and 90 were 207.1 ± 62.9 and 106.2 ± 17.7, respectively. Statistical analyses showed significant differences in MCP-1 levels on day 30 compared with nonoperated eyes (P = 0.018). MCP-1 levels on day 90 after phacoemulsification did not differ significantly between eyes with and without IOL implantation (P = 0.736, unpaired t-test; Fig. 3A). Mean (±SE) serum MCP-1 levels were 135.5 ± 31.2 pg/mL in nonoperated rabbits and 124 ± 20.6 pg/mL in experimental rabbits on day 30. Serum MCP-1 levels did not differ significantly among the rabbits with or without phacoemulsification (P = 0.777; Fig. 3B). In addition, the IOP of rabbit eyes on day 30 and 90 after phacoemulsification were significantly lower than that of nonoperated eyes (P < 0.0001) (Fig. 4).
To identify the cell origin of MCP-1 expression, we conducted RT-PCR experiments using mRNA extracted from the anterior ocular tissues. Our results showed positive mRNA expression in the iris and ciliary body, but not in the cornea and capsular bag in nonoperated eyes. Similar experiments using ocular tissues obtained from eyes after phacoemulsification (on days 30 and 90) showed positive mRNA expression in the capsular bag as well as the cornea, iris, and ciliary body (Fig. 5A). Densitometry analysis \((n = 3)\) showed significantly higher MCP-1 mRNA expression in all tissues on both days 30 and 90 after phacoemulsification compared with the nonoperated eye, except for the iris in which the increase on day 90 was not significant. In the capsular bag, MCP-1 mRNA expression on day 90 was higher than that on day 30, in contrast to the other tissues (Fig. 5B). Thus, MCP-1 mRNA expression in the anterior segment tissues was induced by phacoemulsification in rabbit eyes.

### mRNA Expression in Rabbit Eyes with or without Phacoemulsification

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### Table 2. Correlations among Cytokines/Growth Factors before and after Phacoemulsification in Cataract Patients

<table>
<thead>
<tr>
<th></th>
<th>MCP-1</th>
<th>IL-8</th>
<th>TNF-(\alpha)</th>
<th>PDGF-AA</th>
<th>VEGF</th>
</tr>
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<tbody>
<tr>
<td>Before phacoemulsification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td>0.817</td>
<td>0.152</td>
<td>0.541</td>
<td>0.272</td>
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<tr>
<td>IL-8</td>
<td>&lt;0.0001</td>
<td>-0.049</td>
<td>0.580</td>
<td>0.396</td>
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<tr>
<td>TNF-(\alpha)</td>
<td>0.510</td>
<td>0.832</td>
<td></td>
<td>0.971</td>
<td>0.047</td>
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<tr>
<td>PDGF-AA</td>
<td>0.011</td>
<td>0.006</td>
<td>0.008</td>
<td>0.237</td>
<td></td>
</tr>
<tr>
<td>VEGF</td>
<td>0.233</td>
<td>0.076</td>
<td>0.838</td>
<td>0.301</td>
<td></td>
</tr>
<tr>
<td>After phacoemulsification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td>0.658</td>
<td>-0.185</td>
<td>-0.143</td>
<td>0.549</td>
<td></td>
</tr>
<tr>
<td>IL-8</td>
<td>0.001</td>
<td>-0.247</td>
<td>-0.178</td>
<td>0.583</td>
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<tr>
<td>TNF-(\alpha)</td>
<td>0.422</td>
<td>0.281</td>
<td>0.150</td>
<td>-0.104</td>
<td>0.166</td>
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<td>PDGF-AA</td>
<td>0.537</td>
<td>0.440</td>
<td>0.326</td>
<td>0.471</td>
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<tr>
<td>VEGF</td>
<td>0.010</td>
<td>0.006</td>
<td>0.654</td>
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</tbody>
</table>

Correlation coefficient \((r)\); upper-right half) and \(P\) values (lower-left half) were calculated by Spearman’s correlation test.
Immunohistochemical Studies for MCP-1 and α-SMA Expression

Our immunohistochemical studies for rabbit eyes showed immunoreactivity for MCP-1 in the vascular endothelium of the iris and ciliary body in both nonoperated eyes and operated eyes (Figs. 6A–D; Figs. 6E–H, negative controls). Subsequent immunostaining demonstrated that there were α-SMA positive cells on the posterior capsule (Fig. 7A; Fig. 7B, negative control), which suggested that the lens epithelial cells partially transdifferentiated into myofibroblast-like cells. In addition, MCP-1 positive cells were found in proliferated lens epithelial cells on the posterior capsule (Fig. 7C; Fig. 7D, negative control), but not in lens epithelial cells covered with residual lens material on the anterior capsule in the same eye (Fig. 7E).

