Matrix Metalloproteinases and Tissue Inhibitors of Matrix Metalloproteinases in the Human Lens: Implications for Cortical Cataract Formation

Nitin H. Sachdev,1,2 Nick Di Girolamo,1 Timothy M. Nolan,1,2 Peter J. McCluskey,1,3 Denis Wakefield,1,5 and Minas T. Coroneo1,2

PURPOSE. To characterize the expression of matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) in human cortical cataract and to determine whether there is a correlation with the localization of cortical cataract. To evaluate the expression and activity of MMPs and TIMPs after cytokine and UV-B exposure in a human lens epithelial cell line.

METHODS. Twenty-eight human donor eyes with cortical cataract and 21 normal human donor eyes were photographed. Thirteen cortical cataract and six normal lenses were immunohistochemically analyzed for MMP-1, -2, -3, and -9 and TIMP-1. Three fresh cortical cataract and three control lenses were assessed for MMP-1, -2, -3, and -9 activity by SDS-PAGE zymography. Human lens epithelial cells (HLE-SRA-01/04) were exposed to proinflammatory cytokines and UV-B radiation to determine the protein expression profiles of MMP-1, -2, -3, and -9 and TIMP-1 and -2.

RESULTS. Immunohistochemical analysis revealed specific localization of MMP-1 within lens epithelium and cortical lens fibers of cortical cataract. Normal lenses had equally low MMP-1, -2, -3, and -9 and TIMP-1, -2, and -3. Twelve fresh cortical cataract and 12 normal lenses were divided into quadrants to quantify, by ELISA, the expression of MMP-1, -2, -3, and -9 and TIMP-1. Three fresh cortical cataract and three control lenses were assessed for MMP-1, -2, -3, and -9 activity by SDS-PAGE zymography. Human lens epithelial cells (HLE-SRA-01/04) were exposed to proinflammatory cytokines and UV-B radiation to determine the protein expression profiles of MMP-1, -2, -3, and -9 and TIMP-1 and -2.

CONCLUSIONS. This is the first study to localize the expression of MMP-1 in cataracts with clinically observed opacification in vivo and to examine the expression induced by UV-B, in vitro. (Invest Ophthalmol Vis Sci. 2004;45:4075–4082) DOI: 10.1167/iovs.03-1356

Cortical cataract is a common worldwide disorder. However, its pathogenesis is still poorly understood. Characteristic features include abnormal cortical fiber migration, swelling, and intracellular ß-crystallin aggregation.1–3 Despite the lack of knowledge regarding the pathogenesis of cortical cataract, epidemiologic evidence suggests that exposure to UV-irradiation may play a role in the development of this disorder.

Epidemiologic studies have shown that cortical cataract is commonly found in the inferonasal human lens and correlates with exposure to sunlight.5–7 In the absence of lid retraction, cortical opacities rarely occur in the upper segment of the lens, a segment that is normally covered by the upper lid.8 Previous studies demonstrated a close correlation between the location of the foci of scattered incident light (resulting in a 20-fold concentration of light at the limbus) and the location of pterygium and cortical cataract.9,10 Ray-tracing analysis supports these findings, indicating that the peripheral cornea concentrates light on the opposite peripheral lens equator and that the nasal and orbit block peripheral light, except temporally, resulting in a relative concentration of light on the inferonasal quadrant of the lens.11 More recently, three-dimensional computer-assisted diagrams have revealed that spoke-like cortical cataract forms after foci damage to individual fibers in the cortical equator of the lens.12

