• Review •

Role of corneal collagen fibrils in corneal disorders and related pathological conditions

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Abstract

• The cornea is a soft tissue located at the front of the eye with the principal function of transmitting and refracting light rays to precisely sense visual information. Corneal shape, refraction, and stromal stiffness are to a large part determined by corneal fibrils, the arrangements of which define the corneal cells and their functional behaviour. However, the modality and alignment of native corneal collagen lamellae are altered in various corneal pathological states such as infection, injury, keratoconus, corneal scar formation, and keratoprosthesis. Furthermore, corneal recuperation after corneal pathological change is dependent on the balance of corneal collagen degradation and contraction. A thorough understanding of the characteristics of corneal collagen is thus necessary to develop viable therapies using the outcome of strategies using engineered corneas. In this review, we discuss the composition and distribution of corneal collagens as well as their degradation and contraction, and address the current status of corneal tissue engineering and the progress of corneal cross-linking.

• **KEYWORDS:** cornea; collagen fibril; collagen degradation; collagen contraction; tissue engineering

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INTRODUCTION

The cornea is a soft tissue at the front of the eye that has the principal function of transmitting and refracting light rays[1]. The cornea represents approximately 70% of the total refractive power of the eye[2], and its transparency is essential for visual perception[3]. Accordingly, corneal disease or injury results in the loss of vision, which impacts millions of patients. In particular, the cornea constitutes a connective tissue comprising cells and stromal extracellular matrix (ECM) that relies on the synergistic cooperation of many different components of the ECM to precisely transmit and refract visual information. In turn, the ECM consists of organized lamellae composed of tightly distributed fibrils[4]. The regular packing of these small diameter collagen fibrils with a highly ordered hierarchical organisation leads to the maintenance of corneal shape and curvature[5]. Notably, an alternative conformation of the collagen fibrils caused by damage has been shown to result in altered corneal transparency and physical properties[6]. Therefore, a goal of this review was to examine the formation of the corneal collagen matrix. In addition, at the present time, no clear guidelines are available for examining the status or role of corneal fibrils in the diagnosis of corneal pathologies. Accordingly, we also reviewed the pathophysiologic functions of corneal fibrils to provide a better understanding of their possible roles as a contributing factor and/or biomarker for corneal matrix pathologies.

COMPOSITION OF CORNEAL COLLAGEN FIBRILS

Corneal collagen fibrils serve as the basal component of the corneal matrix and play a role in the morphology and pathology of corneal disease. In turn, cellular interactions with the ECM mediate biological processes including developmental morphogenesis and wound healing. As cells reside within the three-dimensional (3-D) ECM *in vivo*, matrix structure and dimensionality have been shown to impact cell morphology, protein organization, and mechanical behavior[7]. Organization of the corneal stroma matrix involves molecules such as type V collagen, fibril-associated collagens with interrupted triple helixes, and small leucine-rich proteoglycans[2]. Fibril-forming collagens constitute the predominant tensile load-bearing proteins in the corneal stroma and consist of self-assembling triple helical molecules that incorporate electron-dense particles and proteoglycans[8]. Fibrillar collagen fibrils are well organized and are produced to fill structures, adapting to their peripheral environment.

Cell-matrix interactions can help to modulate ECM remodeling to produce matrix architectures and maintain 3-D structures. The metabolism of collagen monomers maintains the balance[9].