Cell Culture

The ELISA experiments (n = 5) showed that the mean (±SE) levels of MCP-1 at 4, 6, 12, 24, and 48 hours after stimulation with TGF-β2 were 75.1 ± 14.0, 118.8 ± 11.8, 256.3 ± 18.8, 398.2 ± 16.5, and 680.3 ± 51.9, respectively; those without stimulation were 63.8 ± 13.9, 83.0 ± 16.5, 168.8 ± 32.3, 282.5 ± 43.8, and 510.8 ± 31.1, respectively. There were significantly higher levels of MCP-1 after 12, 24, and 48 hours in the supernatant with TGF-β2 stimulation than control (P = 0.047, 0.039, and 0.023, respectively, Fig. 8). The value of "0 hour" was below the detection limit.

DISCUSSION

In eye disorders such as glaucoma,18–25 uveitis,26–34 AMD,35–37 proliferative vitreoretinopathy, and diabetic retinopathy,38–45 changes in the levels of cytokines and growth factors in the aqueous humor and the vitreous fluid occur, suggesting their contribution to pathogenesis. Therapeutic modalities, such as corticosteroids and anti-VEGF antibody, are useful for treating some of these disorders by suppressing the effects of elevated proinflammatory cytokines/growth factor levels.37,45–48 We previously reported that the levels of some proinflammatory cytokines, including MCP-1 and IL-8, are increased in the aqueous humor of glaucomatous eyes, especially after phacoemulsification.13 Even modern phacoemulsification causes a poor surgical outcome of trabeculectomy with adjunctive use of mitomycin C.11,12 Because our previous analysis indicated
that elevated MCP-1 levels were significantly associated with poor surgical results for mitomycin C trabeculectomy (Inoue et al., unpublished observations, 2012), and MCP-1 is known to recruit and activate inflammatory cells and to be important for tissue healing, we hypothesized that elevated aqueous MCP-1 levels are a major key factor causing accelerated wound healing activities after filtration surgery. Therefore, in the current study, we focused on the changes in aqueous MCP-1 levels and its cell origin long period after phacoemulsification while IL-8 and TNF-α also increased in that stage. Further studies on aqueous IL-8 or TNF-α after phacoemulsification might be also important.

Our multiplex immunoassay revealed prolonged elevations in the levels of MCP-1 and IL-8 in aqueous humor samples after phacoemulsification in cases with cataract. The present study provides clear evidence that phacoemulsification induces increases in proinflammatory cytokines, including MCP-1, based upon comparison of aqueous humor samples before and after phacoemulsification in the same patients. Notably, elevations in MCP-1 and IL-8 were observed even after a mean postoperative period of 17 months when clinical examinations including slit-lamp tests showed no postoperative inflammatory responses in the eye. Also, because elevations in MCP-1 and IL-8 in aqueous humor samples were found in all of the examined patients, this phenomenon appears to be very common in eyes after phacoemulsification. These findings are consistent with our previous observation of the elevation of these cytokines in pseudophakic glaucomatous eyes. Furthermore, because MCP-1 levels were significantly associated with elevated IL-8 levels, these representative proinflammatory cytokines could be confounding factors to each other. Because chronic use of topical antiglaucoma
medications causes aqueous inflammation, it is likely that the elevated MCP-1 levels are induced in glaucomatous eyes. Indeed, our previous study showed significantly higher MCP-1 levels in glaucomatous eyes compared with nonglaucomatous eyes. Thus, it is likely in that the high aqueous MCP-1 levels in pseudophakic glaucomatous eyes may be due to additive effects of phacoemulsification and glaucoma pathology. Additionally, our analysis showed significant correlation in the percentage change after phacoemulsification between MCP-1 level and IOP value. Since the IOP-lowering effects of cataract surgery has been well known, our observation implies that MCP-1 can be a contributing factor to reduced IOP levels in eyes after phacoemulsification. Taken together, our results revealed that phacoemulsification is a universal clinical background to cause elevated MCP-1 levels for a long period (more than 1 year), resulting in changes in the microenvironment of the anterior ocular segments.