Matrix metalloproteinases (MMPs) are proteolytic enzymes closely controlled by a family of natural antagonists, the tissue inhibitors of matrix metalloproteinases (TIMPs). The balance between the levels of activated enzymes and free TIMPs determines the overall activity of MMP. Maintenance of this balance is essential, and any disturbance in the balance results in proteolysis and extracellular matrix (ECM) remodeling. MMPs are capable of denaturing most components of the lens capsule ECM. At least 28 members have been cloned and grouped according to their substrate specificity.13 These include the collagenses (MMP-1), capable of cleaving intact fibrillar collagen, and the gelatinases (MMP-2 and -9), which can further degrade these collagens, and basement membrane collagen type IV. The third group of MMPs comprises the stromelysins (MMP-3), which possess broad substrate specificity and can cleave fibronectin, laminin, and proteoglycans, and the membrane-associated MMPs.14 MMPs play a role in many ocular physiologic processes, including embryogenesis, angiogenesis, and wound healing,15–17 and they are upregulated in several pathologic ocular disorders, such as scleritis, uveitis, and pterygium.18–21

The broad MMP substrate specificity also includes molecules involved in lens differentiation, such as cytokines, cell adhesion molecules, and growth factors. Recently, several cytokines and growth factors such as tumor necrosis factor (TNF)-α, basic fibroblast growth factor (bFGF), and transforming growth factor (TGF)-β,2 have been localized to both lens epithelial cells and lens germinative cells in cortical cataract. Such cytokines and growth factors have been shown to play a key role in altered lens fiber migration and differentiation processes.22,23 all of which are commonly observed in cortical cataract.

MMPs and TIMPs are present in the aqueous humor in eyes with and without cataract.24 It has been suggested that excessive lens fiber remodeling may be one of the processes in-
volved in cataract formation.\textsuperscript{25,26} MMPs may play a role in this process. MMPs can cause intracellular β-crystallin aggregation\textsuperscript{27} and also act as a growth factor receptor sheddase.\textsuperscript{28–30} Therefore, there are several potential mechanisms for MMPs to be involved in the process of cortical cataract formation. We hypothesize that MMP and TIMP molecules may contribute to the altered lens growth and intracellular β-crystallin aggregation that characterize human cortical cataract. Growth factor receptor shedding by MMPs may be crucial in this process.

The purposes of this study were (1) to localize the cellular sources of MMPs and TIMPs in adult human cortical cataract lenses and in age- and sex-matched control lenses; (2) to assess the expression in the SRA-01/04 lens epithelial cell line before and after modulation with IL-1 and TNF-α; and (3) to establish an in vitro model to determine the profile of secreted MMPs and TIMPs from UV-B induced human lens epithelial cells (HLECs).

### MATERIALS AND METHODS

#### Donor Lens Specimens

Twenty-eight donor cataractous eyes (Table 1) and 21 normal age- and sex-matched lenses were obtained from the Sydney Lion’s Eye Bank. This study adhered to the Declaration of Helsinki\textsuperscript{31} and ethics approval for research was obtained from the University of New South Wales ethics committee (Sydney, Australia) for all tissue obtained (CPEHS project no 99069). Cortical cataract lens specimens (n = 15) and age- and sex-matched normal lenses (n = 6) were fixed in formalin and embedded in paraffin immediately after enucleation, as previously described.\textsuperscript{32} Eyes with posterior synechia or posterior subcapsular, nuclear, or other forms of cataract were excluded from the cataractous group of lenses. In addition, patients with a recent history of trauma, steroid treatment, alcohol abuse or premature cataract formation were excluded. The control subjects (n = 21) had no previous or family history of ophthalmic disease and were not taking any medication known to influence cataract formation. Age- and sex-matched cortical cataract (n = 12) and control lenses (n = 12) were also analyzed by ELISA, and three cortical cataract (n = 3) and three normal lenses (n = 3) were examined by zymography.

#### Macropscopic Analysis

Macroposcopically, lenses were oriented and the 12-o’clock position, which was finely marked with red 6-mercaptopterine dye. Under the same conditions, lenses were retroilluminated in phosphate-buffered saline (PBS) and photographed under a microscope. All photographs were assessed for cortical opacification by an experienced masked observer. Photographs were graded and localized according to the Wisconsin Cataract Grading System, as previously described.\textsuperscript{33–35} The photographs were scanned (2.0 scanner in Windows 98; Nikon, Tokyo, Japan), and the extent and density of opacification was calculated after the cortical spokelike opacities were outlined in another computer program (Opti-scan 98; Hewlett Packard, Palo Alto, CA; Fig. 1). The same program was used to analyze the immunohistochemical stained slides.

