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Matrix Metalloproteinases as Mediators of Primary and Secondary Cataracts

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Abstract

The matrix metalloproteinases (MMPs) are a family of endopeptidases involved in numerous remodeling and fibrotic disorders. Although MMPs have been shown to play important roles in regenerative and disease processes in many parts of the eye, including the cornea, retina and trabecular meshwork, the role of MMPs in the normal and cataractous lens has only recently been studied. These investigations have shown that multiple MMPs are expressed in the lens and their expression is altered in a number of cataract phenotypes. However, anterior subcapsular cataract and posterior capsular opacification, cataracts of a fibrotic nature, show a particular involvement of MMPs. This review will highlight recent findings that suggest a causative role for MMPs in these fibrotic cataract phenotypes.

Keywords

cataract; EMT; fibrosis; lens; MMPIs; matrix metalloproteinase

Cataract is the leading cause of blindness worldwide despite the availability of effective surgery in the developed countries [1,2]. The etiology of cataract is diverse (see Allen [3] for review) with the majority of cataracts related to aging. Extracapsular cataract extraction provides quick restoration of vision and is the most frequently performed surgical procedure in the developed world, costing over US$3.5 billion each year in the USA alone [4]. However, it is not without its problems and can lead to complications such as the development of secondary cataract (up to 40–50% incidence of patients), also known as posterior capsular opacification (PCO) [5, 6]. PCO is a major medical problem with profound consequences to the patient's well-being and is a significant financial burden. PCO is considered a proliferative, fibrotic disorder that involves the aberrant deposition of matrix and wrinkling of the lens capsule [7]. Another cataract type, also of a fibrotic nature, is anterior subcapsular cataract (ASC) [6,8,9]. ASC, unlike PCO, is a primary cataract that occurs when lens epithelial cells (LECs), *in situ*, are stimulated to transition into myofibroblasts. These fibroblasts form subcapsular plaques directly beneath the lens capsule. Despite these differences, recent evidence has shown that in both cataract phenotypes the matrix metalloproteinases (MMPs), matrix-degrading enzymes,

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play significant roles and thus inhibition of their activity or expression may be of therapeutic value. In this article, evidence demonstrating that MMPs participate in cataractogenesis will be examined, with particular emphasis on the fibrotic cataract phenotypes, ASC and PCO.

Fibrotic cataracts

The lens is composed of an anterior monolayer of epithelial cells and an underlying fiber cell population, making it a relatively simple tissue. Following embryogenesis, the central lens epithelium remains relatively static and LEC proliferation is confined to the germinative zone, a region just anterior to the lens equator [10]. However, in a pathological situation such as that which occurs following ocular trauma, surgery or systemically, as with diseases like atopic dermatitis and retinitis pigmentosa, the more central LECs are triggered to proliferate and transform into plaques of large spindle-shaped cells, or myofibroblasts, through a phenomenon known as epithelial-to-mesenchymal transition (EMT) [8,9,11]. These myofibroblasts express contractile elements, such as α smooth muscle actin (αSMA) and, unlike LECs, they cease producing type IV collagen (a component of the lens capsule) and the highly organized crystallin proteins and begin to secrete an abnormal accumulation of extracellular matrix (ECM), including type I and III collagen, tenascin and fibronectin. As a result, fibrotic plaques are formed directly beneath the anterior lens capsule, which develop into distinct opacities in the lens. PCO involves similar fibrotic features to ASC. In PCO, LECs, which remain within the capsule after cataract surgery, are triggered to proliferate and migrate to the posterior lens capsule. A proportion of these cells then undergo a transition into myofibroblasts, through EMT, and lay down aberrant types and amounts of ECM. As the proliferating LECs and myofibroblasts accumulate, capsular wrinkling and opacities occur, which disrupt vision.

