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TGFβ pathobiology in the eye

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Transforming growth factor β (TGFβ), a multifunctional growth factor, is one of the most important ligands involved in the regulation of cell behavior in ocular tissues in physiological or pathological processes of development or tissue repair, although various other growth factors are also involved. Increased activity of this ligand may induce unfavorable inflammatory responses and tissue fibrosis. In mammals, three isoforms of TGFβ, that is, β1, β2, and β3, are known. Although all three TGFβ isoforms and their receptors are present in ocular tissues, lack of TGFβ2, but not TGFβ1 or TGFβ3, perturbs embryonic morphogenesis of the eyes in mice. Smads2/3 are key signaling molecules downstream of cell surface receptors for TGFβ or activin. Upon TGF binding to the respective TGF receptor, Smads2/3 are phosphorylated by the receptor kinase at the C-terminus, form a complex with Smad4 and translocate to the nucleus for activation of TGFβ gene targets. Moreover, mitogen-activated protein kinase, c-Jun N-terminal kinase, and p38 modulate Smad signals directly via Smad linker phosphorylation or indirectly via pathway crosstalk. Smad signals may therefore be a critical threrapeutic target in the treatment of ocular disorders related to fibrosis as in other systemic fibrotic diseases. The present paper reviews recent progress concerning the roles of TGFβ signaling in the pathology of the eye.
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The multifunctional growth factor transforming growth factor β (TGFβ) is one of the most important ligands involved in modulation of cell behavior in ocular tissues. This includes modulation of cell migration and proliferation, cell death, and protein synthesis during development, tissue repair, and other physiological or pathological processes.[1–14] In most cases, TGFβ enhances extracellular matrix production and suppresses cell proliferation. Moreover, TGFβ is capable of inducing a number of growth factors, that is, connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), and vascular endothelial growth factor (VEGF), as well as TGFβ1 itself.[15,16] All these factors have important roles in restoration of normal tissue following injury. Although three isoforms of TGFβ, namely, TGFβ1, β2, and β3, are present in mammalian tissues and *in vitro* experiments often elicit similar responses, their *in vivo* roles and expression are not uniform. Studies from gene knockout mice reveal the distinct role of these isoforms in embryonic development and tissue morphogenesis (as discussed later). However, as in other tissues, overactivation of TGFβ underlies the pathogenesis of wound healing-related fibrotic diseases in eye tissues, which impair vision and ocular tissue homeostasis (Figure 1). In the present article, the recent literature is examined in regards to the role of TGFβ and its signaling pathways in the pathogenesis of ocular disorders. We conclude that herapeutic strategies for such diseases may be devised by targeting the TGFβ signaling pathway.

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Cytokines and growth factors in aqueous humor of the eye

The aqueous humor that bathes the inner ocular structures (corneal endothelium, iris, crystalline lens, trabecular meshwork, and retina) contains various cytokines and growth factors. TGFβ, especially TGFβ2, is the predominant cytokine. Physiologically, TGFβ is mainly produced in the ciliary epithelium and lens epithelium as a latent, inactive, form consisting of mature TGFβ, the latency-associated peptide (LAP) (small latent form), and the latent-TGFβ-binding protein (LTBP).[17–24] Heterogeneous expression patterns of each TGFβ isoform in the crystalline lens have been reported in humans and animals.[25] During the clinical course of various ocular diseases, the concentration of TGFβ2 in the aqueous humor changes. For example, in an eye

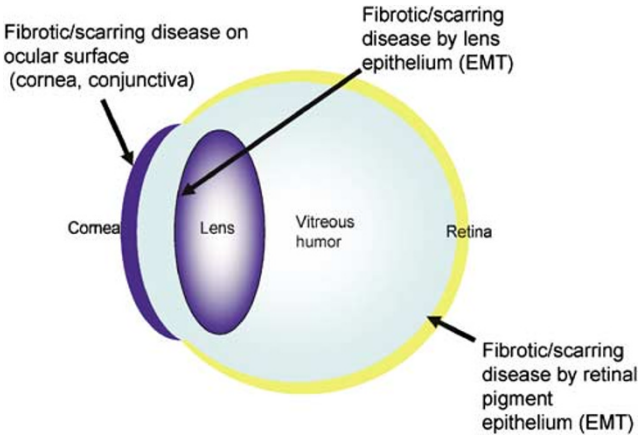

Figure 1 Typical fibrotic diseases or surgical complications that may occur in cornea, conjunctiva, lens, and retina.