In addition, the nonlinear mechanical behavior of the cornea is synchronized with the crimping morphology of collagen fibrils. Conversely, the aberrant microstructure of collagen fibrils has been shown to result in pathologic corneal transformations such as ectasia after laser-assisted *in situ* keratomileusis[10]. The collagen fibers in the anterior cornea extend from the anterior limiting lamina, interfelting with deeper fibers to form bow spring-like structures that are necessary to control corneal shape and in the process of corneal pathology[11]. A network of circumferentially oriented collagen fibrils in the periphery of the human cornea and an orthogonal arrangement of collagen fibrils in the central cornea are also present in the posterior stromal layer. This distribution pattern of collagen fibrils contributes to corneal biomechanical and curvature functions[12]. Collagen bundles in the corneal lamellae demonstrate a complex layout, merging and splitting within a single lamellar plane. The corneal collagens in the superficial and limbal cornea differ compared with those in the deep and central regions; specifically, the collagen bundles in the superficial layer were found to be smaller than those in the deep lamellae[13]. The corneal equivalent that was constructed with collagens was similar to the native cornea. The adherens junction proteins were expressed from the epithelial and endothelial layers, which hinted at the potency of cell junctions and the polarized morphology of these layers[14]. Furthermore, an increase in corneal fibril diameter observed in the peripheral cornea may have arisen through reinforcement involving scleral collagen[15]. In sclerocornea, the level of type I collagen was found to be similar to that in normal cornea, whereas type III collagen was faint in both normal cornea and sclerocornea but strong in normal sclera. Thus, this change could potentially contribute to the abnormal fibril assembly in sclerocornea[16]. In comparison, the immunophenotype of the corneal scars found in Peters anomaly and congenital glaucoma differs from that of normal cornea by the intensity of type I and type III collagen labelling[17]. In turn, the structural alterations exhibited by collagen XII and XIV null mice, which demonstrate delayed endothelial maturation, suggest that functional changes in endothelial function result in increased corneal thickness. The endothelial-stromal interactions suggest the involvement of a signal transduction pathway for signal transduction[18]. Type XII collagen isoforms constitute the surface component of type I collagen fibrils, which contribute to the stability of the fibrils in Bowman's layer and the associated interfacial matrix that lies between Bowman's layer and the stroma proper[19]. Notably, type XII collagen is overexpressed in permanent human and mouse corneal scars and may therefore represent a novel target to treat corneal scarring[1], although it should be noted that the structure of the cornea of different species differs because of the surrounding environment[20]. At a gross morphological level, the collagen fibers and the collagen fibril-

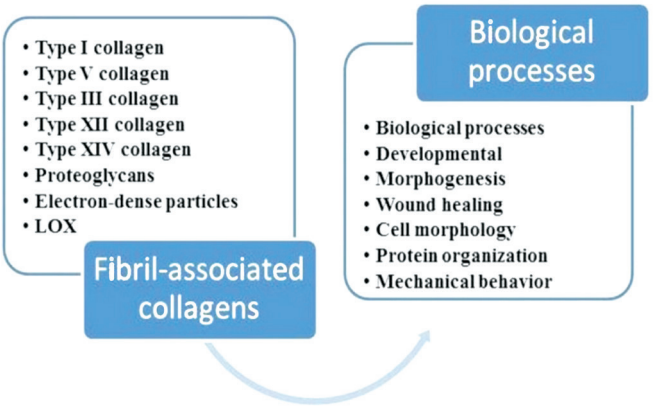

Figure 1 Collagen component analysis and relative functions.

maturating enzyme, lysyl oxidase, has also been shown to lead to dysregulation of corneal collagen fibers[21] (Figure 1).