EMT is a feature of a number of fibrotic pathologies, such as pulmonary fibrosis, renal fibrosis, metastatic cancers [12–14] and lenticular fibroses [15]. In addition to pathological conditions, EMT is also an essential biological process involved in many aspects of development. In general, EMT involves the dissociation of epithelial cell-cell contacts, due to the dissolution of intercellular complexes containing E-cadherin, connexin-43 and zonula occludens-1 [16]. This is accompanied by the upregulation of intermediate filaments, such as α SMA and desmin. Together, these changes are thought to promote cellular migration and scatter [16]. Additionally, as is found in other fibroses, the EMT of LECs in ASC and PCO is followed by excessive deposition of extracellular matrix proteins, such as laminin, collagen types I and III, fibronectin and tenascin [15]. Finally, another commonality that has recently been identified between ASC and PCO with other fibrotic disorders is the involvement of the matrix-degrading enzymes, the MMPs [17–19].

Matrix metalloproteinase expression in the lens & cataracts

MMPs are a family of over 25 genetically distinct but structurally related zinc-dependent matrix-degrading enzymes, which require proteolytic activation via the removal of their prodomain. The role that each subfamily of MMPs played in degrading cognate components of matrix was employed in their naming and categorizing. For example, collagenase 1, 2 and 3, known as MMP-1, MMP-8 and MMP-13, respectively, are able to digest collagen I, II and III with different substrate preferences [20,21]. Gelatinase B (MMP-9) cleaves gelatin (collagen IV, V) and elastin preferentially. MMP-2 or gelatinase A is able to cleave the same matrix components as MMP-9 in addition to collagen VII, X, XI and fibronectin [20]. Additional family members were then named, such as the subfamily, the stromelysins, which include MMP-3, MMP-10 and MMP-11. MMPs that are membrane associated include the MT-MMPs 1–6 that are also known as MMP-14,-15,-16,-17,-24 and -25, respectively [20,21]. Finally, other groups are the matrilysins, metalloelastases, enamelysins and epilysins (Reviewed by McCawley and Matrisian [20] and Wong *et al*. [22]). Importantly, in addition

to their established roles as matrix-degrading enzymes, more recent evidence has shown that many of these MMPs are able to cleave receptors, adhesion molecules and activate ligands [23].

MMPs have been shown to play important roles in regenerative and disease processes in many parts of the eye, including the cornea, retina and trabecular meshwork [24]. However, the role of MMPs in the normal and cataractous lens has been far less studied, with the majority of investigations occurring in just the last 7 years. A number of these studies, however, demonstrate that MMPs and their endogenous inhibitors, the tissue inhibitors of MMPs (TIMPS), are constitutively expressed in the lens of multiple species (summarized in TABLE 1). For example, the gelatinases, MMP-2 and MMP-9, have been reported to be constitutively expressed in the rat and mouse lens through the use of multiple detection techniques, including zymography, western blot analysis and reverse transcriptase PCR [18,25,26]. Endogenous expression of MMPs has also been reported for a number of human LEC lines, including *MMP-2*, *MMP-9*, *MMP-14*, *TIMP-2* and *TIMP-3* [17,27,28]. Using western blot analyses, postmortem human lenses were also found to express MMP-14 [29]. The expression profile of MMPs in the human postmortem lens has been further examined by realtime quantitative PCR [30]. These investigators reported the constitutive expression of multiple MMPs and TIMPs in various regions of the lens (TABLE 1). Interestingly, *MMP-2* and *MMP-9*, were found to be expressed at low levels in the lens epithelium, whereas *TIMP-1*, *TIMP-2* and *TIMP-3* exhibited high basal expression in this lens region. With respect to the MT-MMPs, the anterior epithelium was found to express much higher levels of *MMP-14* than the equatorial epithelium, whereas *MMP-15* was found to be the opposite, with higher levels in the equatorial region [30]. Studies regarding the role for the constitutive expression of MMPs in the lens are limited; however, one recent study has identified MMP-2 as a putative survival factor due to its ability to release FGF-2 from the lens capsule [31]. Other studies show that MMP expression is induced after treatment with growth factors (summarized in TABLE 1). For example, Seomun and colleagues reported that TGF-β triggers *MMP-2* mRNA expression in a human LEC line and induces immunoreactivity for MMP-2 in cataractous plaques of rat lenses [17]. Similarly, treatment of whole, excised, rat lenses with TGF-β resulted in a significant induction in secretion of both MMP-2 and MMP-9 protein, which was correlated with the appearance of ASC plaques [18]. The induction of *MMP-9* in the ASC of rats was also confirmed recently at the mRNA level with laser capture microdissection and real-time quantitative PCR [32]. Finally, TGF-β has also been shown to stimulate secretion of MMP-2 and MMP-9 in cultured annular pad cells of the chick lens [33].

