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Review Article

Roles of matrix metalloproteinases in the cornea: A special focus on macular corneal dystrophy

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ABSTRACT

Matrix metalloproteinases (MMPs) are endopeptidases that are responsible for the degradation of several components of the extracellular matrix (ECM) and some non-ECM proteins. MMPs are subdivided into 6 groups according to their structure and substrate specificity: collagenases, gelatinases, membrane-type MMPs, stromelysins, and matrilizines. Collagenases are important proteolytic tools during ECM remodeling, tissue regeneration, and organ development. MMPs, especially collagenases, have important roles in ocular processes such as retinal neurogenesis and corneal wound healing. MMP studies on eye research are limited, but there is growing evidence that MMP physiology is key for the ocular system, especially for the cornea. The cornea is predominantly composed of collagen fibrils, which form uniform lamellar lattices. Collagenase-driven ECM remodeling is essential for the cornea. Macular corneal dystrophy (MCD) is a rare inherited disease and characterized by progressive, insoluble accumulation of irregular substances in the corneal ECM. MCD can cause visual acuity loss up to blindness, and there is currently no treatment available. It has been recently reported that certain collagenases are downregulated in MCD disease progression. Here, we review the roles of MMPs in eye diseases and propose possible treatment strategies for MCD.

Contents

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1. Introduction

Matrix metalloproteinases (MMPs) are calcium- and zinc-dependent endopeptidases that are responsible for the degradation of several extracellular matrix (ECM) components. These proteases can also cleave many non-ECM molecules such as growth factors, integrins, and receptors [1]. There are 25 identified MMPs that are classified into two main groups based on their cellular location: “secreted” and “membrane-bound”. MMPs are also subdivided into 6 groups according to their structure and substrate specificity: (i) collagenases (MMP-1, -8, -13), (ii) gelatinases (MMP-2, -9), (iii) membrane-type MMPs (MMP-14, -15, -16, -17, -24, -25), (iv) stromelysins (MMP-3, -10, -11), (v) matrilizines (MMP-7, -26), and (vi) others (MMP-12, -19, -21, -22, -23, -26, and -28) [2]. As demonstrated in Fig. 1, while all MMPs have a prodomain, a catalytic domain with a conserved zinc-binding active site, and three histidine residues. They also contain unique domains that are responsible for different functions.

MMPs have different roles in several physiological processes such as embryogenesis, cell differentiation, wound healing, angiogenesis, apoptosis, and also in pathological processes including rheumatoid arthritis, fibrosis, tumor growth, and metastasis [3]. The activities of MMPs under physiological conditions are tightly regulated by gene expression, activation of zymogens (cysteine switch mechanism), and inactivation of enzymes with inhibitors such as endogenous tissue inhibitors (TIMPs). TIMPs, the specific inhibitors of MMPs, are noncovalently bound to the MMP active site to prevent activation. TIMPs are located in tissues, whereas there are also nonspecific inhibitors of MMPs in plasma such as α2-macroglobulin and α1-antiprotease [4]. There are four different TIMPs (TIMP-1, -2, -3, -4) and their expression is regulated by cytokines, growth factors, and cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 and -6 (IL-1 and IL-6) during development and tissue remodelling [5]. Some MMPs including MMP-1, -2, -3, -7, -9 can activate TNF-α, initiating TNF-α-induced MMP activation, which is linked with some autoimmune diseases such as rheumatoid arthritis, Crohn's disease, and multiple sclerosis [6–8]. The balance between the tissue activities of MMPs and TIMPs has critical importance in ECM homeostasis, as loss of control on MMP activity may cause diseases such as atherosclerosis, fibrosis, and cancer [9]. There is growing evidence that MMPs play a key role in cancer, especially in metastasis, and it is known that increased activities of particular MMPs lead to uncontrolled cell migration, tumor growth, metastasis, and angiogenesis [10]. Overexpression of MMPs is associated with poor prognosis [11–13]. In invasive cancer cells, the balance between TIMPs and MMPs is disturbed in favor of the latter, and the development of MMP inhibitors has been proposed as a new therapeutic approach for cancer treatment [14].

Although MMPs are mostly studied for their potential uses in cancer treatment, their importance in other disease states is usually underrepresented. MMPs are getting more attention because they are demonstrated to be involved in diverse pathological conditions throughout the body—ranging from cardiovascular diseases to ocular diseases. Although it is known that MMPs are virtually found in every tissue of the eye [15], their *in vivo* functions are still being explored for ocular physiology and pathology.