#### Immunohistochemical Analysis

Lenses were removed by careful dissection of the zonules keeping the anterior and posterior lens capsule intact, placed in 10% buffered formalin, kept at room temperature overnight, and transferred to 70% ethanol. The lenses were processed, embedded in paraffin, and sectioned for differential staining. Hematoxylin and eosin (H&E) staining of the lenses was used to examine the morphology after dissection.

After orientation, lenses were cut into four quadrants and paraffin embedded, and and 4-μm serial sections were placed on 3-aminopropyltriethoxy-silane (TES)-coated slides for immunohistochemical analysis, using a panel of monoclonal antibodies directed against MMP-1, -2, -3, and -9 and TIMP-1, -2, and -3. Sections were immunostained as previously described\textsuperscript{36} (Table 2).

All 19 lenses were viewed by three masked observers, and particular areas of the lenses were graded from 0 to 3 for stain intensity. These areas were chosen because each area plays a distinct role in lens remodeling. Each antibody was graded in one sitting by at least two observers under the same conditions. Lenses for each antibody were graded multiple times for observer consistency, with no alteration in observed grading. The median grade of staining from all three masked observers was calculated for the areas in all lenses and for all seven antibodies and controls. This number was used to record the intensity of staining in each zone of the lens. Staining intensity of 0 to 1 was assigned as negative staining; grading of 2 or 3 was denoted as positive staining.

#### Cell Culture

Epithelial cell growth was established from the SRA-01/04 human cell line (a gift from Venkat N. Reddy, University of Michigan) by using a technique previously reported.\textsuperscript{37} HLECs were subsequently expanded in 75-cm\textsuperscript{2} tissue culture flasks (Nunc, Roskilde, Denmark) in Dulbecco’s modified essential medium, supplemented with 20% fetal bovine serum, 100 U/mL penicillin, 100 mg/mL streptomycin, and 2.5 μg/mL amphotericin (all from Trace Biosciences, Sydney, NSW, Australia).

#### Cytokine Stimulation Assay

For cytokine stimulation assays, HLECs were treated as in our previous investigations.\textsuperscript{36} Briefly, cells were counted and seeded in triplicate at 0.8 × 10\textsuperscript{4} cells per flask. On reaching semiconfluence, they were placed in serum-free medium (SFM) for 24 hours. The medium was removed, and cells were washed again with PBS and placed in fresh SFM with recombinant human TNF-α (50 ng/mL) and IL-1α (20 ng/mL; R&D Systems, Minneapolis, MN). Supernatants were harvested at 0, 24,
48, and 72 hours and stored in aliquots at −70°C, for analysis by zymography and ELISA.

**UV-B Irradiation of HLECs**

Epithelial cells were counted and seeded at $0.8 \times 10^6$ cells per 10-cm$^2$ culture dish (Corning Glass Co., Corning, NY). On reaching semiconfluence, cells were washed three times with 5 mL PBS and placed in serum-free DMEM for 24 hours. The medium was removed, and cells were washed again before irradiation in 5 mL PBS. UV absorption by PBS is zero at a 1.0-cm thickness. Cells were irradiated with a light bulb (FL20SE bulb; Phillips, Sydney, Australia) that emitted radiation ranging from 275 to 410 nm. The maximum emission peak was 310 nm at the source. A UV-B photometer (IL400A; International Light, Newburyport, MA) was used to quantify incremental UV-B doses up to 10 mJ/cm$^2$. The irradiation intensity selected was 100 mJ/cm$^2$, with the emission peak and doses of UV similar to the range used by previous investigators for this cell line at incremental UV-B doses of 0, 2, 4, 6, 8, and 10 mJ/cm$^2$.