Additional cataract phenotypes have been shown to be associated with an induction in MMP expression. For example, MMP-2 and MMP-9 were shown to be induced during hydrogen peroxide-induced cataract formation in the porcine lens [34]. UV-B irradiation was shown to induce MMP-1 expression in LECs and the same investigators showed that MMP-1 expression was induced in the lens epithelium and cortical fibers of human cortical cataracts [35]. In human diabetic cataracts, MMP-2 expression was also shown to be induced [36]. Human lens capsular bags were found to express both MMP-2 and MMP-9 and these MMPs were also induced following sham cataract surgery in the porcine lens [7,19,34]. Interestingly, while the majority of studies show an induction in MMPs during cataractogenesis, John *et al*. showed that MMP inhibition, not induction, was associated with cortical cataract formation in the rat lens following oxidative stress [25]. Nonetheless, the previously mentioned studies collectively provide evidence that altered MMP expression is associated with multiple cataract phenotypes. Some controversy remains, however, as to which of the MMPs are constitutively expressed in the lens. This may be due to the difference in MMP expression profile across species or may be a reflection of the level of sensitivity of the MMP detection methods employed in each study. Further studies, using current molecular, genetic techniques and more reliable antibodies for immunolocalization are still greatly warranted.

MMP & ASC

In general, proteases are known to play important roles in lens development and cataract [37]. However, the question as to whether MMPs play a functional role in mediating cataractogenesis has been largely unexplored. A recent study showed that treatment of mouse lenses with exogenous, active MMP-9 resulted in immediate cortical cataracts demonstrating that elevated levels of this gelatinase is deleterious to the lens [26]. These investigators further showed that the main substrate for MMP-9 was βB1-crystallin. However, the effect of elevated, endogenous levels of MMPs on cataractogenesis has only recently been addressed in the fibrotic cataracts phenotypes, PCO and ASC.

Initial evidence that MMPs may have an active role in mediating ASC formation was provided by Seomun and colleagues who showed that overexpression of *MMP-2* in the human lens epithelial B-3 lens cell line, by stable transfection resulted in a conversion of the cells into a myofibroblastic-like phenotype, reminiscent of the EMT observed in ASC [17]. Additionally, these investigators showed that induction of these cells into a fibroblastic phenotype by treatment with TGF-β was prevented by cotreatment with an MMP inhibitor. These data further demonstrated that MMP-2 plays an important role in mediating the TGF-β-induced transformation of LECs. Biologically active TGF-β has been detected in the ocular media from patients suffering with cataracts and is considered to be the likely trigger in human ASC formation [38,39]. Multiple *in vitro* and *in vivo* models of TGF-β-induced ASC have also been developed, including a transgenic mouse model in which active TGF-β is ectopically expressed in lens fiber cells, under the control of the α-A crystallin promoter [40]. In these mice, the ASCs formed closely resemble those observed in humans. An additional model includes excised rat lenses, which when cultured with TGF-β develop distinct ASC plaques within 6 days that closely mimic human ASC [41]. This model has been used to provide further evidence for a causative role(s) for MMPs in the development of ASC. For example, Dwivedi and colleagues showed that co treatment of excised rat lenses with TGF-β and either of two commercially available MMP inhibitors (MMPIs), GM6001, a broad MMPI, or a MMP2/9-specific inhibitor, significantly suppressed ASC formation [18]. Importantly, while histological cross-sections of the lenses treated with TGF-β revealed the presence of numerous plaques, exhibiting strong immunoreactivity to αSMA, all of lenses cocultured with TGF-β and GM6001 or the MMP2/9 inhibitor, did not. These data further confirmed the requirement for MMPs in the transformation of LECs, as well as for the first time demonstrating that MMPIs can block ASC formation in a whole (excised) lens.