2. Roles of MMPs in noncorneal eye diseases

MMPs have been found in almost every tissue of the eye at developmental stages and disease processes. MMP-1, -2, -3, -9 and TIMP-1, -2, -3 have been detected in human vitreous and interphotoreceptor matrix. In addition to this, the retinal ganglion cell layer expresses gelatinase B (MMP-9) constantly. The role of these enzymes in normal retinal matrix turnover is unknown, but the expanding list of retinal

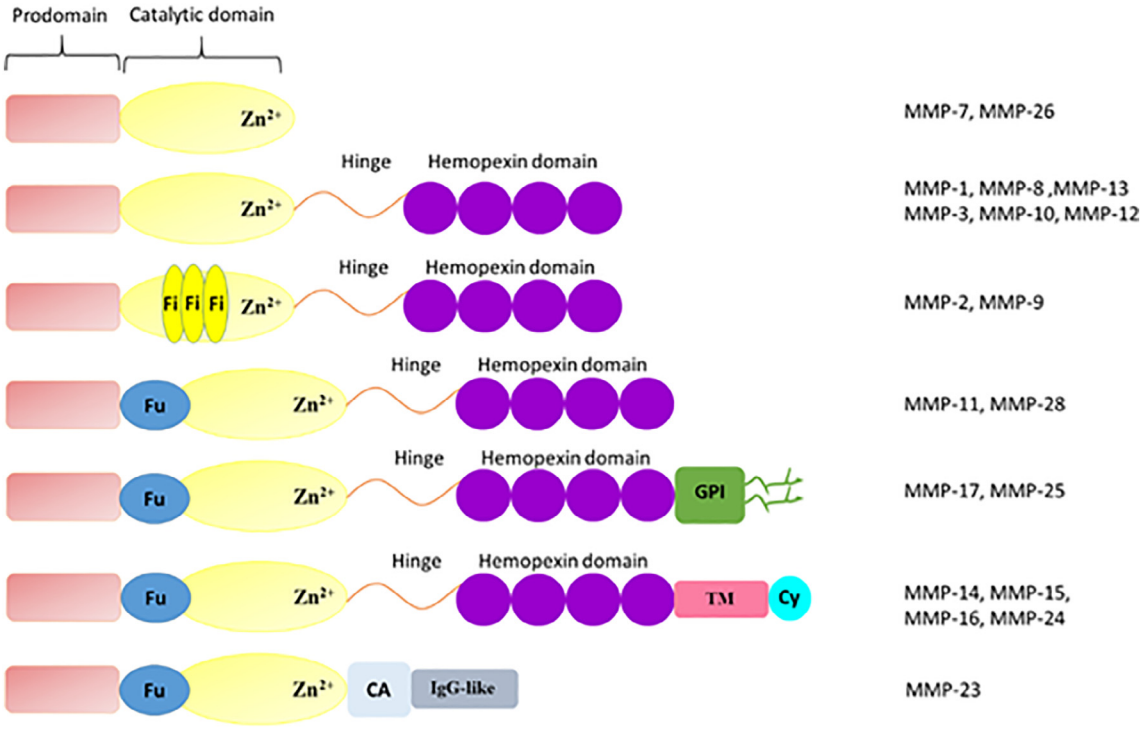

Fig. 1. Domains of MMPs. Prodomain functions as an auto inhibitor and keeps MMPs inactive through a cysteine switch. Catalytic domain provides the required enzymatic activity through an active site containing zinc-binding motif (HEXXH). Hemopexin (HPX)-like domain is responsible for substrate positioning/binding, and it is linked to the catalytic domain through a flexible hinge region [113]. Although some MMP classes do not contain HPX-like domains, some have additional domains such as fibronectin (Fi), furin (Fu), transmembrane (TM), cytosolic (Cy), cysteine array (CA), immunoglobulin-like (IgG-like), and glycosylphospatidylinositol (GPI) anchoring domains (for membrane attachment) [114].

diseases with which they have been linked may provide hints about their physiological roles [15].

MMPs and their overactivities are believed to play dominant pathophysiological roles in retinal diseases. Both increased levels of MMPs and their physiological dysregulation by a change in MMP–TIMP balance can lead to ECM disruption and play a role in retinal disease onset and progression. The relationship between the expression of MMPs and retinal diseases is extensively studied. MMP-14 paralog MMP-14a is known to have a critical role in retinal neurogenesis, differentiation, and lamination in the zebrafish eye. MMP-14 was also found in retinal ganglion cells and glial Müller cells in mice, according to immunohistochemistry [16]. MMP-14 is an activator of MMP-2, which might also contribute to the pathogenesis of retinal diseases [17]. The roles of MMP-9 in retinal structure and function were documented in MMP-9 knock-out mice, which displayed subdued changes in their retina as reflected in the overall ocular neurophysiological parameters [18]. Also, MMP-2, -3, and -9 basal expression levels were observed in Müller glial endfeet, radial fibers of Müller glia, and microglia, respectively [16].

