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TGF-β/SMAD Pathway and its Inhibitors in Ocular Diseases

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Abstract

To provide insights and guidance for future investigations in this field, this review summarizes the role of the transforming growth factor β (TGF-β)/Sma and Mad related protein (SMAD) signaling pathway in the pathogenesis of ocular diseases, and compiles inhibitors of this pathway involved in studies of various eye conditions.

This review summarizes the mechanisms of the TGF-β/SMAD pathway in corneal diseases, glaucoma, lens disorders, and retinal diseases, as well as potential inhibitors targeting this pathway. In corneal diseases, it accelerates fibrosis and delays healing; in glaucoma, it promotes trabecular meshwork epithelial-mesenchymal transition (EMT), increasing intraocular pressure; in lens disorders, it triggers lens fibrosis diseases via lens epithelial cell EMT; and in retinal diseases, it mediates retinal pigment epithelium (RPE) cell EMT and subretinal fibrosis. TGF-β/SMAD pathway targeted inhibitors, including histone deacetylase inhibitors, natural compounds and pathway-specific agent, show promise by inhibiting SMAD phosphorylation or receptor expression.

TGF-β/SMAD pathway is deeply involved in ocular diseases and its inhibitors show great potential in treating ocular diseases. However, further research is needed to overcome the existing challenges and fully realize their therapeutic benefits.

Keywords: TGF-B/SMAD Pathway; Ocular Diseases, Inhibitors; Extracellular Matrix (ECM)

Introduction

TGF-β is a ligand that activates the downstream signaling by binding to serine threonine kinase receptors [1]. The canonical TGF-β signaling is mediated by intracellular SMAD protein and thus is known as TGF-β/SMAD signaling pathway. Studies have demonstrated that it plays a crucial role in physiological and pathological process [2]. Physiologically, TGF-β/SMAD pathway participates in wound repair, embryogenesis, immunological homeostasis and tissue balance [3]. However, it induces EMT in the pathogenesis of many diseases through upregulating the expression of the EMT transcription factors, Snail and/or Slug, which repress the expression of the epithelial adherens junction molecule E-cadherin and the epithelial progenitor transcription factor KLF5 [4]. In hepatocellular carcinoma, TGF-β/SMAD pathway induced EMT exerts as a vital step at the onset stage of cancer metastasis [5]. Another mechanism which is activated by TGF-β/SMAD pathway is ECM deposition. Renal fibrosis attributes to the deposition of EMC in different area of kidney through TGF-β/SMAD signaling pathway [6]. Analogously, TGF-β/SMAD signaling pathway is also associated with the onset and progression of many ocular diseases.

It has been revealed dysfunction of TGF-β/SMAD signaling pathway leads to diseases of the anterior ocular segment, middle ocular segment and posterior ocular segment. EMT may occur in residual lens epithelial cells after cataract removal surgery and eventually result in posterior capsular opacification (PCO) [7]. In the pathogenesis of glaucoma, EMT in the trabecular meshwork leads to impaired aqueous humor outflow, with the TGF-β/SMAD signaling pathway playing a role in this mechanism. Subretinal and retinal fibrosis in neovascular age-related macular degeneration (nAMD) and proliferative vitreoretinopathy (PVR) is significantly correlated with EMT of RPE.For the diseases discussed above, despite current therapeutic approaches, there remain challenges such as side effects or suboptimal efficacy [8-10]. To pursuit advanced therapeutic strategies , studies have been being conducted in vivo or in vitro about inhibiting TGF-β/SMAD pathway to attenuate pathological changes induced by EMT or ECM deposition [11].

In this review, we elucidate the mechanism by which the TGF-β/SMAD pathway contributes to the pathogenesis of ocular diseases, and inhibitors that directly or indirectly block the TGF-β/SMAD pathway. By summarizing current evidence, we aimed to provide insights and guidance for future investigations in this field.