The ability of MMPs to regulate EMT has been demonstrated in a number of other systems and diseases, including cancer and development [14]; yet the mechanism by which MMPs control EMT is not well understood. Recent studies, however, suggest that MMPs may promote EMT by altering the E-cadherin/β-catenin pathway [14,23,42,43]. Specifically, the association between the cell-cell adhesion molecule, E-cadherin, and cytoskeletal protein, β-catenin has been shown to be vulnerable to enzymatic attack by multiple MMPs, including MMP-9 and MMP-2 [42,44,45]. Proteolytic cleavage of the N-terminal extracellular domain of E-cadherin by MMPs results in the shedding of E-cadherin and formation of extracellular domain fragments ranging in size from 50 to 85 kDa, that are often secreted into the conditioned media of cultured cells [46] and have been detected *in vivo* in urine, blister fluid of cutaneous diseases and the circulation of cancer patients [47–49]. Interestingly, MMP inhibitors have been shown to stabilize cadherin junctions and more specifically, the MMPI, GM6001, can suppress E-cadherin shedding [23,42,43]. In the excised rat lens model, the presence of a 72kDa E-cadherin fragment was observed in the conditioned media from lenses treated with TGF-β but was not detected in media from untreated lenses [18]. Importantly, media from lenses cotreated with TGF-β and either the GM6001 inhibitor or the MMP-2/9 inhibitor, did not contain the E-

cadherin fragments, suggesting that suppression of this phenomenon may be the means by which MMPs suppress ASC formation in this model.

MMPs & PCO

Multiple models of PCO have been created and generally involve seeding of LECs onto structures such as Plexiglass, plastic or bovine capsules with or without intraocular lenses (IOLs) to determine their effects on proliferation and migration [50,51]. A technique created by Gimble and Neuhann called continuous curvilinear capsulorhexis (CCC) was able to advance the study of LEC migration in PCO [52]. Specifically, CCC is the creation of continuous circular tear in the anterior lens capsule which allows for the removal of the lenticular nucleus while maintaining the integrity of the posterior capsule. Nagamoto and Bissen- Miyajima created a new model using the CCC technique and adding a poly(methyl methacrylate) (PMMA) ring to the equatorial region, creating a capsular bag [53]. With this model, LEC migration can be monitored and assessed as migration occurs from the anterior equatorial margin onto the posterior capsule [54]. Other derivations of this capsular bag model have been undertaken by Wormstone *et al*. [55] and Saxby *et al*. [56]. Importantly, utilizing their capsular bag model, Wormstone *et al*. were able to demonstrate that addition of TGF-β accelerated LEC transformation and capsule wrinkling both of which are thought to induce light scattering [7]. Furthermore, coculturing with an anti-TGF-β antibody (CAT-152) suppressed TGF-β-induced development of PCO, implicating TGF-β in its etiology [7]. As discussed earlier and outlined in TABLE 1, the expression and induction of MMPs were shown to be associated with the capsular bag model. In particular, MMP-2 and MMP-9 were implicated, similar to findings for ASC. Studies that directly test whether MMPs promote PCO, however, are relatively few. However, Wong and colleagues have demonstrated, using a human capsular bag model, that GM6001, the broad-spectrum MMP inhibitor, significantly inhibits LEC migration on human donor lens capsules [19]. A significant reduction in capsular contraction was also observed in the GM6001-treated capsular bags; however, whether this MMPI impacted LEC transformation was not investigated.