Age-related macular degeneration (AMD), diabetic retinopathy, and glaucoma are the most known examples of eye diseases associated with MMPs. Although current MMP studies involve both posterior and anterior segment tissues, retina has significantly experienced rapid growth in MMP studies, especially with regard to retinal dystrophies and degenerations involving excessive MMP activities.

In the pathogenesis of AMD, MMP-1, -2, -3, -9, -14, and TIMP-2 and -3 are known to play significant roles [19]. When the retina pigment epithelium (RPE) and endothelial cells malfunction, continuous rebuilding of ECM occurs in early and advanced AMD disease, simultaneously. Pathological degradation or accumulation of ECM structural components is usually caused by the impairment or hyperactivity of specific MMP-TIMP interactions and is also influenced by genetic and environmental factors [19]. MMP-2 and MMP-9 secreted from RPE cells stimulated by angiogenic molecules promote choroidal neovascularization [20], which is the primary cause of significant vision loss in AMD patients [21]. Another study also depicted that plasma levels of MMP-2 and MMP-9 were upregulated in AMD [22].

Diabetic eyes are also affected by disturbed MMP-TIMP balance [23,24]. MMP-2, -9, -10, -14, and -19 have been implicated as factors in the development of diabetic retinopathy (DR) [19,23]. In particular, activated MMP-9 has been thought to be involved in hemorrhagic transformation in patients affected with proliferative DR [25]. TIMP-1 and TIMP-2 were found in a large proportion of proliferative DR membranes suggesting the existence of common pathways of ECM degradation in pathological processes leading to retinal neovascularization and fibrosis [26].

TIMPs and interleukins (ILs) have been extensively studied as Primary Open Angle Glaucoma (POAG) risk factors. The trabecular meshwork plays an important physiological role in regulating intraocular pressure (IOP) which is predominantly mediated by cytoskeletal contractile mechanisms and signal transduction pathways. Altered ECM is known to contribute to impaired aqueous humor outflow in POAG. An imbalance between ECM-degrading MMPs and TIMPs within trabecular meshwork contributes to the pathogenesis of POAG [19], which has been demonstrated as a shift toward raised TIMP levels in the aqueous humor of glaucomatous eyes. This shift may result in the inhibition of MMP activities, leading to an altered ECM composition in the trabecular meshwork and contributes to increased outflow resistance. Other studies have shown increased expression of MMP-1, -9, and -12 in the aqueous humor in patients with POAG, in comparison to control samples [27]. An increase in local concentrations of nitric oxide (NO_2) and MMPs leading to remodeling by the digestion of ECM components can further contribute to the development and progression of glaucomatous optic neuropathy phenotype [28].

3. Roles of MMPs and collagenases in corneal diseases

The cornea is predominantly composed of collagen fibrils which form uniform lamellar lattices. There are 28 different types of collagens; 13 of which are known to be present in the human cornea and are dominated by type I collagen with more than 50% presence [29]. MMPs, especially collagenases, play crucial roles in the maintenance of corneal integrity and transparency.

The cornea is a quiescent tissue with minimal remodeling in homeostasis. Penetrating corneal damage leads to the upregulation of many proteins including MMPs, especially collagenases, which in turn remodel collagen lattice [30]. MMP research on the cornea is mostly centered on corneal wound healing, which involves the migration of the epithelial cells to the wound, their proliferation, restratification, and differentiation; followed by stromal remodeling to maintain integrity and transparency of the cornea. Collagenases are found in small amounts in normal cornea and they are induced in the wound healing process [31]. Collagenolytic MMP-driven ECM remodeling is essential for corneal healing. Collagenolytic activity is observed in corneal wounds causing corneal ulceration [15]. MMP-1, -2, -3, and -9 have been demonstrated contributing to epithelial repair and remodeling of the stroma [32]. MMP-2 is a non-ECM substrate for MMP-1 which is held responsible for corneal melting. Additionally, corneal stromal degradation was associated with high levels of MMP-9 which is the non-ECM substrate of both MMP-1 and MMP-13 [33]. MMP-9 has been demonstrated to promote the migration of basal epithelial cells and is associated with the remodeling of the subepithelial basement membrane region [34]. Moreover, MMP-9 knockout mice are resistant to corneal barrier disruption when exposed to desiccating stress. MMP-2 and -9 inhibitors such as corticosteroids and tetracycline group antibiotics demonstrated to have the potential to prevent desiccation induced corneal epithelial barrier disruption in animal models [35–41].