TGF-β/SMAD Signaling Pathway

To date, five TGF-β isoforms have been identified. TGF-β 1-3 are all involved in the fibrotic process in mammal and demonstrate a high degree of amino acid sequence conservation. TGF-β1 primarily mediates fibrotic processes in liver, kidney and lung [12, 13]. TGF-β2 expression in the aqueous humor of cataract patients is significantly elevated compared to TGF-β1 and TGF-β3, indicating a potential role of TGF-β2 in the fibrotic mechanisms of lens epithelial cells. TGF-β is secreted and stored in the ECM as a latent complex consisting of latency-associated peptide (LAP) and latent TGF-β-binding protein (LTBP) [14]. Integrin modulates cellular tension forces, triggering the release of bioactive TGF-β from latent complexes. This released TGF-β then binds to cell surface TGF-β receptors, specifically TGF-β type I receptors(TβRI) and TGF-β type II receptors(TβRII), to initiate downstream signaling [2, 15]. TβRI and TβRII are structurally similar, both of which are the serine-threonine and tyrosine kinases.

SMADs are downstream molecules of the TGF-β signaling pathway. The SMADs proteins are divided into three subfamilies, including receptor-regulated SMADs (R-SMADs), common SMAD (Co-SMAD), Inhibitory SMADs (I-SMAD) [16]. R-SMADs comprise SMAD1, SMAD2, SMAD3, SMAD5, and SMAD9, among which SMAD2 and SMAD3 mediate the TGF-β canonical signaling pathway. Co-SMAD specifically refers to SMAD4, which regulates target gene expression by forming complexes with R-SMADs. I-SMADs, including SMAD6 and SMAD7, function as inhibitory regulators of the TGF-β/SMAD signaling pathway via two distinct mechanisms: (1) competitive binding to TβRI receptors, thereby preventing the phosphorylation and activation of R-SMADs, (2) direct interference with the transcriptional activity of SMAD multimers, ultimately suppressing the downstream biological responses mediated by the TGF-β signaling [17].

The process of the TGF-β/SMAD pathway can be essentially described as follows. TGF-β ligand is firstly identified by TβRII and forms the TGF-β-TβRII complex. TβR II ,equipped with an intracellular kinase domain, recruits and phosphorylates TβR I with a conversed Gly/Ser-rich "GS sequence" from serine/ threonine kinases [18-20]. Hence, TβR II, TGF-β and TβR I become a heteromeric complex. Subsequently, SMAD2 and SMAD3 phosphorylates by activated TβR I at the carboxy-terminal SXS motif [19]. The p-SMAD2/3 cooperates with SMAD4 to form a SMAD transcription complex, which translocates into nucleus and modulates the transcription of target genes [3, 16] (Fig. 1).