Control cells were subjected to the same conditions, but were not irradiated. After irradiation, cells were placed in fresh SFM for continuing culture at 37°C in a 5% CO$\text{\textsubscript{2}}$ incubator, and the supernatants were harvested at the 0, 24, 48, and 72-hour time points. Experiments were performed at each dose and time point in triplicate. Cell supernatants were aliquoted and stored at −70°C for ELISA.

**Cell Viability Assay**

For detection of UV-B and cytokine cytotoxicity, a simple quantitative (0.4%) trypan blue (Sigma-Aldrich, Sydney, Australia) staining method was applied for cell viability. Subconfluent cells were cultured for at least 72 hours before stimulation with cytokines or UV-B. After stimulation at each dose and time point, cells were collected by trypsin dissociation, as reported previously in our laboratory. Control cells were subjected to the same conditions, but were not irradiated. After irradiation, cells were placed in fresh SFM for continuing culture at 37°C in a 5% CO$_2$ incubator, and the supernatants were harvested at the 0, 24, 48, and 72-hour time points. Experiments were performed at each dose and time point in triplicate. Cell supernatants were aliquoted and stored at −70°C for ELISA.

**Sodium Dodecyl Sulfate–Polyacrylamide Gel Electrophoresis Gelatin Substrate Zymography**

Zymography was performed by using a technique previously reported by our laboratory. Briefly, lenses were divided into quadrants, and samples of equal weight from three eyes with cortical cataract and three matched control eyes were compared. Lenses were placed in RIPA buffer with protease inhibitors to prevent auto digestion and were homogenized with a sonicator (Soniprep 150; Arndell Park, NSW, Australia) for 10 seconds. Supernatants were diluted with nonreducing sample buffer (10% sodium dodecyl sulfate [SDS], 4% sucrose, and 0.25 M Tris-HCl [pH 6.8], with 0.1% bromophenol blue) and loaded without boiling in nonreducing conditions. After electrophoresis, the gels were washed twice for 30 minutes each in 2.5% Triton X-100 (Sigma-Aldrich). Gels were rinsed and incubated overnight at 37°C in substrate buffer (50 mM Tris-HCl [pH 7.4], 10 mM CaCl$_2$, and 0.02% NaN$_3$) and stained (Coomassie blue R-250; Bio-Rad, Sydney, Australia). Enzymatic activity was identified as clear zones in a blue-stained background. A low-range molecular weight standard (Bio-Rad) was run in adjacent lanes. MMP identity and activity were verified by running a sample of conditioned media derived from phorbol myristate acetate (PMA; Sigma-Aldrich) stimulated pterygium epithelial cells (a potent enhancer of MMP expression). Photographs were taken and scanned with a densitometer (Gel Doc; Bio-Rad) to obtain semiquantitative data.

---

**Table 2. Monoclonal Antibodies Used for Immunohistochemical Analysis**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Source</th>
<th>Dilution</th>
<th>Clone</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP-1 (collagenase)</td>
<td>ICN*</td>
<td>1:100</td>
<td>41-1E5</td>
</tr>
<tr>
<td>MMP-2 (gelatinase A)</td>
<td>ICN</td>
<td>1:80</td>
<td>42-5D11</td>
</tr>
<tr>
<td>MMP-3 (stromelysin)</td>
<td>ICN</td>
<td>1:100</td>
<td>55-2A4</td>
</tr>
<tr>
<td>MMP-9 (gelatinase B)</td>
<td>ICN</td>
<td>1:100</td>
<td>56-2A4</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>ICN</td>
<td>1:100</td>
<td>147-6D11</td>
</tr>
<tr>
<td>TIMP-2</td>
<td>ICN</td>
<td>1:100</td>
<td>67-4H11</td>
</tr>
<tr>
<td>TIMP-3</td>
<td>Calbiochem</td>
<td>1:100</td>
<td>136-13H4</td>
</tr>
<tr>
<td>Mouse IgG$_1$</td>
<td>R&amp;D</td>
<td>1:100</td>
<td>11711.11</td>
</tr>
<tr>
<td>Goat-antimouse IgG</td>
<td>Dako</td>
<td>1:100</td>
<td>—</td>
</tr>
<tr>
<td>Streptavidin-HRP</td>
<td>Dako</td>
<td>1:100</td>
<td>—</td>
</tr>
</tbody>
</table>

All antibodies used are specific to human antigens, as specified by the manufacturers and are mouse monoclonal antibodies. HRP, horse-radish peroxidase.