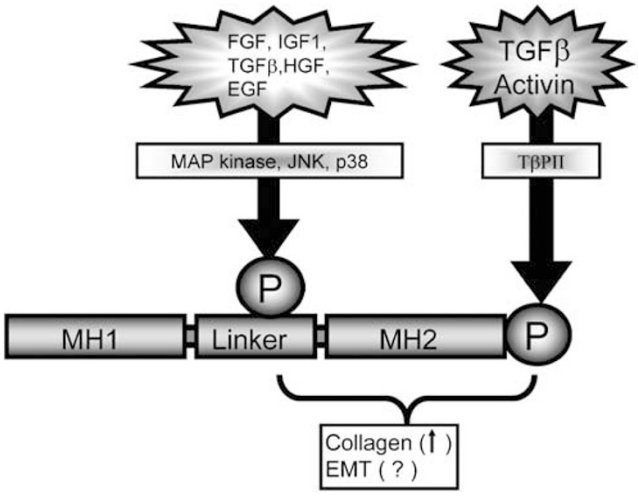

Figure 2 Smad2/3 can be activated by non-TGFβ growth factors at the middle linker region.

with proliferative vitreoretinopathy (PVR), a disorder of post-retinal detachment and retinal fibrosis, the concentration of TGFβ2 in the vitreous humor increases in association with the progression of retinal fibrosis. The concentration of total and active TGFβ2 is also higher in patients with diabetic retinopathy and open-angle glaucoma than in normal subjects. In diabetic retinopathy, chronic obstruction of retinal microvessels induces upregulation of VEGF and chemotaxis of macrophages, a potent source of TGFβs. VEGF and TGFβ cooperate to induce both retinal neovascularization and fibrosis around these new vessels, which may potentially cause retinal detachment or bleeding. Increased TGFβ2 levels induce matrix expression and deposition in trabecular meshwork cells, leading to obstruction of the aqueous drainage route and an increase of intraocular pressure in a glaucomatous eye. In each of these examples, TGFβ plays a role in disease pathogenesis. In eyes with pseudoexforiation syndrome, a kind of glaucoma with deposition of exforiative material on the lens, iris, or trabecular meshwork, the level of TGFβ1 increases, but the exact role of TGFβ1 in the pathogenesis of this disease is unknown.

TGFβ signal transduction

Upon TGFβ binding to its receptor, signaling occurs through a pair of transmembrane receptor serine–threonine kinases and the downstream mediator Smad proteins. Receptor-activated Smad proteins, Smad2 and Smad3, are phosphorylated directly by the TGFβ receptor type I kinase. They then partner with the common mediator, Smad4, and translocate to the nucleus where they play a prominent role in the activation of TGFβ-dependent gene targets. Smad6/7 are known to be inhibitory Smads, which block phosphorylation of Smads2/3.[26,27] However, the roles of Smad2 and Smad3 differ because the lack of Smad2 is lethal for mice at the embryonic stage, whereas those lacking Smad3 survive.[28]

The bone morphogenetic proteins (BMPs), which are members of the TGFβ superfamily, bind to their own receptors and phosphorylate Smads 1, 5, and 8 which then bind to Smad4 for translocation to the nucleus. Additionally, in some cell types, TGFβ can potentially activate different arms of the mitogen-activated kinase (MAPK) pathway, including stress kinases (ie, c-Jun-N-terminal kinase, JNK), p38MAPK pathway, RhoA-related signals, phosphatase2A,[29] or PI3-kinase/AKT.[30–32]