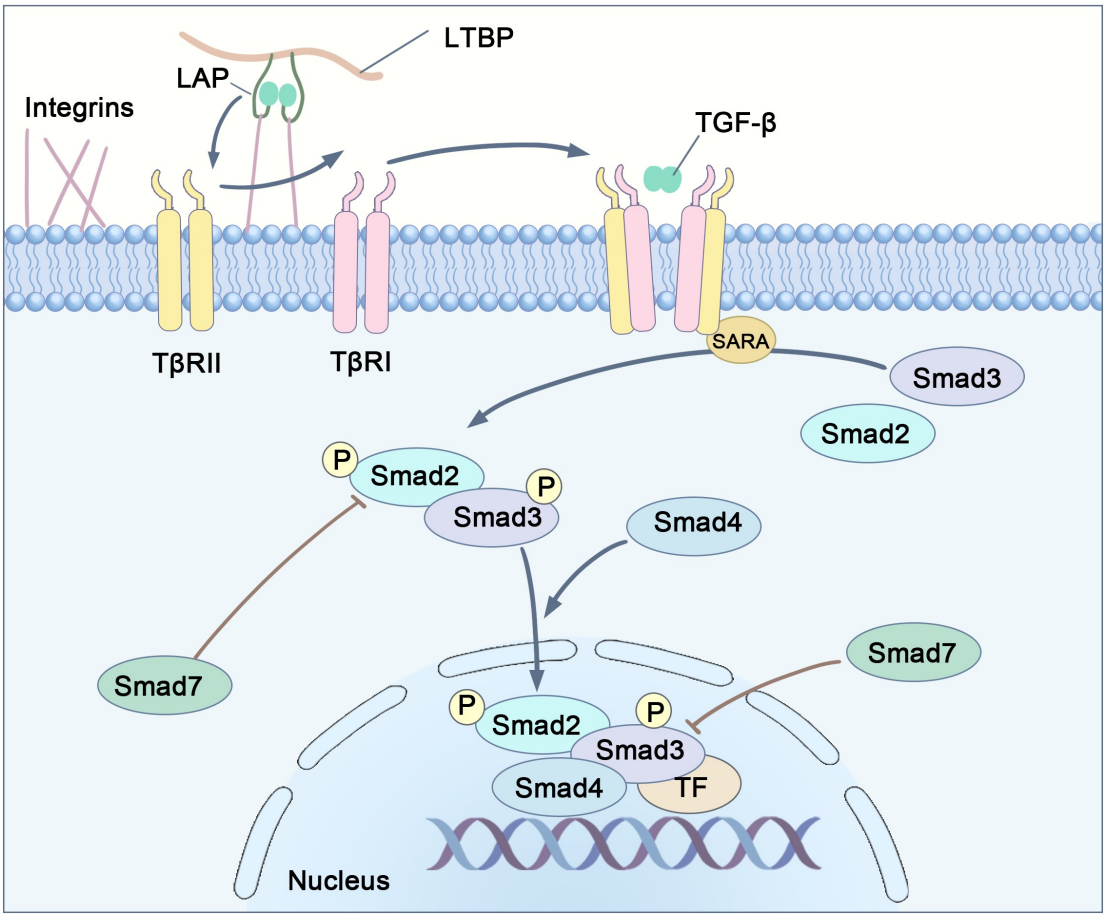

Figure 1: Schematic illustration of the TGF-β signaling network

Active TGF-β activates TβRs, phosphorylates SMADs, which enter nucleus to bind promoters.

TGF-β/SMAD pathway plays a vital role in tissue fibrosis. In the process of fibrosis, various damage factors can lead to tissue impairment and initiate the inflammatory response. TGF-β is expressed in normal tissue and is upregulated when tissue got injured [21]. Subsequently, the upregulation of TGF-β triggers the activation of the intracellular signal transduction pathway, and stimulates a phenotypic transformation in epithelial cells, either directly by promoting EMT and subsequent differentiation t myofibroblast which are characterized by the expression of α-smooth muscle actin (α-SMA), or indirectly by stimulating secretion of fibroblast-activating mediators [22]. Activated myofibroblasts synthesize and secrete a large amount of extracellular matrix components, mainly including collagen, fibronectin, ect. With the continuous deposition of the ECM, the tissue undergoes fibrosis and may even progress to the formation of a scar (Fig. 2) [23].