* Aurora, OH.
† La Jolla, CA.
Enzyme-Linked Immunosorbent Assay

After orientation, the normal eyes (n = 12) and cortical cataract (n = 12) lenses were weighed and placed on a grid for dissection into four quadrants under a microscope, and each quadrant of all lenses was weighed individually. Two lenses from each group were used for each antibody analysis. Quadrants weighing the same were homogenized with the sonicor (Soniprep 150; Sanyo) for 10 seconds. Individual supernatants were aliquoted for ELISA, performed in triplicate with a panel of monoclonal antibodies directed against MMP-1, -2, -3, and -9 and TIMP-1 and -2, and the total concentration of complexed MMP activity was determined. Individual supernatants derived from cycloheximide-stimulated HLECs were also analyzed by commercial ELISA for MMP-1, -2, -3, and -9 with the MMP-1 and -2 and TIMP-1 expressed as the mean ± SEM. The level of significance was determined by unpaired Student’s t-test, assuming unequal variance. To compare the extent of mean lens quadrant opacification, a non-parametric, one-way ANOVA was used, assuming unequal variance (Kruskal-Wallis test).

RESULTS

Localization of Cortical Opacities

The prevalence and severity of cortical opacification increased with age with concordance between eyes. Twenty-six eyes were from male and 23 eyes from female donors (mean age, 53.4 years; age range, 44–64 years). A total of 28 eyes were found to have cortical cataracts (Table 1). Of these, 13 were selected for macroscopic and immunohistochemical analysis. The principal locations of opacification in this group were inferonasal in eight lenses, inferotemporal in two, superotemporal in one, and supranasal in two. There was a significantly higher opacification in the inferonasal quadrant (P < 0.001). The 13 cataractous lenses had a mean extent of opacification equal to 37.2% ± 1.7% (SE) of the total two-dimensional photographic image of the lens (n = 13). In terms of individual quadrant opacified on average, 35.7% occurred in the inferonasal quadrant, 31.5% in the inferotemporal, 25.7% in the superotemporal, and 14.1% in the supranasal. The inferonasal quadrant was significantly opacified compared with the supranasal quadrant (P < 0.001). The mean area of opacification in brown-eye lens was 39.6% compared with 29.2% in blue-eye lenses.

Histopathologic Features of Cortical Cataract

Typical histologic features of cortical cataract are demonstrated in Figure 1 and include irregular lens cellular stratification in the bow area, posterior lens fiber migration, a lack of meridional row arrangement, disorganized nuclear bow, and apoptotic lens epithelial cells. There were remnants of nuclear material in deep cortex fibers. These features were observed only in lens fibers if the section of lens was sliced through a cortical lens opacity.

Immunohistochemistry of Normal Adult Lenses

Normal lenses revealed an equally low immunoreactivity for MMP-1, -2, -3, -9, and TIMP-1, -2, and -3. The positive immunoreactivity was localized to within the lens epithelium and intracellularly within a few early differentiating fibers at the lens cortex. The distribution was equal in all four quadrants of the six control lenses. The lens cortex and nucleus did not show positive staining for any antibody in any of the lenses. MMPs are stable for up to 24 hours after death in harvested ocular tissue.38