DISTRIBUTION OF CORNEAL COLLAGENS

Corneal stromal collagen fibers (lamellae) are systematically ordered in a 3-D reticulum of lateral fibers that increases stromal stiffness and sustains corneal shape[22]. The corneal and scleral compaction at the corneal limbus by annular highly aligned collagen is necessary for corneal curvature and, hence, for the focusing power of the eye[23]. The corneal stroma primarily consists of a reticulum of fibrillar collagens that effects corneal optical and biomechanical actions. The use of X-ray diffraction to map the fibrillar organization, comprising the orientation and distribution of collagen lamellae in the corneal planum, has further demonstrated that this organization may vary owing to disease and surgical procedures[12]. In particular, collagen fibrils in the anterior part of the cornea are more isotropic, whereas collagen fibrils are directed toward the four major rectus muscles in the posterior part. The multitudinous orthogonal arrangement of collagen fibrils in the mid- and posterior parts of the corneal stroma helps to resist the strain from extraocular muscles. Simultaneously, the more isotropic arrangement of the anterior part of the cornea may play a key role in the biomechanics of the cornea by withstanding the intraocular pressure and corneal curvature[24-25]. Furthermore, collagen fibrils in the prepupillary cornea appear to be more compact than those in the peripheral cornea. The characteristic alignment of collagen fibrils can help to sustain the transparency and refractive index requirements of the cornea. Specifically, the high packing density of collagen fibrils is important for corneal strength and curvature in thinner areas of the cornea[26-28]. The regular arrangement of the collagen fibrils is critical for the transparency of the human cornea as is the maintenance of optimal hydration. Such arrangement is based on the presence of stromal proteoglycans and glycosaminoglycans[29]. Proteoglycans specifically regulate the organization of collagen fibrils in the corneal stroma *via* their protein core and highly anionic glycosaminoglycan side chains[30]. In addition, corneal collagen fibril orientations along

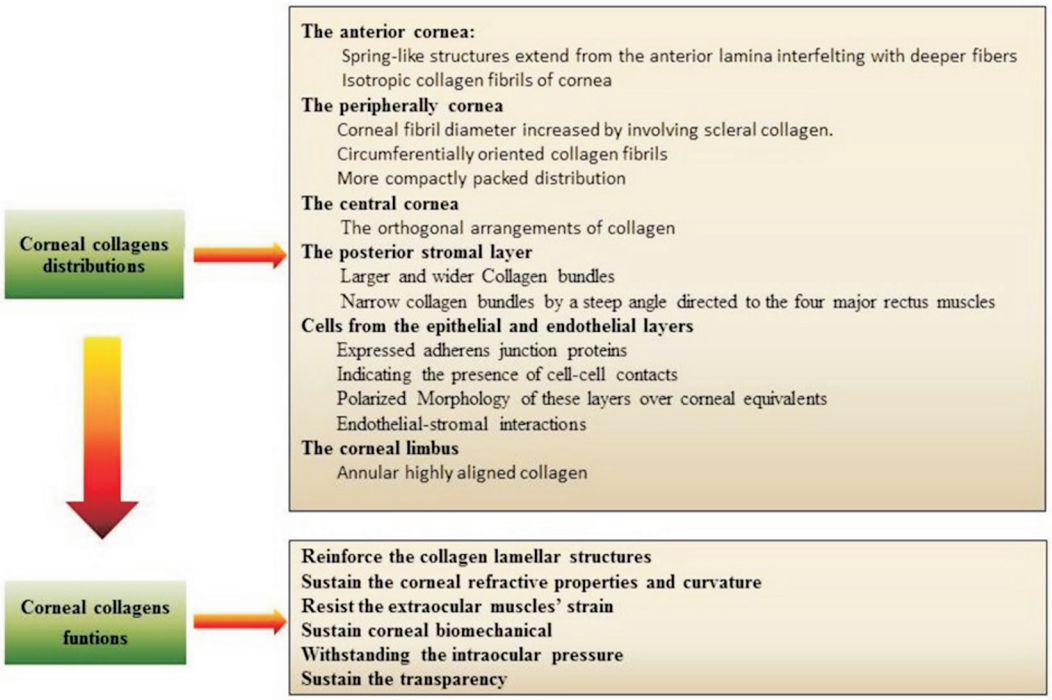

Figure 2 Distributions of corneal collagens, their architectural features, and functional advantages.