It was suggested that the imbalance in collagenase levels, especially between MMPs and their TIMPs may lead to the keratolytic process [42]. The imbalance of MMP/TIMP levels can also destroy basement membrane structure, thus contributing to corneal ulcerations [43]. Corneal ulceration or ‘corneal melt’ can be a result of many precipitation factors such as dry eye, eyelid defects, physical and chemical traumas, and microbial infections. If corneal inflammation is persistent, tissue damage may lead to visual loss and even perforation with resultant blindness. The MMPs most relevant to corneal ulceration include collagenases (MMP-1, -8, and -13) that cleave collagen types I, II, and III; and gelatinases (MMP-2 and -9) that cleave collagen types IV, V, and VI [44]. MMP-9 contributes to corneal barrier disruption by the destruction of tight junctions in the superficial epithelium [45,38,39]. Similarly, nonsteroidal anti-inflammatory drug (NSAID)-induced corneal melt was found to be associated with enhanced expression of MMPs within corneal epithelial cells, stromal keratocytes, and at the level of Descemet’s membrane [44]. Among the commonly used NSAIDs, diclofenac and ketorolac were found to induce expressions of MMP-1, -2, and -8 [46]; whereas prostaglandin analogs were associated with increased MMP-1, -2, and -9 in the tear film [47]. At present, topical and systemic administration of anti-inflammatory agents, and surgical approaches are treatment options for corneal ulceration. Corticosteroids and tetracycline group of antibiotics are known to suppress MMP-9 expression and are frequently used in the clinic for this purpose [38]. New therapeutic approaches involving collagenases could be promising for many corneal diseases including intractable melts. These include MMP-deactivating contact lens designs for corneal melting [48], and tumor necrosis factor-α (TNF-α) inhibitors such as infliximab or etanercept [49,50] since inflammatory mediator TNF-α demonstrated to stimulate MMP-9 activity in a dose-dependent manner [37].

Moreover, gelatinase type MMPs, MMP-2 (gelatinase A) and MMP-9 (gelatinase B) are present in tear and corneal tissue during wound healing, in ocular surface diseases such as dry eye, and stromal disorders such as keratoconus. A strong relationship between tear MMP-9 levels and dry eye syndrome has been exhibited [51,52]. Hyperosmolar stress is known to have a direct proinflammatory effect on the ocular surface epithelium and it stimulates the secretion of MMP-3 and -9 and induces apoptosis [45,53,54]. MMP-9 increases in response to hyperosmolar conditions—leading to the disruption of corneal barriers and an increase in the rate of dry eye intensity [55]. Keratoconus, a progressive noninflammatory biomechanical weakening of the cornea is also reported to be associated with increased levels of MMP-1 and -9 [56].

Macular corneal dystrophy (MCD) has been associated with downregulated production of collagenases within the stroma [57], where abnormal matrix deposits accumulate with loss of corneal transparency *in vivo*. Although many corneal disorders are associated with dysregulation and overexpression of MMPs, the MCD is unique in that the activity of MMP-1 and -13 was found to be downregulated leading to abnormal matrix deposits and loss of corneal transparency *in vivo*. It is suggested that downregulation in the WNT pathway induces downregulations of two protein groups: MMP-1/13 and integrin/cadherin leading to the accumulation of abnormal collagens and disruption of epithelial layers, respectively. Although MMP/TIMP imbalance was documented in many ocular diseases, there is currently no documented evidence for the role of TIMP balances in MCD [57].

These findings depict that MMPs interact with each other in the pathological processes of the cornea. Collagen metabolism is one of the important factors that maintain corneal structure and function. Thus, functions of corneal collagenases should be deciphered to develop new treatment strategies for corneal diseases.

4. Structure and biochemistry of collagenases

Collagens are the most abundant proteins of the human body and the core components of ECM. Collagen molecules are formed in a triple helix structure with the combination of three alpha chains. Triple-helical structure gives collagens an exceptional mechanical ability, strong resistance to proteolytic enzymes, and a distinct topology of protein–protein interactions. The proteolysis of collagen is involved in several physiological and pathological processes such as tissue remodeling, wound healing, and regeneration [58]. Collagenases are important proteolytic tools in tissue regeneration and organ development during ECM remodeling. There are three types of collagenases: (i) MMP-1 (collagenase 1/interstitial collagenase), (ii) MMP-8 (collagenase 2), and (iii) MMP-13 (collagenase 3). They play an important role in cleaving fibrillar collagen types I, II, and III into typical 3/4 and 1/4 fragments which are denatured into gelatin, but they also exhibit activity against other ECM molecules and soluble proteins [59] (Table 1).

Table 1
An overview of collagenases.