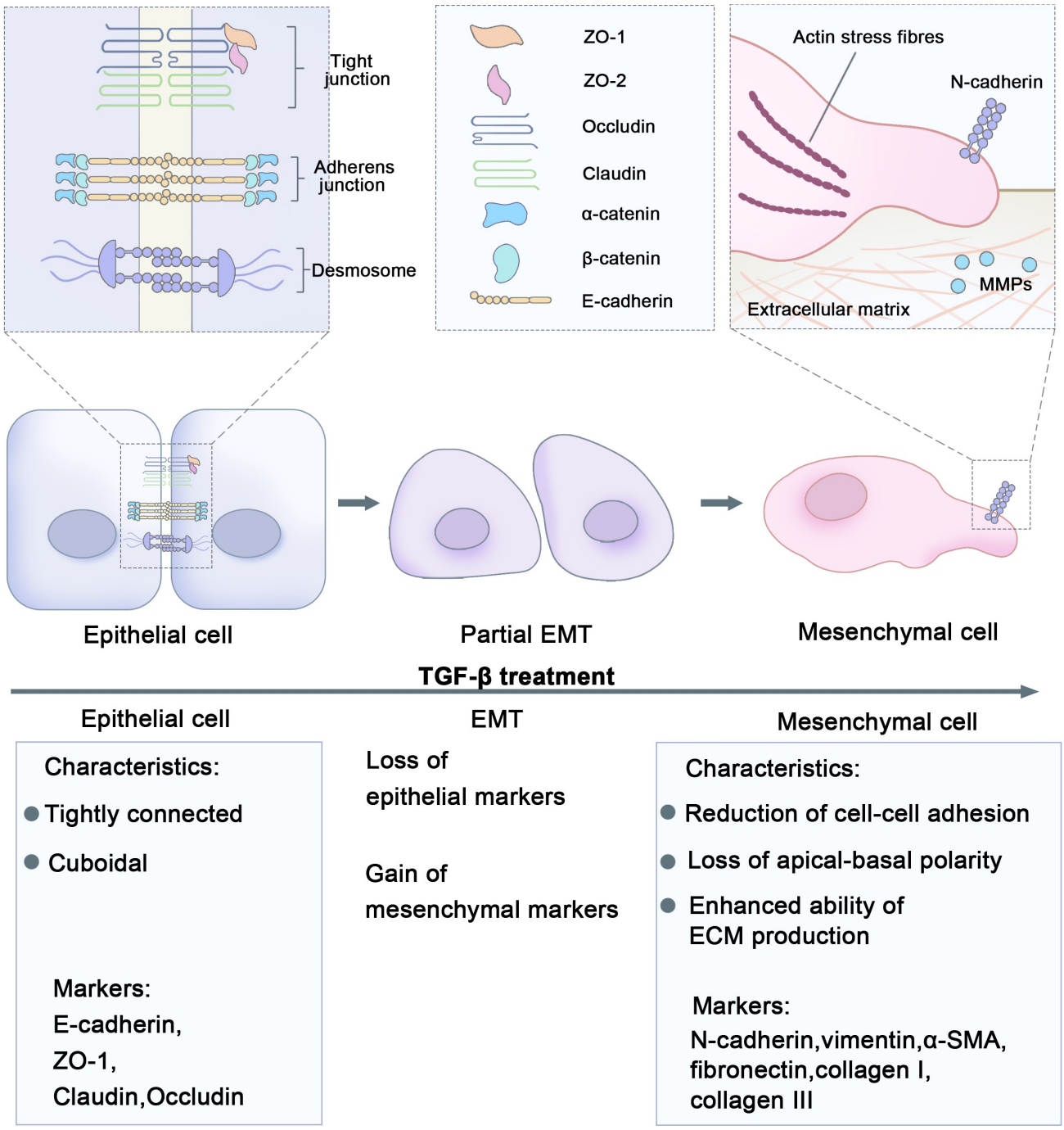

Figure 2: Schematic illustration of EMT

TGF-β upregulation activates pathway, inducing epithelial EMT to myofibroblasts.

TGF-β/SMAD Pathway in Ocular Diseases

TGF-β/SMAD Pathway in Corneal Fibrosis Diseases

Cornea permits light transmission to photoreceptor cells in the retina and protects the eye from the external environment. The tight junctions of the corneal epithelial cells and the high-density Na^+ / K^+-ATPase pump of the endothelial cells maintain the stroma in hydrated state, thereby ensuring the parallel arrangement of collagen fibers within the stroma to preserve corneal transparency [24]. Deeper corneal injuries—those affecting both the epithelium and stroma—can cause significant structural damage, including disruption of the epithelial basement membrane and loss of the collagen fibers' parallel alignment, ultimately leading to corneal opacity [25, 26]. Additionally, such injuries induce the upregulation of TGF-β, particularly TGF-

β2 [27]. The subsequent repair process is tightly regulated by a network of cytokines, with the TGF-β/SMAD signaling pathway critically involved. However, dysregulated activation of this pathway can disrupt healing, leading to delayed corneal repair and pathological scar formation.