Although Smad2/3 signaling is relatively specific to the binding of ligands of the TGFβ/activin family to cell surface receptors, investigators are discovering that MAPKs (p42/p44 Erk1/2, JNK, or p38MAPK) phosphorylate specific sites in the middle linker region of Smad2/3, sites that are distinct from the C-terminus that is phosphorylated by the TGFβ II receptor (Figure 2).[33–36] Thus, ligands capable of activating MAPKs potentially modulate Smad signaling induced by TGFβ. It has recently been demonstrated that p38MAPK activate phosphorylation of Smad3 in the middle linker region, which enhances Smad3/4 complex formation and nuclear translocation,[37] consistent with our finding of diminished Smad3/4 reporter gene activity in the presence of a p38MAPK inhibitor. Such phosphorylation by MAPKs in the Smad3 linker region is reportedly required for the full activation of Smad signaling.[38,39] For example, inhibition of p38MAPK by the specific inhibitor SB202190 interferes with stimulatory effects of exogenous TGFβ2 on migration of cells and on production of ECM components, such as collagen type I and fibronectin, while having no effects on the basal activity. Moreover, p38 MAPK may affect these end points not only by direct phosphorylation of the Smad proteins in the middle linker region[40] but also

by activation of cooperating transcription factors. For example, TGFβ-activated kinase (TAK1) has been shown to be an upstream activator of MKK6 and activation of this pathway results in phosphorylation of activating transcription factor 2 (ATF2) and enhancement of complex formation between Smad4 and ATF2.[41,42] However, another report shows that Smads and p38MAPK independently regulate collagen I α1 mRNA in hepatic stellate cells,[43] demonstrating the complexity of regulation of gene expression by TGFβ. Furthermore, TGFβ/Smad signaling is susceptible to modualtion by other cotranscription factors such as c-Ski and SnoN.

Embryogenesis and developmental disorders

Classical gene targeting techniques have provided important information about the role of each TGFβ isoform in eye morphogenesis, although the mice also have various systemic abnormalities. Although a mouse embryo that lacks TGFβ1 or TGFβ3 does not have any ocular abnormalities, a mouse embryo lacking TGFβ2 has multiple defects in ocular structures, that is, thin cornea with a loss of the corneal endothelium and anterior chamber, immature retina, and persistent vitreous vessels.[44–48] These findings may coincide with the fact that TGFβ2 predominates in eye aqueous humor. Overexpression of TGFβ1 by using α-crystalline promoter in TGFβ2-null mice rescues the abnormalities in ocular development caused by the deletion of TGFβ2.[49]

Lens epithelial cells are of ectodermal origin. During embryonic development, surface ectoderm invaginates into the optic cup and the vesicle is separated from surface ectoderm on embryonic day 11.5 in the mouse. At this time, the cells also start to express vimentin, an intermediate cytoskeletal protein of mesenchymal cell types, but also retain their epithelial character by expressing the epithelial surface marker, cadherins. Then, the cells located in the posterior part of the lens vesicle start to express various crystalline proteins to form a transparent lens. Members of the FGF and BMP family are potent inducers of lens fiber differentiation. They are expressed in various ocular tissues, that is, retina, ciliary body, and lens cell themselves. The retina produces FGF and insulin-like growth factor (IGF) family members as potential fiber cell differentiation factors. The nuclei of elongating lens fiber cells are positive for phospho-Smad1, an indicator of signaling through BMP receptors.[50] These data indicate that BMPs participate in the differentiation of lens fiber cells, along with at least one additional, and still unknown factor. In mature lens fibers, the nuclei are degraded by apoptosis and this apoptotic process is also modulated by Smad signals.[50]

In addition to BMPs, TGFβs are also involved in lens fiber differentiation.[50] Overexpression of dominant-negative forms of either type I or type II TGFβ receptors in the lens fibers of transgenic mice using mouse αA-crystallin promoter results in the development of pronounced bilateral nuclear cataracts. The phenotype was characterized by attenuated lens fiber elongation in the cortex and disruption of fiber differentiation, culminating in fiber cell apoptosis and degeneration in the lens nucleus.

Although all three TGFβ isoforms are expressed in cornea, the lack of any one of them does not affect embyonic morphogenesis/differentiation of corneal epithelium as examined by the expression pattern of cornea-specific cytokeratin, keratin 12. Additionally, loss of Smad3, a prominent TGFβ-signaling molecule, does not produce ocular abnormalities, indicating that multiple signaling pathways are involved in ocular tissue morphogenesis.