Collagenases	Substrates	Expressed by	References
MMP-1	Type I, II, III, VII, VIII, X collagen, gelatin, casein, laminin, entactin, fibronectin, vitronectin, tenascin, pro MMP-1, -2, -9	Fibroblasts, endothelial cells, keratinocytes, macrophages, osteoblasts, tumor cells	[110]
MMP-8	Type I, II, III, V, VII, VIII, X collagen, gelatin, fibronectin, aggrecan, ovostatin	Chondrocytes, mononuclear fibroblast-like cells, bronchial epithelial cells and monocytes, keratinocytes, and melanoma cells	[111]
MMP-13	Type I, II, III, IV, VII, IX, X collagen, gelatin, casein, tenascin, fibronectin, aggrecan, plasminogen, osteonectin, serin proteinases inhibitors	Chondrocytes and synovial cells, tumor cells	[112]

The hydrolysis of triple-helical, interstitial (types I–III) collagen can be catalyzed by several members of the MMP family, mainly collagenases [60]. The triple-helical collagen structure exhibits locally versatile regions, with modulation of interchain salt bridges and water bridges leading to the accessibility of individual chains to collagenases. The collagenolytic MMPs are composed minimally of a zinc-dependent catalytic domain and a four-bladed β-propeller HPX-like domain linked by a linker (hinge) region (Fig. 2), and the cooperation between the catalytic site and HPX domain regulates collagenolytic activity [58]. The HPX-like domain of collagenases initially binds to the triple helix and facilitates the excursion and presentation of individual collagen chains to the active site of the CAT domain [58,61,62].

5. Macular corneal dystrophy: mechanism of deposit formation and roles of collagenases

MCD is a rare disease in which opacities form in the cornea resulting in progressive bilateral loss of vision [63]. MCD is stromal dystrophy that presents symptoms in the first decade of life with significant or total bilateral vision loss by the age of 30–40 [64]. MCD prevalence is registered as 1–9/100.000 in Orphanet (ORPHA:98969), with higher prevalence in populations with high consanguinities such as Iceland, South India, and Saudi Arabia, caused by autosomal recessive transmission [65–67]. MCD is the least common but also one of the most severe forms of all corneal stromal dystrophies. At present, no medical treatment for MCD is available and patients with significant vision loss are treated with corneal transplantation. Cornea donor availability is an issue in developing countries, and half of the world's population does not have access to corneal transplants [68]. Moreover, invasion of a healthy cornea by the recipient's keratocytes causes reformation of deposits as early as 5 years after transplantation [66,69,70].

MCD is linked to the mutations in the carbohydrate sulfotransferase 6 (CHST6) gene leading to the accumulation of low or unsulfated keratan sulfate proteoglycans (KSPG) in the corneal stroma [71,72]. Corneal stroma consists of highly organized collagen-rich ECM and keratocytes. Parallel collagen fibrils are uniformly sized and regularly spaced forming a transparent structural organization, and

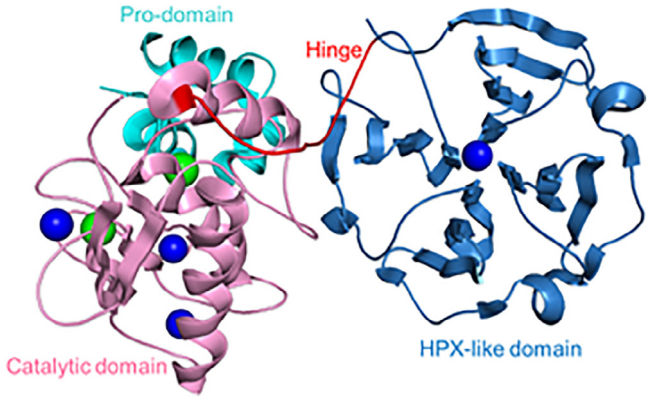

Fig. 2. Crystal structure of MMP-1. Prodomain (cyan), catalytic domain (pink), HPX-like domain (blue), linker hinge region (red) are given in MMP-1 structure (PDB ID: 1SU3). Catalytic zincs are in green and structural calcium ions are in blue.