In the normal repair process of corneal stromal injury, matrix metalloproteinases (MMPs), along with other cytokines, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), coordinate to ensure the normal progression of corneal repair. Among MMPs, MMP-9 is the most characterized member and functions to degrade the ECM [26]. The expression of MMPs depends on TGF-β signaling through activation of the downstream SMAD proteins [28]. Experimental studies have demonstrated that TGF-β1 induced upregulation of MMP-2,MMP-7 and MMP-9 expression in murine corneal/limbal epithelial cells and canine corneal fibroblast, which is accompanied by elevated levels of pSMAD2/3 and nuclear translocation of SMAD4 [29, 30]. Moreover, additional research has revealed that MMP-9 expression in corneal epithelial cells requires the synergistic action of both IL-1 and TGF-β, along with involving the participation of SMAD3 [28] .However, under pathological conditions, the excessive activation of the canonical TGF-β pathway In diabetic corneas leads to delayed repair of corneal injuries. A study has revealed that the interplay between TGF-β1 and TGF-β3 plays a critical role in delayed healing of diabetic corneal injuries. TGF-β1 primarily mediates inflammatory responses through the classical signaling pathway, while TGF-β3 accelerates corneal healing via non-canonical pathways, such as ERK and PI3K/Akt activation [26]. The research found that in healthy corneas, injury triggers a simultaneous increase in both TGF-β1 and TGF-β3 levels. However, in diabetic corneas, the expression of TGF-β3 is suppressed, resulting in an imbalance between TGF-β1 and TGF-β3. This imbalance disrupts the repair process, ultimately leading to delayed corneal wound healing in diabetic condition [31] (Fig. 3).

Trauma to the cornea leads to EMT, which subsequently induces corneal fibrosis and scar formation, ultimately resulting in vision impairment [32]. The EMT and fibrosis processes in the cornea are closely associated with the TGF-β/SMAD signaling pathway. Morishige et al. [33] found in human corneal fibroblasts that under TGF-β induction, the expression of α-SMA and palladin was significantly elevated, and it was demonstrated that their expression is regulated by SMAD2/3. Furthermore, the researchers showed that depletion of palladin can downregulate α-SMA, indicating that α-SMA expression is also influenced by palladin. Additional studies have demonstrated the involvement of the TGF-β-induced SMAD-dependent pathway in the pathological process of corneal fibrosis. Specifically, under TGF-β induction, corneal α-SMA exhibited concentration-dependent and time-dependent upregulation, and key components of the signaling pathway, such as SMAD4 and pSMAD2/3, were significantly increased [34-36] (Fig. 3).

TGF-β/SMAD Pathway in Glaucoma

Glaucoma is associated with increased intraocular pressure (IOP). IOP is related to the balance between aqueous humour (AH) secretion and its outflow. AH drainage mainly through trabecular pathway: involves drainage through the trabecular meshwork (TM) and Schlemm's canal. The TGF-β/SMAD signaling pathway plays a central role in glaucoma pathogenesis through three aspects affecting TM homeostasis:(1) ECM and cytoskeleton remodeling; (2) Oxidative stress and autophagy dysfunction; (3) Crosstalk with other pathways (Fig. 3).

In glaucomatous TM, increased TGF-β levels cause the EMT in TM cells, excessive ECM deposition and cross-linked actin networks (CLANs) formation, which further lead to TM dysfunction [37, 38]. The role of CLANs in the pathogenesis of glaucoma has been widely discussed. CLANs, composed of dome-like structures consisting of hubs and spokes, are the result of cytoskeletal rearrangement. The formation of CLANs in trabecular meshwork cells increases the stiffness of the trabecular meshwork, impairs aqueous humor outflow, and elevates intraocular pressure [39-41]. What's more, experiments have demonstrated that TGF-β2-induced CLANs formation in human trabecular meshwork cells is primarily mediated by the SMAD-dependent signaling pathway [42].