TGFβ signal transduction and tissue fibrosis

TGFβ generally enhances gene expression related to tissue fibrosis *in vivo* and *in vitro* in mesenchymal cells in the eye. Details of differences between Smad2 and Smad3 were recently investigated using a gene expression array made of embryonic fibroblasts obtained from embryos lacking either Smad2 or Smad3.[51,52] Expression of α-smooth muscle actin (αSMA), important in fibroblast-myofibroblast conversion, is mediated by Smad2.[53–55] However, expression of *Snail*, the master transcription factor involved in the earlier step of the epithelial–mesenchymal transition (EMT), as an important step in the process of tissue fibrosis in the eye, is controlled by Smad3.[56] The expression of the majority of the extracellular matrix components and enzymes involved in matrix reorganization/maturation depends on Smad3, whereas expression of matrix metalloproteinase-2 is Smad2 dependent. In Smad3-null mice, re-epithelialization is accelerated and fibrosis is reduced during tissue repair in skin.[57] However, blocking TGFβ type II receptor function by dominant negative expression in collagen I-expressing fibroblasts in a transgenic mouse results instead in a paradoxical systemic tissue fibrosis in association with an uncontrolled Smad signaling activation.[58] The mechanism of this phenomenon could be explained the fact that Smad3 is phosphorylated by various MAPK at their middle linker region, which might promote nuclear translocation of Smad and might stimulate fibrosis-related gene expression.

Wound healing reaction in the lens and post-cataract surgery complications

The crystalline lens is a unique tissue, consisting of epithelial cells, lens fibers, and the anuclear lens

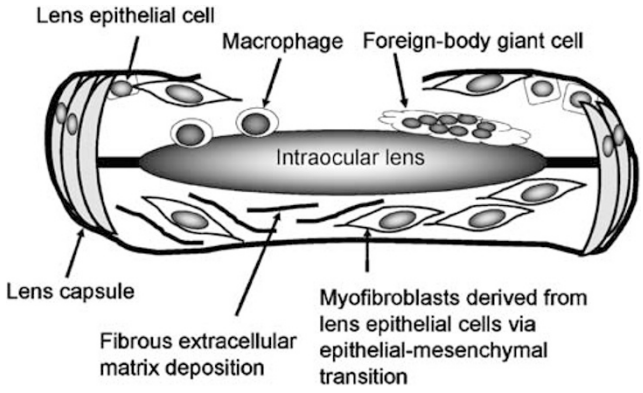

Figure 3 Summary of biological reaction against an implanted IOL. A foreign body reaction is mediated by macrophages and foreign body giant cells generated through a fusion of many macrophages. A wound healing reaction occurs in lens epithelium. The equatorial region of the capsular bag is occupied by regenerated lenticular fibers of Sommerring's ring. Lens epithelial cells on the posterior capsule exhibit an elongated, fibroblast-like shape or Elschnig's pearl formation.

content inside a specialized basement membrane, the lens capsule. Following cataract surgery or lens capsular injury, cuboidal lens epithelial cells undergo EMT and transdifferentiate to myofibroblasts, expressing αSMA on the residual lens capsular tissue (Figure 3).[59–66] Tissue fibrosis in association with EMT is also a key step in the process of fibrotic diseases in other tissues and organs, characterized by the presence of fibrous tissue accumulation and contraction by αSMA-expressing myofibroblasts.[67,68] In this process, an epithelial cell changes its morphology and its transcriptional program to those characteristic of a mesenchymal cell type. Lens epithelium-derived myofibroblasts become capable of expressing components of the fibrous ECM and matrix-degrading enzymes. Structural and histological organization of postoperative capsular opacification is quite similar to that seen in healing tissue or tissue granulation formed around an implanted foreign body. Clinically, this fibrotic reaction in postoperative lens epithelium results in opacification and contraction of the residual lens capsule. Optical transparency is reduced, and implanted artifical intraocular lens (IOL) move off center, both of which decrease the patients' vision.