the superior-inferior and the nasal-temporal meridians are dispersed to reinforce the collagen lamellar structures, which sustain the corneal refractive properties[31]. However, changes in the modality and alignment of corneal collagen lamellae have been observed in some pathological states. In the normal human cornea, collagen lamellae near to Bowman's layer are narrow by a steep angle, whereas a decrease in width and angle relative to Bowman's layer can be observed with the approach toward Descemet's membrane. Conversely, the characteristics of the collagen lamellae are altered in keratoconus, inducing abnormalities in corneal shape[32-33]. In addition, the space between collagen fibrils is decreased and collagen fibrils with a large anteroposterior diameter can be observed in macular corneal dystrophy type I, with the deep stroma being affected to a greater degree[34]. Corneal collagen fibril orientation is also altered consequent to some pathological changes and injuries. For example, corneal exposure to alkali induced the irregular arrangement of a large number of fibroblasts and collagen fibers, combined with inflammatory cell infiltration[35]. Furthermore, during the healing process of a penetrating rabbit corneal wound, collagen could be observed to exhibit a circular pattern around the wound. Subsequently, the orientation of corneal collagen fibrils during the healing process of penetrating wounds gradually became more normal[36] (Figure 2).

CORNEAL COLLAGEN DEGRADATION

Collagen architecture is important for corneal structure and function. Abnormalities in the concentration of collagenase can lead to the destruction of the normal collagen of the cornea, whereas a decrease in the activity of collagenase can reduce the degradation of corneal collagen[37]. In particular, extracellular accumulation of fibrillarcollagen can lead to tissue scarring. Alternatively, extra collagenfibrils were shown to be cleaved by proteolytic enzymes including zinc-dependent endopeptidase matrix metalloproteinases (MMPs)[38]. Notably, we demonstrated that MMPs are significantly upregulated in collagen-destructive disorders of the cornea[39]. The corneal degradation in corneal diseases is widely seen in clinical practice, such as in infectious keratitis, autoimmune ocular surface disorders, chemical burns, and refractive surgery. The common wound healing-related proteins, MMP-2, -8, -9, -13, and tissue inhibitor of MMP1,2 (TIMP-1,2) were detected at different time points in a fungal keratitis mouse experiment[40]. The transcriptional and translational levels of MMP-8, -9, -13, and TIMP-1 were proved to be increased during the early stages of *Candida albicans* keratitis. MMP-9 and TIMP-1 were also detected in other infectious keratitis models[41]. *Pseudomonas aeruginosa* keratitis is characterized by severe corneal collagen degradationand corneal ulceration. MMP activation plays a key role in bacterial keratitis and was found to be a major target for chronic inflammation involving pathologic tissue destruction[42]. MMP13 may contribute to *P. aeruginosa* keratitis through corneal basement membrane degradation, and it could be an additional therapy to treat microbial keratitis[43]. Imbalances in the MMP/TIMP system during virally induced inflammations are responsive to changes in the disease progression[44-45]. Lipopolysaccharide (LPS) increases MMPs and cytokine expression in corneal fibroblasts from patients with microbial keratitis, providing a local theory to remedy bacterial infection, even corneal ulceration and severe collagen degradation[46-47]. Autoimmune disorder was associated with dry eye syndrome, peripheral ulcerative keratitis, scleritis, and corneal melts. Tissue damage on the

ocular surface of patients was autoimmune-mediated and could be treated by the inhibition of MMPs and T-cell subsets, B-cell signaling, or cytokines[48]. Inflammatory responses and neovascularization after the chemical burn aggravate corneal damage. MMPs are the angiogenic factor involved in the pathologic process of corneal chemical burn[49-50].

Accordingly, the degradation of preexisting and synthesized ECM is thought to play an important role in tissue remodelling. In particular, the degradation of 3-D collagen gels has been shown to be affected by the production and activation of MMPs[51]. Variation in corneal modality can also lead to corneal disease. For example, enzymes involved in glycosaminoglycan deficiencies in mucopolysaccharidoses (MPS) syndromes lead to a range of alterations in both interfibrillar and fibrillar ECM components of the cornea. Mechanisms involving excess matrix dermatan sulphate, chondroitin sulphate, heparin sulphate, or keratin sulphate in MPS VII may lead to the dysregulation of fibril shape[52]. Conversely, two majorcollagen peptides, prolyl-hydroxyproline (Pro-Hyp) and hydroxyprolyl-glycine (Hyp-Gly) exert a chemotaxis effect on dermal fibroblasts and enhance cell proliferation. Accordingly, the application of collagen hydrolysate with a higher content of Pro-Hyp and Hyp-Gly led to marked improvement in facial skin conditions, including facial skin moisture, elasticity, wrinkles, and roughness[53]. In addition, the reconstruction of the corneal surface using type I collagen membranes might be considered in patients with disunioning ulcerations, as transforming growth factor β-induced protein (TGFBIp) represents an ECM protein cross-linked to type XII collagen through a reducible bond in the cornea[54]. However, whether membranes with faster or slower degradation properties would be preferable for the treatment of persistent corneal ulcerations may depend on the underlying corneal pathology and the degree of coinstantaneous inflammation[55]. Furthermore, to increase the resistance to enzymatic degradation, pretreatment with intrastromal and superficial very high-fluence corneal cross-linking (CXL) in conjunction with Bostontype1keratoprosthesis may represent a safe and effective adjunctive treatment.