Autophagy dysfunction and oxidative stress and are critically involved in TM fibrosis through TGF-β/SMAD signaling, which have been verified in some studies. A research revealed autophagy as a synergistic regulator of

TGF-β/SMAD-induced fibrogenesis in TM cells [43]. TGF-β treatment in TM cells induced a dose-dependent increase in the levels of the autophagosome marker microtubule-associated protein 1 light chain 3, which was completely prevented with silenced SMAD2/3 expression. Meanwhile, knocking down autophagy-related gene 5 and autophagy-related gene 7 resulted in a decrease in the levels of the α-SMA, collagen I and fibronectin [44]. Oxidative stress can also induce an upregulation of fibrosis-related markers in the TM and exert an impact on SMAD proteins [38]. Human TM cells exposure in H_2O_2 triggered a bilateral regulation of pSMAD2 and pSMAD3 characterized by initial suppression within the first five minutes followed by a subsequent increase, alongside progressive TGF-β1 upregulation and mild increases in vimentin, α-SMA, and collagen I protein expression [38]. Increased fibrosis markers may damage the human trabecular meshwork cells drainage system and enhance resistance to aqueous humor cycling, resulting in glaucoma [38].

The TGF-β/SMAD signaling pathway has crosstalk with Wnt and BMP pathways to affect the TM and driving the pathogenesis of primary open-angle glaucoma (POAG). Specifically, the Wnt pathway and TGF-β/SMAD pathway collaboratively regulate TM homeostasis. Research showed that TGF-β2 suppresses Wnt pathway activation, while Wnt3a reciprocally inhibits TGF-β2-induced activation of the TGF-β/SMAD pathway. Researchers further identified that this crosstalk is mediated by SMAD4 [45]. This mutual cross-inhibition between the canonical Wnt and TGF-β/SMAD pathways highlights their dynamic balance [46, 47]. In addition, elevated levels of TGF-β2 and SFRP1(Secreted Frizzled-Related Protein 1, a Wnt signaling inhibitor) have been observed in the aqueous humor and trabecular meshwork of POAG eyes [48, 49], suggesting that both the Wnt and TGF-β/SMAD pathways may cooperatively drive pathogenic mechanisms of POAG. An inhibitor of BMP signaling, Gremlin, has also been found elevated in the aqueous humor of POAG patients. Experimental study has demonstrated that gremlin induces IOP elevation and ECM deposition [50]. Further investigation showed TGF-β2 increased expression of gremlin and gremlin increased expression of TGF-β2 in the TM, and established that SMAD3 is indispensable for gremlin-mediated ocular hypertension, strongly suggesting that gremlin exerted its pathogenic effects through the TGF-β/SMAD signaling axis [51].

TGF-β/SMAD Pathway in Lens Diseases

Fibrosis lens diseases, such as posterior capsular opacification (PCO) and anterior subcapsular cataract (ASC), which are thought to be caused by EMT, aberrant proliferation and migration of lens epithelial cells (LECs), are common complications after cataract surgery or other ocular traumas [52]. The lens EMT has been extensively linked to ASC and PCO, with characteristic molecular changes including significantly elevated α-SMA and reduced E-cadherin expression observed in these conditions [53-56]. This pathological transformation is primarily mediated through the TGF-β/SMAD signaling pathway. Notably, TGF-β2 has been widely utilized in experimental models to induce EMT in LECs, with studies demonstrating that TGF-β2 stimulation leads to significant increase of α-SMA, vimentin and fibronectin coupled with decreased E-cadherin levels and upregulation of SMAD2/3 expression [7, 56-59]. It is noteworthy that SMAD2 and SMAD3 have been found to play distinct yet interactive roles in TGF-β2-induced lens EMT. Experimental evidence revealed that SMAD2 primarily mediates α-SMA expression, whereas SMAD3 governed cellular proliferation along with the production and remodeling of ECM. Intriguingly, blocking of SMAD2 expression enhances SMAD3-mediated biological activities, while conversely, inhibition of SMAD3 potentiates SMAD2-driven cellular responses [60] (Fig. 3).