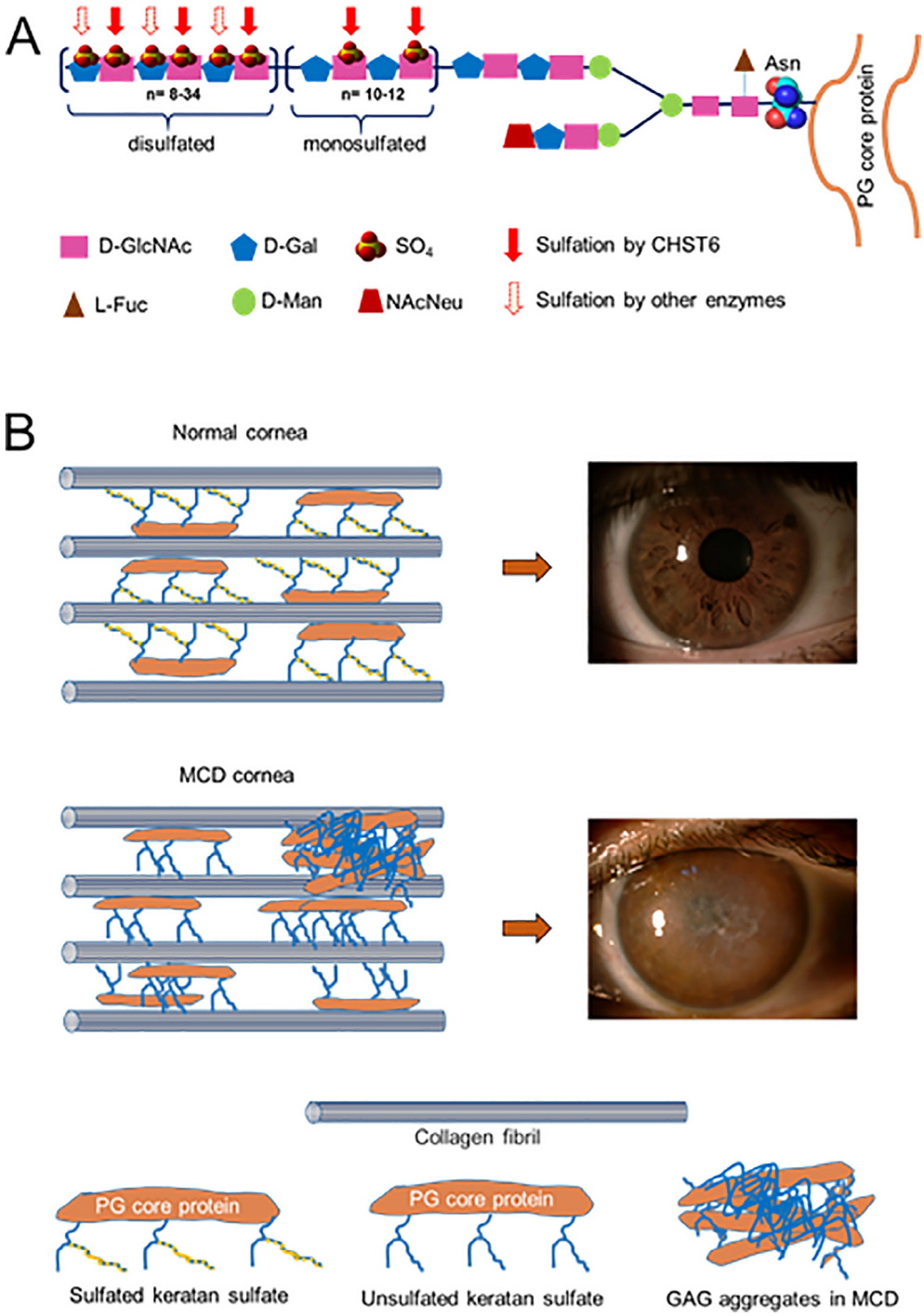

Fig. 3. Molecular mechanism of macular corneal dystrophy. (A) Structure of corneal keratan sulfate chains. Keratan sulfate proteoglycans (KSPGs) of the eye are primarily KS type I, in which keratan sulfate chain is N-linked to an asparagine residue of proteoglycan (PG) core. Keratan sulfate chain is characterized by Gal-GlcNAc disaccharide repeats that can be monosulfated or disulfated. GlcNAc 6-O sulfotransferase (CHST6) sulfates D-GlcNAc at the nonreducing terminal during elongation. Gal 6-O sulfotransferase (i.e., CHST1) sulfates D-Gal at internal positions. Arrows indicate sulfation positions of respective enzymes. (B) Schematic representation of collagen fibril-KSPG interaction. The size of collagen fibrils and the distance between them are uniform in a healthy cornea. KSPGs interact with collagen fibrils and they are found in between collagen fibrils. For simplicity, only KSPG, but not CS/DS proteoglycan, is depicted and the structure of lumican [115] is used as a template. Owing to the mutations in CHST6 gene, keratan sulfates are either less sulfated or unsulfated in MCD patients. Loss of sulfation on KSPGs leads to accumulation as insoluble aggregates which causes clouding of the cornea. The size of collagen fibrils and the distance between fibrils may also be altered in MCD cornea. D-Gal: D-galactose, GlcNAc: N-acetyl glucosamine, Asn: asparagine, D-GlcNac: N-acetyl-D-glucosamine, SO_4: sulfate, L-Fuc: L-Fucose, D-Man: D-Mannose, NacNeu: N-acetyl-neuraminate.