MMPs are responsible for the degradation of ECM proteins participating in different pathological processes including tissue remodelling, cancer development, and wound healing. For example, resident corneal fibroblasts have been shown to mediate degradation through the release of MMPs following injury and infection[56-58]. Specifically, keratinocytes are changed to myofibroblasts to phagocytose debris in the corneal stroma wound healing process. Keratinocyte production of MMPs is mediated by interleukin-1 (IL-1), plasminogen, and urinary plasminogen activator (uPA)[59-60]. Subsequently, the excessive dissolution of corneal tissue by MMPs that have been activated by cytokines and chemokines may lead to corneal ulcer[61]. In turn, MMP-9 can be cleaved by α6β4 integrin and collagen XVII, which is defective in the blistering disease junctional epidermolysis bullosa. Furthermore, an MMP-9 inhibitor has been shown to reduce the lamina lucida of epithelial-stromal separation damage in the cornea[58], and the inhibition of MMP expression and activity in IL-1β-stimulated corneal fibroblasts was found to suppress collagen degradation by these cells[62]. Therefore, the inhibition of corneal collagen degradation induced by cytokines has been suggested as a potential target for the treatment of corneal ulcer[57]. This application may also enhance the biomechanical stability and external disease resistance of the donor cornea in patients with advanced external disease[63]. Conversely, collagen degradation may be considered a potentially suitable intervention for mediating the damage following corneal injuries and infections.

CORNEAL COLLAGEN CONTRACTION

Collagen synthesis and collagen degradation are precisely balanced to maintain normal corneal tissue architecture. In particular, collagen contraction mediated by corneal fibroblasts is implicated in the maintenance of corneal shape[64-65]. Conversely, fibrosis in the lung represents the destruction of the normal architecture with the appearance of inflammatory cells and excess collagen[66]. Transforming growth factor beta 1 (TGF-β1), which plays a key role in mediating ECM gene expression[67], significantly increased ECM contraction. In mice, decreasing the severity of tissue fibrosis is required for the removal of the accumulated collagen[68]. In addition, although appropriate corneal scarring can prevent the cornea from excessive damage during wound healing and corneal infection, excessive tissue repair can be characterized by inhibited degradation and enhanced ECM deposition, which has been shown to be involved in tissue destruction and fibrogenesis[67]. Notably, collagen overproduction is associated with many diseases such as cancers and fibrosis[69]. As previously mentioned, irregular collagen fiber arrangements were produced by corneal alkali exposure in addition to excess fibroblasts and inflammatory cells[35]. Keratoconus is a progressive disease relative to defects in the corneal stroma. TGF-β1 exposure significantly increased ECM contraction, collagen I, and collagen V expression by human keratoconus cells[70].

Small-incision lenticule extraction is superior to femtosecond lenticule extraction in early ocular surface changes and nerve growth factor. TGF-β1 and IL-1α may contribute to the process of ocular surface recovery[71].

Burn scar contracture based on α-smooth muscle action (α-SMA) and collagen deposition induced by TGF-β1 can lead to an increase in myofibroblast population, which can induce severe deformation and functional impairment. To prevent the contraction of burn wound without delaying, the aim of the therapy will be wound closure[72].