MMP inhibitors as therapeutics for managing ASC & PCO

The fact that MMPs have been shown to have potential causative roles in PCO and ASC suggests that inhibiting them directly may be an effective strategy for preventing or treating these ocular fibrotic diseases. The design of synthetic inhibitors that directly block the proteolytic activity of MMPs (MMPI) was initiated over two decades ago and many of these MMPIs have been investigated in numerous disease entities including cancer, arthritis and ocular disorders [57–60]. The first generation of MMPIs included pseudopeptides that inhibit MMP activity by specifically interacting with Zn^{2+}in the catalytic site and include the broad-spectrum inhibitors, such as batimastat, BB94 and GM6001 (Ilomastat/galardin) [58]. These MMPIs are not orally bioavailable but can be applied topically. In fact, one of the first MMPIs to go into clinical trials, GM6001, was used in topical treatment of corneal ulcers resulting from bacterial keratitis [61]. The second generation of MMPIs can be administered orally and show some increased specificity. Many of these second-generation MMPIs entered Phase III clinical trials to treat cancer patients; however, they failed to reach end points and increase survival rates and also caused adverse musculoskeletal side effects and, as a result, were not approved. The lack of efficacy of MMPIs is thought to stem from inadequate drug target validation in their design, resulting in a broad-spectrum action that likely causes loss of the beneficial and protective action that some MMPs play in a disease process [57–59]. Due to these clinical findings there has been an overall decrease in enthusiasm for MMPIs in the treatment of disease. This is unfortunate since substantial evidence indicates that MMPs contribute to multiple human disease entities, and MMP inhibition has been shown to significantly modulate disease progression in animal models. This also appears to be true for

PCO and ASC, as outlined in this review. The fact that MMPIs could be locally delivered in the eye, for example from an IOL, could circumvent the systemic effects that were observed in cancer patients. In addition, as with many other diseases, multiple MMPs appear to be involved in ASC and PCO. Thus, studies aimed at further determining the specific role that each of the MMPs play in these fibrotic diseases will be important for providing proper drug target validation in achieving efficacy and safety. Discerning which of the MMPs are critical in promoting PCO and ASC may be accomplished with drug-genetic experiments, such as those that employ MMP knockout mice.

Expert commentary

The studies summarized in this review clearly demonstrate that MMPs are involved in multiple cataractous events and probably play a direct role in promoting fibrotic cataracts, such as PCO and ASC. Since the MMPs are a diverse family with complex roles in matrix remodeling, cell migration, invasion and cellular transformation, further studies are needed to determine the mechanism(s) by which MMPs participate in cataractogenesis. Nonetheless, investigation of the effectiveness of MMPIs in preventing cataractogenesis, in particular PCO, is an exciting avenue worth pursuing.

Five-year view

The links between MMP induction and inhibition with cataractogenesis, particularly PCO and ASC, are still emerging, but are consistent with implicating MMPs as playing a direct role in these cataract phenotypes. Thus, within 5 years, we anticipate that, through the use of multiple *in vivo* and *in vitro* models in combination with more sophisticated molecular tools, much more will be learned about the expression profile of MMPs and TIMPs in the normal and cataractous lens. Additional work utilizing techniques to knockdown or overexpress the different MMP family members in these experimental models should help to discern which of the MMPs are specifically involved in the different cataract phenotypes, and thus help in designing appropriate targets. Within 5–10 years, there may be progress in the use of specific MMPIs in a preclinical setting, particularly for PCO, which can then be used in translation to a clinical setting.

Key issues

- Although anterior subcapsular cataract (ASC) and posterioi capsular opacification (PCO) are distinct cataract phenotypes the latter, a secondary and the former, a primary cataract, they exhibit common characteristics including, transformation of epithelial cells into mesenchymal cells, deposition of matrix and an involvement of the matrix metalloproteinases (MMPs), matrix-degrading enzymes.
- Recent studies have demonstrated that multiple MMP family members and their endogenous inhibitors, the tissue inhibitors of matrix metalloproteinases, are constitutively expressed in the lens of multiple species and can be induced during cataractogenesis.
- The use of broad spectrum and specific MMP inhibitors (MMPIs) have been shown to effectively suppress the development of ASC and PCO in both in vivo and in vitro animal model settings.
- Additional studies identifying the specific MMP family members involved in each of the different cataract phenotypes are needed to design appropriate MMPIs to be used in a clinical setting.

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Table 1

Expression of matrix metalloproteinases in the lens.