proteoglycans (PG) are in close contact with collagen fibrils playing critical roles in this organization. PGs have a protein core and linked glycosaminoglycan (GAG) side chains, which are long polysaccharides that comprise repeating disaccharide units. Keratan sulfates are a class of GAGs that are characterized by galactose-N-acetylated glucosamine (Gal-GlcNAc) disaccharide repeats. Keratan sulfate proteoglycans (KSPGs) together with chondroitin/dermatan sulfate proteoglycans are important for the maintenance of transparency and collagen fibril

organization. Long PG side chains connect two or more fibrils, whereas shorter PG side chains fill the space between adjacent fibrils [73,74]. The spacing between neighboring collagen fibrils is a result of the balance between attractive forces and repulsive forces caused by the binding of PGs to fibrils and osmotic pressure generated upon hydration of sulfated PGs, respectively [73]. KSPG sulfation is defective in MCD patients, leading to the aggregation of KSPGs and disruption of the collagen organization. KSPGs of the eye are keratocan, lumican, and mimecan all bearing highly sulfated keratan sulfate side chains. KSPGs are sulfated at both galactose and GlcNAc sugars by different enzymes; however, corneal CHST6 enzyme (also named as N-acetylglucosamine-6-O-sulfotransferase) encoded by the CHST6 gene seems to play a major role [75–77]. CHST6 enzyme adds a sulfate group to the C6 of GlcNac during the elongation of the KS chain; however, sulfation of galactose is also decreased or eliminated when the CHST6 gene is mutated leading to abnormal KS chain length [78]. Interestingly, chain lengths of CS/DS PGs decrease whereas their concentrations increase in MCD. Unsulfated KSPGs accumulate as insoluble aggregates and they get bigger over time, indicating the lack of mechanisms that can metabolize unsulfated KSPGs (Fig. 3).

There are three immunophenotypes (I, IA, and II) of MCD with regard to the availability of sulfated keratan sulfate (KS) epitopes in serum and cornea. Sulfated corneal KS-specific mAb 5-D-4 which recognizes disulfated KS disaccharides is used for the diagnosis of MCD immunophenotypes in clinical research. Immunostaining with this antibody exhibits three possible immunophenotypes of MCD. Immunophenotype I is diagnosed with undetectable KS antigen in both serum and cornea. Immunophenotype IA is diagnosed with undetectable or very low serum levels of KS and no KS antigen in stromal ECM, whereas some KS are detected in keratocytes. In immunophenotype II, the serum level of KS antigen is below normal or normal, and KS antigen in the stroma can be observed [79,80].

The relationship between KS and MMPs has been exhibited in different diseases and tissues. One of the major corneal KSPGs, lumican, was first identified in the cornea, but it is also present in many other tissues. In melanoma cells, it was demonstrated that lumican inhibits MMP-14 activity. When lumican binds to MMP-14, proteolytic activity is inhibited. It indicates that MMP-14 inhibition may lead to the protection of collagen fibrils from enzymatic degradation [81]. Lumican can inhibit proangiogenic activity of endothelial cells by reducing MMP-14 activity [82]. It was also demonstrated that lumican can protect collagen matrix degradation by masking collagenase MMP-1 and MMP-13 cleavage sites [83].

An increase in collagen fibril diameter, a decrease in interfibrillar space, and irregular spacing of fibrils were observed in the cornea of MCD patients [84,85]. The decrease of interfibrillar spacing is likely caused by the decrease in the water holding capacity of unsulfated KSPGs (which decreases the repulsive forces), and decreased KS chain length [78,86]. *In vitro* studies depicted that fibril size is inhibited by lumican core protein, not by the keratan sulfate chain, which is supported by findings in mouse and zebrafish models [87–89]. Interestingly, ECM core proteins such as lumican and fibromodulin bind to the collagen fibrils, adjacent to the hydrolysis regions of collagenase enzymes, and this structural hindrance sterically inhibits collagenase activity. Recombinant MMP-13 was demonstrated to first separate relevant core proteins and then break down collagen [90]. This suggests that collagenases can play important roles in proteoglycan metabolism which is defective in MCD patients.

6. Promising and challenging treatment strategies for macular corneal dystrophy

There is no permanent cure available for MCD in the clinic, yet. Corneal transplantation has been the most common surgical strategy to treat MCD, but disease recurrence and transplantation-related complications are commonly reported. Therefore, less invasive, new treatment strategies are urgently needed.