Collagen I and III augmentation in the corneal matrix promotes

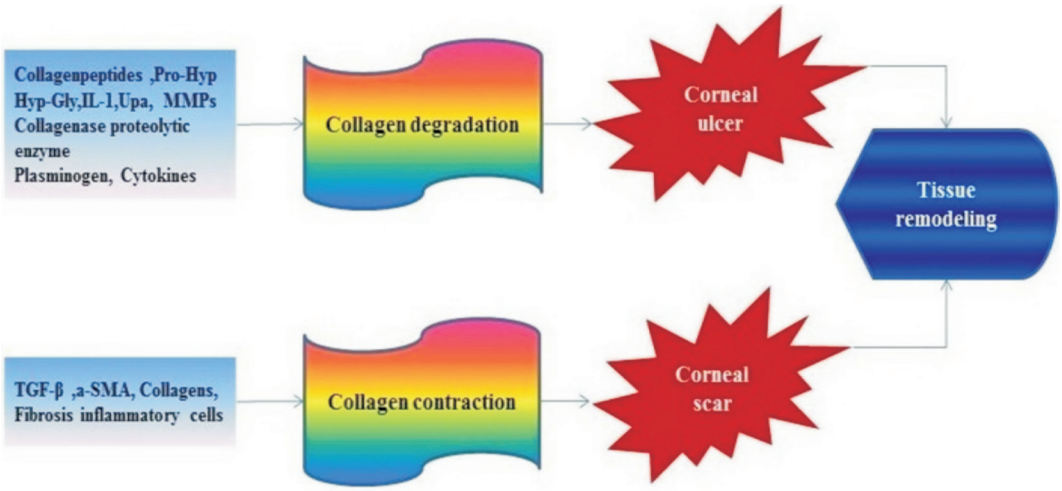

Figure 3 Balance of corneal collagen degradation and contraction.

defects from scarring[73]. Furthermore, ECM remodelling is thought to have profound effects on tissue architecture and function. Thus, the matrix accumulation stimulated by TGF-β leads to altered morphology[74]. In addition, the transformation of quiescent keratinocytes to active phenotypes and the ensuing fibrotic response play important roles in corneal scar formation. Accordingly, the mediation of an antifibrotic effect may represent a novel approach for the treatment of corneal opacity and scar formation during the corneal wound healing process[75]. Furthermore, the formation of a collagen network composed of fibrillar collagens in the corneal ECM has a decisive effect on tissue stiffness. Thus, additional investigation is required to elucidate the characteristics and regulation of corneal collagen fibrils[76] (Figure 3).