Study (year)	Region of the lens/cell line	Species	Detection method	MMP/TIMP (Constitutive [C] or induced [I] expression)	Ref.
Hodgkinson *et al*. (2007)	Whole lens (regions)	Human (postmortem)	Real-time quantitative PCR	MMP-2 [C] MMP-9 [C] MMP-10 [C] MMP-11 [C] MMP-14 [C] MMP-15 [C] MMP-16 [C] MMP-17 [C] MMP-19 [C] MMP-21 [C] MMP-23 [C] MMP-24 [C] MMP-28 [C] TIMP-1 [C] TIMP-2 [C] TIMP-3 [C] TIMP-4 [C]	[30]
Chang *et al.* (2007)	Human LECs	Human	Real-time quantitative PCR	MMP-2 [I] by radiation MMP-3 [I] by radiation MMP-9 [I] by radiation	[28]
Chang *et al.* (2007)	HLF cells	Human	Real-time quantitative PCR	MMP-2 [I] by radiation MMP-3 [I] by radiation MMP-9 [I] by radiation	[28]
Dawes *et al.* (2007)	FHL-124 cells	Human	Real-time quantitative PCR Microarray	MMP-2 [C] & [I] by TGFβ MMP-14 [I] by TGFβ TIMP-3 [I] by TGFβ	[27]
Li *et al*. (2007)	Capsular Bag	Human	Immunolocalization ELISA assay	MMP-2 [I] by sham operation MMP-9 [I] by sham operation	[62]
Dwivedi *et al*. (2006)	Whole lens	Rat	Western blot Zymography	MMP-9 [C] & [I] by TGFβ MMP-2 [I] by TGFβ	[18]
Jiang *et al.* (2006)	Human LECs	Human	Zymography	MMP-2 [I] by EGF	[63]
Deschamps *et al.* (2005)	Whole lens	Mouse	Zymography	MMP-2 [C] MMP-9 [I] by sham operation	[26]
John *et al*. (2004)	Lens epithelium	Rat	Western blot Zymography Reverse transcription PCR	MMP-2 [C] MMP-9 [C] MMP-14 [C] MMP-16 [C] TIMP-1 [C] TIMP-2 [C] TIMP-3 [C]	[25]
Sachdev *et al*. (2004)	Whole lens	Human	Immunolocalization	MMP-1 [C] & [I] by UV-B MMP-2 [C] & [I] by TNFα/IL-1 MMP-3 [C] & [I] by TNFα/IL-1 MMP-9 [C] & [I] by TNFα/IL-1 TIMP-1 [C] TIMP-2 [C] TIMP-3 [C]	[35]
Wong *et al*. (2004)	Whole lens Capsular bag	Human	ELISA assay	MMP-2 [C] & [I] by sham operation MMP-9 [C] & [I] by sham operation	[19]
Wormstone *et al.* (2002)	Capsular bag	Human	Zymography	MMP-2 [C] & [I] by TGFβ MMP-9 [C] & [I] by TGFβ	[7]
Seoman *et al.* (2001)	LEC-B3	Human	Reverse transcription PCR	MMP-2 [C] & [I] by TGFβ MMP-14 [C] TIMP-2 [C]	[17]

Study (year)	Region of the lens/cell line	Species	Detection method	MMP/TIMP (Constitutive [C] or induced [I] expression)	Ref.
Kawashima *et al*. (2000)	Capsular bag	Human Donor tissue (fibrous capsule)	Immunolocalization	MMP-1 [C] MMP-2 [C] MMP-3 [C] MMP-9 [C] TIMP-1 [C] TIMP-2 [C]	[64]
Tamiya *et al.* (2000)	Whole	Porcine	Zymography	MMP-2 [I] by H_2O_2	[34]
Tamiya *et al.* (2000)	Capsular bag	Porcine	Zymography	MMP-9 [I] by sham operation	[34]
Richiert *et al*. (1999)	Annular pad cells	Chicken	Zymography	MMP-2 [I] by TGFβ/PDGF MMP-9 [I] by TGFβ/PDGF	[33]
Smine *et al.* (1997)	Whole lens	Human (postmortem)	Western blot	MMP 14 [C]	[29]

LEC: Lens epithelial cell; MMP: Matrix metalloproteinase; TIMP: Tissue inhibitors of MMPs.