Localization of MMPs and TIMPs in Cortical Cataract

Immunohistochemical analysis revealed specific localization of MMP-1 and relatively little observed staining for MMP-2, -3, and -9 and TIMP-1, -2, and -3 intracellularly within the cortical fibers of opacified lenses. There was no staining observed for MMP-2 within the 13 cataractous lenses. The inferonasal quadrant contained a proportionally higher number of intracellular lens fibers staining and intensity of observed staining for MMP-1 (Fig. 1). The superotemporal quadrant contained the least number and lowest intensity of observed MMP and TIMP immunoreactivity. In comparison, observed immunostaining in control lenses was low for MMP-1, -2, -3, and -9 and TIMP-1, -2, and -3 and was equal in all quadrants (Fig. 2).

Expression of MMP-1 and TIMP-1 in Cortical Cataract

Normal lenses had an equally low presence of MMP-1, -2, -3, and -9 and TIMP-1 and -2 by ELISA (n = 12). Similarly, zymogram analysis (n = 3) revealed equally negligible MMP-1, -2, and -9. The distribution of these enzymes was equal in all four quadrants of the 15 lenses. Lenses with cataract showed a mean increase of 8.2 ± 0.4-fold (n = 2) in MMP-1 to 42 ± 3.4 ng/mL, determined by ELISA in the quadrant with maximum opacification, compared with the lowest quadrant. In contrast, TIMP-1 expression increased by 1.2 ± 0.2-fold (n = 2) to 8.6 ± 0.3 ng/mL, determined by ELISA in the same quadrant (Fig. 3).

Cell Survival

Trypsinization had negligible effect on cell viability in the HLE SRA-01/04 cell line, with 99% of cells remaining intact, as
measured by trypan blue uptake. The cell viability gradually decreased with increasing UV-B dose exposure and post UV-B and cytokine time exposure, to 86% at 72 hours, indicating a UV-B dose-dependent response.

**HLEC Production of MMPs**

Individual cell supernatants that were analyzed for MMP-1 and -2 and TIMP-1 by zymography and ELISA showed an accumulating protein concentration over a 72-hour period (Fig. 4). Therefore, cells in culture constitutively expressed MMP-1, TIMP-1 (Fig. 5), and MMP-2 (Fig. 4).

**Effect of Proinflammatory Cytokines on the Expression of MMPs**

HLECs were cultured in the presence or absence of the proinflammatory cytokines IL-1 and TNF-α, which have been localized in the lens. The optimal concentration and kinetics of exposure to these cytokines for MMP induction in several cell lines have been established in our laboratory.36 Culture media derived from HLECs stimulated with proinflammatory cytokines over a 72-hour period were harvested and analyzed. Semiquantitative zymographic analysis over the time course demonstrated the constitutive expression by unstimulated epithelial cells of MMP-1, -2, and -9 (Fig. 4, lanes 6–9). There was a 2.5-fold induction of pro-MMP-2 and active MMP-2 at 48 hours (Fig. 4, lanes 4, 8). In addition, there was a significant induction of MMP-9 expression at all time points between control (Fig. 4, lanes 2–5) and cytokine-stimulated cells over the same time course (Fig. 4, lanes 6–9). Exposure to phorbol myristate acetate resulted in a potent induction of pro- and active MMP-2 and -9 (Fig. 4, lane 1).

ELISA confirmed zymography, revealing that MMP-1, -2, -3, and -9 were upregulated to the maximum at 48 hours, after which the levels gradually decreased. There was no significant increase in TIMP-1 or -2.

**Modification of MMP and TIMP Expression by UV-B Irradiation**

Figure 5 demonstrates the dose dependency of MMP-1 expression by cultured SRA-01/04 cells after UV-B exposure, as determined by ELISA 72 hours after irradiation. MMP-1 expression increased 2.2, 6.2, and 3.9-fold after 2, 4, and 6 mJ/cm² of UV radiation, respectively (n = 3). TIMP-1 expression remained relatively unchanged over the dose exposure range. The time course of MMP-1 expression after irradiation with UV-B light at the dose of 4 mJ/cm² revealed an increase in expression becoming significant 24 hours after irradiation (Fig. 6). Maximum expression was attained after 48 hours and MMP-1 expression subsequently declined 72 hours after irradiation.