TGFβ and Smad signaling in lens epithelium EMT

In the quiescent normal lens epithelial cell, Smads2/3 are detectable in the cytoplasm, indicating that the cells either are not or are minimally affected by endogenous TGFβ through this signaling pathway, as they are not detectable in the nucleus. However, TGFβ signaling is rapidly activated following wounding.[69] Following cataract surgery, Smad2/3 translocates to the nucleus prior to the appearance of αSMA-positive cells (heralding the ocurrence of EMT). Similarly, in mice, an injury in the anterior capsule induces Smads3/4 nuclear translocation within 12 h, being followed by expression of *Snail* and subsequent EMT in the lens epithelium. This Smad nuclear translocation was abolished by local administration of anti-TGFβ2-neutralizing antibody. TGFβ is the growth factor involved in EMT of lens epithelial cells *in vivo,* as has been shown for other epithelial cell types *in vitro*. For example, overexpression of TGFβ1 in lens cells by transgenic techniques induces cataractous changes in the lens epithelial cells in association with EMT and accumulation of fibrous/collagenous extracellular matrix.[70,71]

Loss of Smad3 attenuates injury-induced EMT in the lens or renal epithelium. However, the suppression of EMT in lens epithelium seems to be dependent on the level of TGFβ stimuli. Our unpublished data show that severe intraocular inflammation caused by corneal exposure to alkali is associated with EMT in lens epithelium even in Smad3-null mice, although the extent of EMT is much lower. Similarly, overexpression of active TGFβ1 in lens epithelium using adenoviral gene introduction or transgenic technology induces EMT in lens epithelium in mice and this EMT (although to a lesser extent) is also seen in the absence of Smad3 (West-Mays J, personal communication, 2005). These findings suggest that upon uncontrolled stimulation by TGFβ, lens epithelium is capable of undergoing EMT, possibly via signaling via other as yet unidentified molecules. Alternatively, Smad2 might bypass the loss of Smad3. Nevertheless, the involvement of Smad3 signal in lens epithelium EMT raises the possibility of therapies for EMT-related fibrotic diseases gene transfer of Smad7 or other molecules which are capable of blocking Smad signaling, that is, BMP-7, Id2 or Id3, as discussed below.[72]

Other signaling cascades are also required for TGFβ-induced EMT.[66,73] Our unpublished data show that specific inhibitors of PI3-kinase or Rho kinase also suppress TGFβ2-induced EMT of lens epithelium in organ culture.

PVR and retinal pigment epithelium (RPE)

PVR is a disease caused by the formation of fibrotic tissue on the detached retina, which reduces the flexibility of the retina and may potentially make it difficult to reattach the retina. RPE cells are normally located in the cell layer external to the retina. Following retinal break and detachment, RPE cells disseminate in the subretinal space and vitreous humor through the retinal break(s), and then settle on the luminal retinal surface following development of rhegmatogenous retinal detachment.[74,75] RPE cells then undergo transformation to fibroblast-like cells, proliferate, and produce

extracellular matrix components, participating in this fibrotic sequelae. Muller glia cells are also involved in the fibrotic reaction of the detached retina.

As in the EMT-related fibrosis in the lens, TGFβ can induce transformation of RPE cells to myofibroblast-like cells *in vitro*,[76–78] suggesting that TGFβ is likely a key player in the development of PVR, although various other growth factors, including PDGF, HGF, and activin, are all reportedly involved in its pathogenesis.[79–85] The concentration of TGFβ2 in the vitreous humor of the eye correlates with the severity of the PVR, underlying its importance.[79] Similar to other cell types, RPE-cell-EMT is also suppressed by the loss of Smad3 *in vivo*, resulting in the attenuation of development of PVR. Unlike gene introduction of active TGFβ1 in the lens epithelium, adenoviral TGFβ1 does not induce EMT in RPE in the absence of Smad3 (J West-Mays, personal communication, 2005).

Gene introduction to suppress EMT and subsequent tissue fibrosis in lens or retinal pigment epithelia

Suppression of EMT might be beneficial to prevent or treat the lens capusar fibrosis that leads to fibrotic-type cataracts, or post-cataract surgery capsular opacification, both of which potentially reduce vision. Based on the finding that loss of Smad3 attenuates injury-induced lens epithelial EMT, we tested adenoviral gene introduction of cDNAs for Smad7, BMP-7, Id2 or Id3, all of which antagonize TGFβ/Smad signal, *in vivo* to an injured mouse lens epithelium. While all of these genes attenuated injury-induced EMT of the lens epithelium,[86] Smad7 gave the greatest degree of inhibition of *in vivo* lens cell EMT.