After phacoemulsification in rabbit eyes, we observed elevated MCP-1 levels compared with nonoperated eyes, suggesting that elevated MCP-1 levels are common after phacoemulsification among animal species. Generally speaking, the induction of proinflammatory cytokines is regarded to be due to an impaired blood-aqueous barrier, infiltration of inflammatory cells that secrete cytokines, and local production in resident cells in the eye. Indeed, our preliminary study showed that marked elevation of MCP-1 occurs within 24 hours after phacoemulsification, but the elevated MCP-1 levels return to near basal levels within several days (data not shown). On the other hand, mild but prolonged increases in the MCP-1 level were observed in the present study, which focused on the changes in aqueous MCP-1 levels after a long-term follow-up of phacoemulsification. Thus, we conducted molecular biologic and immunohistochemical studies to identify the cell origin of the mild, but prolonged, elevation in MCP-1 level in the aqueous humor after phacoemulsification, which was an experimental model of our clinical investigation.

Our RT-PCR experiments showed MCP-1 mRNA expression in the iris and ciliary body even nonoperated eyes. As suggested by the fact that physiologic levels of MCP-1 are relatively high compared with other cytokines and growth factors in the aqueous humor, it is quite likely that MCP-1 is constitutively expressed in the uveal tissues. Our immunohistochemical results revealing MCP-1 positive cells in the vascular endothelial cells in the iris and uveal tissues may support this speculation. Interestingly, only the capsular bag tended to have increased MCP-1 mRNA expression from days 30 to 90 after phacoemulsification, while other tissues showed decreased MCP-1 mRNA expression during that same period. This observation implies that the induction of MCP-1 after a long period following phacoemulsification may derive from cells that proliferated in the capsular bag after surgery. Our
Figure 8. The time course of the MCP-1 levels in supernatant with and without stimulation with TGF-β2. There are significantly higher levels of MCP-1 at 12, 24, and 48 hours (P = 0.047, 0.059, and 0.023, respectively) in the supernatant with TGF-β2 stimulation than the control. *P < 0.05 versus the control by the unpaired t-test.

immunohistochemical studies showed that MCP-1 is localized in the proliferated lens epithelial cells on the posterior capsule, but not in those cells on the anterior capsule covered with residual lens material, which was accidentally left behind after the phacoemulsification, in the same eye. After phacoemulsification, transdifferentiation into myofibroblasts in lens epithelial cells causes fibrotic posterior capsular opacification (PCO), and proliferation or migration in those cells causes regenerative PCO. Therefore, in our animal experiment, the presence of abundant α-SMA positive cells on the posterior capsule is consistent with the known features of myofibroblasts derived from transdifferentiated lens epithelial cells, and the MCP-1 positive cells on the posterior capsule may be proliferated lens epithelial cells, as a result of regenerative PCO.

As previously demonstrated, TGF-β and TNF-α can cause an epithelial-mesenchymal transition phenomenon in the eye. TGF-β is abundantly present in the aqueous humor, and our present study revealed the presence and induction of TNF-α in the aqueous humor after phacoemulsification. Taken together, after phacoemulsification, those multiple cytokines/growth factors in the aqueous humor are exposed to proliferated lens epithelial cells, probably resulting in MCP-1 production. Moreover, MCP-1 excreted from such proliferated cells can enter the aqueous humor directly after phacoemulsification. This possibility can explain the mild but prolonged elevation in MCP-1 for more than a year in the clinical cases. Additional in vitro experiments showed that human lens epithelial cell culture supernatants had a significantly higher level of MCP-1 when stimulated by TGF-β2 compared with the control. A high concentration of TGF-β is present in normal human aqueous humor, the predominant form of which is TGF-β2. This result might confirm our speculation that proliferated lens epithelial cells produce MCP-1 when exposed to aqueous humor after phacoemulsification.

In conclusion, our immunohistochemistry studies showed that detectable levels of MCP-1, IL-8, TNF-α, PDGF-AA, and VEGF were present in the aqueous humor, even in nonglaucomatous (cataract) patients, and that MCP-1 (and IL-8, TNF-α) levels remained elevated for at least 1 year after surgery. Our animal experiments showed that proliferated lens epithelial cells in the capsular bag might be the cells of origin of MCP-1 production. Our results suggest that phacoemulsification causes prolonged alterations of the microenvironment in aqueous humor.

References


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