**DISCUSSION**

Previous studies have localized MMPs and growth factors in cataractous and normal lenses25,26; however, no attempt was made to associate the localization with clinically observed cortical cataract or observe the effect of UV-B exposure on MMP-1 in a lens epithelial cell line. Several novel observations have been made as a part of this study such as the localization of MMP-1 within cortical cataract, the presence of active and latent MMPs in cortical cataract, and UV-B exposure upregulating expression of MMP-1 in the SRA-01/04 human lens cell line.

Characteristic features of cortical cataract include localized abnormal lens migration, differentiation, and intracellular β-crystallin aggregation.1–4 The mechanism responsible for these features is currently unknown. In the present study, the overexpression of MMP-1 by lens fiber cells in regions with opacification is a significant finding and suggests that these proteins may contribute to the matrix remodeling and crystal-lin aggregation found in cortical cataract.
Despite the specific localization of MMPs and TIMPs in cortical cataract, MMP staining does not necessarily translate to MMP activity. Furthermore, the antibodies used in this study do not discriminate between active and latent MMPs. However, zymogram analysis demonstrated that the human lens epithelial cell line secreted both active and latent MMPs. Thus, it is likely that at least some of the MMP immunostaining (Figs. 1, 2) represents proteolytically active molecules.

Induction of MMP-1 has been reported in the skin after exposure to UV light. Increased MMP-1 expression by UV irradiation has been shown to be due to production of IL-1, -6, and -8 and TNF-α in cultured human corneal stromal cells and whole human corneas. This mechanism may be relevant to the pathogenesis of cortical cataract. UV-A has been shown to increase MMP-1 expression as much as 10-fold and TIMP-1 expression 2-fold in cultured keratinocytes.

Previous studies indicate that deregulation of normal matrix dynamics results in proliferative activity leading to cataract formation. It has been shown that overall lens growth is decreased after UV exposure. However, this study failed to assess whether this was due to altered lens matrix dynamics. The lens capsule plays an important role in cell attachment, migration, and proliferation of lens epithelial cells as a basement membrane. Both epithelial and fiber cells continuously synthesize and secrete the lens capsule. Highly regulated production of the ECM proteins occurs due to regional compositional differences observed between the anterior, equatorial, and posterior lens capsule. Normal lens fiber migration and capsule remodeling is an essential prerequisite for fiber cell stratification. The precise packing of the fiber cells is important for lens transparency. Because increased fluctuations in refractive index at cellular interfaces result in increased light-scattering, this order is disrupted in increased fluctuations in refractive index at cellular interfaces such as FGF-2. FGF-2 plays important roles in lens fiber cleavage or by MMPs' releasing FGF-2 from ECM stores may be a result of normal lens remodeling, as observed in the cell culture model. These enzymes are expressed at low levels in normal tissues. However, they can be markedly upregulated by UV irradiation both in vivo and in cultured cells. Irradiation of human skin with just a single dose of UV light has been shown to increase the activities of MMPs. UV irradiation did not induce TIMP-1, which helps to counterbalance the degradative effects of the MMPs. Thus, UV exposure clearly encourages a more proteolytic environment within the lens.

The highest intensity of staining of MMP-1 was in the germinative zone (Figs. 1, 2). This is also the lens area that receives the highest light intensity according to the peripheral light-focusing effect. Therefore, MMP-1 in these early-differentiating cortical fiber cells may be upregulated by the focused UV-B light. The in vivo and in vitro data provide strong evidence to implicate MMP-1 and its effect on growth factors in the regressive nature of this disease. Understanding the mechanisms involved in the formation of cortical cataract may provide an alternative to surgery for prevention and treatment. MMP inhibitors may slow the progression of cortical cataract and provide an alternative to surgery as a form of therapy.

References