Attenuation of injury-induced EMT of lens epithelial cells by Smad3 gene ablation or Smad7 gene introduction also suggests that such approaches might suppress EMT in RPE cells, and therefore prove beneficial in the treatment of PVR. Indeed, loss of Smad3 attenuates PVR *in vivo*,[87] and Smad7 gene introduction actually does suppress PVR in mice (S Saika, unpublished data, 2005).

Activation of Smads by phosphorylation at its middle linker region by MAPK is also a potential target of inhibition of TGFβ signaling. It has been reported that p38MAPK is involved in EMT in cultured cells. A p38MAPK inhibitor reduces reporter gene expression using an Smad-dependent promoter, indicating that p38MAPK signal may be involved in Smad-dependent gene expression. Chemical inhibition of p38MAPK attenuates migration and ECM production of the RPE cell line, ARPE-19.[88] *In vivo* adenoviral gene transfer of dominant-negative p38MAPK suppresses the fibrotic reaction by RPE cells in an experimental mouse PVR model.[88] Further study is needed to establish the clinical application of this treatment strategy.

Roles of TGFβ siganling in corneal wound healing

The cornea consists of a nonkeratinizing stratified epithelium, lying on Bowman's membrane, and a stroma consisting of collagenous lamellae and keratocytes (corneal fibroblasts) (Figure 4). Although the cornea lacks vasculature, the main components are quite similar to those of the skin; stratified epithelium and a collagenous matrix containing mesenchymal cells lying beneath it. TGFβ is expressed in corneal tissue.[89–97]

An epithelial defect in the cornea must be rapidly resurfaced to avoid microbial infection and further damage to the underlying stroma. Healing of an epithelial defect is achieved by migration of epithelial cells, followed by an enhancement of cell proliferation for re-establishment of the epithelium stratification. Although there is some difference in the expression pattern of TGFβ isoforms in the cornea, it is believed that TGFβ is upregulated upon wounding. In mouse cornea, intracellular TGFβ1 is detected in corneal epithelium, but extracellular, secreted TGFβ1 is not observed in an uninjured healthy cornea; but TGFβ2 and TGFβ3 are both detected in uninjured epithelium. Following an injury, extracellular TGFβ1, TGFβ2, and TGFβ3 are all detected in subepithelial stromal tissue. *In vitro* cell or organ culture reveals that endogenous TGFβ enhances cell migration of corneal epithelium. Such migrating epithelium lacks proliferative activity presumably due to inhibition of cell proliferation by TGFβl.

Unlike epidermis, loss of Smad3 does not affect re-epithelialization following corneal debridement in mice (S Saika, unpublished data, 2002). Nevertheless, this finding does not exclude the possibility that TGFβ has an important function in modulation of corneal epithelial healing. Migrating epithelium upregulates phosphorylation of p38MAPK as early as 1 h postinjury. Organ-culture experiments using

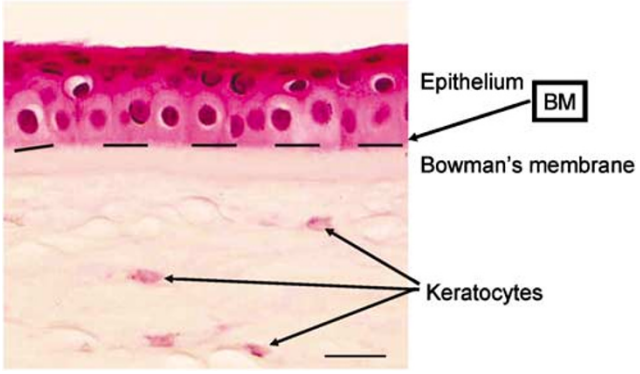

Figure 4 Light microscopic histology of the human cornea. The surface is covered with nonkeratinizing stratified epithelium. Keratocytes are the mesenchymal (fibroblast-like) cells in the stroma. Dense matrix membrane of Descemet's membrane locates beneath the epithelial basement membrane. Bar, 10 μm.

a TGFβ-neutralizing antibody and the specific p38MAPK inhibitors, SB202190 and SB203580, revealed that TGFβ/p38MAPK signal is required for epithelial cell migration and cessation of cell proliferation in migrating cells.[98] p38MAPK is known to modulate signaling cascades toward cell death or extracellular matrix expression, depending on cell types and kinds of stimuli.[99–101] Involvement of p38MAPK in cell migration has been observed in various cell types including corneal epithelium and cancer cell lines. However, it has not been fully elucidated whether or not p38MAPK's involvement in the cell migration is mediated by the phosphorylation of the linker regions of Smads2/3 or by its direct effect.