CORNEAL COLLAGEN IN CORNEAL ENGINEERING

Corneal scarring is predominately treated with allogeneic graft tissue. However, the clinical treatment of corneal disease is limited because of a severe shortage of high-quality allogeneic corneal tissues and the potential for bacterial infection after corneal transplantation[77]. Therefore, a well-tolerated scaffold is required for a tissue engineered cornea that permits the adequate growth of incorporated cells and that is not immunogenic[78]. Collagen scaffolds represent good choices for the construction of artificial corneas with good resilience, long-term culture capability, and handling properties[79]. Specifically, collagen vitrigel membranes characterized by regular, well-organized fibrillar structures are transparent biomaterials that appear to be optimal for the therapeutic treatment of corneal disease, tissue engineering, and corneal repair and regeneration[80-83]. In particular, it was shown that expression of the myofibroblast marker α-SMA decreased and that of corneal crystallin-transketolase increased on collagen nanofiber substrates compared with that on flat glass control substrates. Matrix nanotopography reduced the fibrotic phenotype, induced formation of the quiescent keratinocyte phenotype, and influenced matrix synthesis[84]. Simultaneously, the mechanical properties including the suture retention strength of the collagen-based scaffolds must be further developed with an emphasis on clinical applications[85]. In addition, to be clinically useful, collagen fibrils would require a lack infiltration of inflammatory cells and fibroblast-like cells into the implant[86]. Under general circumstances, cells and ECM are randomly distributed in tissue engineered cornea. It will be a challenge to adjust the orientation of the cell layers and secreted ECM in a self-assembled tissue sheet[87]. Notably, cell-free implants comprising carbodiimide-cross-linked recombinant human collagen were found to enable endogenetic corneal cell recruitment and were able to relieve a shortage of donor tissue during keratoplasty[88]. Furthermore, tripeptides derived fromcollagenare absorbed efficiently by the body. Type I collagen and its daughter peptide, collagen hydrolysate, have functioned as highly popular reconstructive materials for tissue engineering applications, showing significant reduction in the mucosal damage score and facilitated faster regeneration of damaged mucosa than did controls[89-91]. In addition, polycaprolactone film cross-linked with collagen-derived proteins was able to further enhance the biocompatibility[92]. Another study generated a novel gelatin hydrolysate using a cysteine-type ginger protease, which exhibited unique substrate specificity with preferential peptide cleavage with Pro at the P2 position. Substantial amounts of X-hydroxyproline (Hyp)-Gly-type tripeptides were generated concomitantly with Gly-Pro-Y-type tripeptides using ginger powder. This study demonstrated that orally administered X-Hyp-Gly was effectively absorbed into the blood, probably owing to the high protease resistance of this type of tripeptide[93]. Thus, the arrangement of stromal collagen fibrils may be used to influence the engineered corneas, which appear to exhibit great promise as valid treatments for facilitating corneal health and transparency. Specifically, engineered corneal tissues containing long parallel collagen fibrils with uniform diameter represent a novel, cell-generated biomaterial for the therapy of corneal blindness[94].

IMPROVEMENTS IN CORNEAL CROSS-LINKING

CXL is a process wherein riboflavin sensitization with ultraviolet A radiation is used to induce stromal cross-links. This alters corneal biomechanics, improving corneal stiffness and decreasing its damping capability and deformability. CXL plays roles in the therapy of chemical burns, corneal infections, corneal edema, and bullous keratopathy[2,95]. In particular, CXL offers the possibility of halting the progression of keratoconus and strengthening the cornea[96].

Therapy of keratoconus with riboflavin/ultraviolet A (UVA) causes obvious stiffening of the cornea due to cross-linking[97]. Although CXL can leave residual stromal scarring, it can also make a rapid resolution of the infective keratitis[98]. CXL can induce healing in microbial keratitis patients by the method of improving symptoms and signs of reduced inflammation and achieving epithelial healing[99]. Pretreatment with CXL associated with Boston type 1 keratoprosthesis proved to be a safe and effective method for achieving donor cornea rigidity and increased resistance to enzymatic degradation[63]. In refractory keratitis in patients with the Boston type I keratoprosthesis, CXL can present a shield covering by reducing the infiltration of refractory keratitis[100]. CXL combined with lamellar keratoplasty and amniotic membrane transplantation can be an optimal choice to treat recurrent corneal melting after Boston type I keratoprosthesis implantation[101].

The method of CXL has been refined through many technical artifices[102]. Gamma irradiation-based CXL has helped generate clearer and thinner corneas without endothelium for transplant compared to cryopreserved and fresh corneas, and thus can be used as a lamellar substance[103]. CXL has also served as an option in the treatment of infectious keratitis[104]. CXL may increase corneal strength and refractive power in patients[105]. In addition, riboflavin-UV-CXL can reduce suture-associated complications such as haze formation and ocular surface irregularity. However, further studies are required to ascertain the biostability of CXL and to identify additional applications[106].

CONCLUSION

This review has presented the roles of collagenous fibrils in the physiology and pathology of the cornea. We reviewed corneal dynamics from a structural perspective, considered the roles and interrelationships of collagens, proteoglycans, and MMPs on collagen pathology, collagen degradation, contraction balance, and corneal tissue engineering. These data shed light on the maintenance and reconstitution of collagen-associated corneal transparency.

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