The traditional treatment for stromal dystrophies including MCD, is full-thickness transplantation of an allogeneic graft, i.e., penetrating keratoplasty (PK), for visual rehabilitation [91]. However, in addition to graft-related complications such as astigmatism, suture problems, endothelial cell loss, or immunologic rejection, the risk of dystrophy recurrence at the corneal graft is a significant challenge for long-term visual rehabilitation in MCD [92,93,70]. In a longitudinal study, repeated PK was required for 15% of eyes that had undergone PK for MCD, owing to disease recurrence [94]. At present, cornea donor availability is an issue in developing countries, and half of the world's population does not have access to corneal transplants [68].

Gene therapy for ocular diseases has been a focus of research, yielding to several clinical trials for retinal diseases. Introduction of exogenous therapeutic DNA (i.e., WT gene), or editing the mutated gene in the patient genome (often through CRISPR/Cas9 mediated genome editing) are different gene therapy approaches [95]. Cornea tissue is easily accessible and small tissue makes it a strong candidate for gene therapy; moreover, avascularity of the tissue eliminates the risk of off-target effects in other tissues. Corneal dystrophies with known genetic causes can potentially be treated by gene therapy, although no such approach has been validated in humans yet. There are examples of gene editing strategies in genetic corneal diseases. It is depicted that gene editing by CRISPR/Cas9 has effectively prevented endothelial cell loss in a mouse model of Fuchs' Endothelial Corneal Dystrophy (FECD), which is caused by missense mutations in Collagen 8A2 (COL8A2) gene [96]. We recommend recent comprehensive reviews for more information on the methodology and possible applications of gene therapy in ocular diseases and MCD [97,98]. Moreover, the use of viral vectors, such as adeno, adeno-associated, retro, lenti, and herpes simplex, and nonviral approaches, have been studied over the last two decades to incorporate DNA into *in vitro*, *in vivo*, and *ex vivo* corneal cells [99]. In the light of these previous studies, viral gene therapy may become a strategy for the treatment of corneal dystrophies in the future. However, it remains challenging to develop such strategies both because of the lack of animal disease models and also the highly variant nature of mutations detected in MCD patients [91].

Another promising treatment strategy is enzyme replacement therapy (ERT), which is a therapeutic approach where a specific enzyme that is either absent or inactive in affected patients is replaced by the functional enzyme. These enzymes are commonly developed by recombinant DNA technology. ERT is currently the most suitable therapy available for several lysosomal storage conditions [100]. The first effective treatment with ERT was applied in Gaucher disease and other lysosomal storage disorders, including certain forms of mucopolysaccharidoses (MPS)[101]. Mucopolysaccharidoses (MPS) are a group of inherited metabolic disorders in which GAGs, similar to MCD, are not properly degraded and built up in tissue [102]. Visual impairments such as corneal opacification and retinopathy are common in MPS and they lead to severe visual disability [103]. ERT is a major treatment strategy for MPS patients. Clinically approved recombinant laronidase replaces deficiency in the enzyme by supplying a catalytically active enzyme through intravenous administration. Treatment of MPS I patients with laronidase demonstrates a reduction in lysosomal GAG concentration [104]. However, the effects of ERT on corneal opacification and retinopathy are not yet clearly defined. Animal studies indicate clearance of accumulated keratan sulfate in body tissues by long-term ERT in the treatment of systemic MPS [105]. It was previously demonstrated that alpha-galactosidase in MCD corneal tissue has substantially lower activity compared to normal cornea [106]. It was suggested that alpha-glycosidase replacement with topical therapy or the use of other methods to boost alpha-galactosidase activity is a potential treatment strategy for MCD. These studies reveal the

potential role of ERT in the future treatment of MCD [91]. ERT approach to replace CHST6 enzyme seems like a potential route to treat MCD. However, CHST6 enzyme is localized in the golgi apparatus and intracellular delivery of this enzyme is not plausible. Future studies should aim at elucidating the relationship between CHST6 gene mutation(s), CHST6 enzyme function, and the mechanism of deposit formation to investigate new treatment strategies.

Finally, MMPs have crucial activities in the pathway of diseases and can be a therapeutic target. Overexpression of several MMPs was documented in some ocular diseases [19] and suppression by MMP inhibition was suggested for therapy [107,108]. Conversely, it has been demonstrated that MMP-1 and MMP-13 enzymes in ECM are reduced in MCD disease, which are important for corneal reshaping and in the removal of abnormal accumulations [57]. Restoring the activities of these collagenases may stop or even reverse the accumulation of KSPGs. The cornea is the primary route for topical drug delivery, so any topical therapy targeting corneal diseases holds high potential. Cellular delivery of large molecules is still a big challenge, but the delivery into corneal ECM is through simple diffusion. Any molecule as large as 66 kDa might diffuse into the cornea [109]. Because most of the MMPs are localized in ECM, topical delivery of these enzymes into the cornea would be a potential therapy for diseases related to MMP downregulation.

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Ethical approval

Not applicable.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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