Stromal healing is initiated by inflammatory cells, that is, macrophages that activate mesenchymal cells via their expression of cytokines, including TGFβ. The activated mesenchymal cells (keratocytes) express matrix components and various growth factors and contract the scarring stroma. VEGF, expressed in both invading macrophages and myofibroblasts, induces stromal neovascularization that also potentially causes corneal opacification.

Gene therapy for the treatment of corneal inflammation and fibrosis by targeting TGFβ signaling

In corneas affected by chemical or thermal burn, or Stevens–Johnson's syndrome, various cytokines and growth factors, including interleukins, EGF, KGF, HGF, TNF α, TGFβ, VEGF, and macrophage/monocyte chemoattractant protein-1 (MCP-1), are believed to orchestrate cellular interactions and behaviors. The resulting pathological outcomes include scarring, conjunctivalization of the corneal surface and neovascularization. TGFβ is chemotactic to macrophages and also activates stromal fibroblasts (keratocytes), leading to the generation of myofibroblasts and induction of other cytokines such as VEGF and MCP-1 which also have chemotactic activity. A key outcome is EMT-related tissue fibrosis. It is then reasonable to posit that an excessive wound healing reaction from inflammation and fibrobalst acticvation can also be a target of TGFβ-inhibition therapy. Blocking the activity of TGFβ by systemic expression of soluble TGFβ receptor by adenoviral gene transfer results both in the suppression of liver fibrosis and acceleration of tissue repair in injured corneas in rats.[102,103] Although these studies clearly demonstrate that endogenous TGFβ is critical in the corneal tissue destruction after alkali exposure, blocking TGFβ activity at the receptor level might potentially perturb healing of the corneal epithelial component by interfering with the p38MAPK activity that is required for epithelial cell migration. Smad3-null cutaneous repair is associated with hyperproliferation of epidermal keratinocytes and decreased chemotaxis of macrophages, resulting in acceleration of epithelial resurfacing and less scarring. This information prompted us to test whether blocking TGFβ activity at the level of Smad signaling level might yield a more favorable result, since other TGFβ signaling cascades would remain intact. Using a mouse corneal alkali burn model, we have shown that loss of Smad3 suppresses tissue destruction of the healing cornea in association with a reduction of macrophage infiltration, inhibition of myofibroblast generation, and suppression of growth factor expression.[104]

Neovascularization also potentially impairs vision. Adenoviral gene transfer of mouse Smad7 cDNA has been used in the treatment of tissue fibrosis in several disease models, that is, bleomycin-induced pulmonary fibrosis, drug-induced liver fibrosis, or kidney fibrosis by unilateral ureteral obstruction.[105–107] Our results show that in mice Smad7 gene introduction by topical application suppresses scarring and neovascularization of the burned cornea, restoring its transparency.[104] Smad7 also suppressed generation of myofibroblasts, macrophage invasion, and the expression of wound healing-related cytokines. The effects were more marked than those seen in Smad3-null mice, probably because Smad7 also suppresses phosphorylated RelA of the NF-κB pathway, which leads to suppression of inflammation cascades.[104,108] Signals derived from bone morphogenic protein-7 (BMP-7) are known to antagonize TGFβ/Smad signal via Smad1/5/8 signal and induction of Id2 and Id3. We have shown that gene introduction of BMP-7 also has a therapeutic effect on an alkali burn in mice, although its efficacy is less than that of Smad7.[109]

Unlike in an alkali-burned cornea, Stevens–Johnson's syndrome is an inflammatory ocular surface disease caused by an autoimmune mechanism. Nevertheless, the main component of the disease consists of inflammation and scarring that are similar to those seen in a burned eye. Thus, there is a possibility that interference of TGFβ signaling might have a therapeutic effect on this disorder.

In conclusion, it is apparent that further understanding of the roles of TGFβ in physiological and pathological processes of the eye is needed to develop new strategies in the treatment of ocular diseases; and Smad signaling is an important target for development of treatments of fibrosis-related diseases in the eye.

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