Beyond fibrotic disorders, the TGF-β/SMAD signaling axis exhibits extensive regulatory roles in lens pathophysiology. Emerging evidences highlight the involvement of TGF-β/SMAD pathway in both congenital cataracts and myopia-related lens abnormalities. In posterior subcapsular congenital cataracts (PSC), Lin et al. identified pathological activation of this pathway through their RT-qPCR data which revealed significant upregulation of TGF-β1, TGF-β2 and phosphorylated SMAD2/3 in PSC patients compared to controls, suggesting the activation of the TGF-β/SMAD signaling pathway [61]. This signaling cascade also participates in myopia-associated lens changes. Zhu et al. demonstrated that LECs from highly myopic eyes exhibit upregulated TβRI expression accompanied by increased SMAD2/3 and

SMAD4 levels. Their investigation revealed that exposure to TGF-β1 at a concentration of 5 ng/ml significantly increased both mRNA expression and protein levels of key β/γ-crystallins (CRYBB1, CRYGD, CRYBA2, CRYBA4, and CRYBA1) in human LECs ,and consequently leading to pathological lens growth [62] (Fig. 3).

TGF-β/SMAD Pathway in Retinal Diseases

The retina, a light-sensitive neural tissue, that receives light and converts it into nerve signals. Retinal fibrosis disrupts the normal structure and function of the retina, seriously affecting vision. This pathological process occurs in various retinal diseases, including PVR, nAMD and proliferative diabetic retinopathy (PDR), where chronic inflammation and recurrent tissue injury drive progressive fibrotic remodeling (Fig. 3).

PVR is a clinical syndrome associated with retinal traction and detachment. RPE have long been implicated as key players in the pathophysiology of PVR. In the context of PVR development, RPE undergo EMT and adopt a fibroblastic phenotype. When ARPE-19 cells were induced by TGF-β, they exhibited a series of changes. This phenotypic conversion was confirmed through three hallmark changes: (1) morphological shift toward spindle-shaped cells, (2) downregulation of epithelial biomarkers (E-cadherin and ZO-1), and (3) upregulation of mesenchymal markers including fibronectin and α-SMA [63, 64]. The EMT-induced alterations in RPE cells disrupt intercellular tight junctions, enhance ECM production, and promote abnormal ECM remodeling, ultimately leading to the formation of retinal fibrotic membranes characteristic of PVR on the retinal surface [65, 66]. This process is primarily driven by TGF-β through the SMAD-dependent signaling pathway [67], which is mechanistically supported by a research which found a significant increase in SMAD3 and a concurrent decrease in SMAD7 during TGF-β1-induced EMT in ARPE-19 cells [68]. Besides that, a study has reported interactions between the TGF-β pathway and other pathways in PVR. Chen et al. demonstrated the involvement of the -canonical TGF-β signaling pathway in RPE cells and further elucidated the interplay between the canonical TGF-β pathway and ERK1/2 signaling during EMT in RPE cells [69].

AMD is a progressive ocular disease affecting the macula, leading to gradual central vision loss. nAMD is defined by the pathological growth of abnormal blood vessels within the subretinal space, termed choroidal neovascularization (CNV). As the disease progresses, fibrous tissue proliferates, leading to subretinal and retinal fibrosis. Studies have elucidated that a variety of cytokines and chemokines mediate the pathogenesis of nAMD, among which TGF-β plays a pivotal role. The TGF-β/SMAD canonical pathway exhibits opposing roles in CNV and retinal fibrosis: it exerts inhibitory effects during the CNV process, while conversely promoting pathological progression in retinal fibrosis. Under physiological conditions, the balance between the TGF-β/activin receptor-like kinase (ALK) 5/SMAD2/3 and TGF-β/ALK1/SMAD1/5/8 signaling axes jointly maintains the stability of mature vasculature [70]. The TGF-β/SMAD2/3 axis suppresses neovascularization, while the TGF-β/ALK1/SMAD1/5/8 axis promotes angiogenesis [71]. In CNV endothelial cells of nAMD, phosphorylation levels of SMAD2/3 were notably reduced compared to those in normal choroidal vessels, indicating that the imbalance between these two axes drived pathological neovascularization [72]. However, in another study, researchers observed overexpression of TGF-β and upregulated p-SMAD2/3 in the RPE-choroid complex of laser-induced CNV mice, suggesting that the TGF-β/SMAD2/3 pathway plays a pro-angiogenic role in CNV development which seemingly contradicts previous studies that supported the anti-proliferative effect of TGF-β/SMAD2/3 [73, 74]. When CNV progresses to subretinal and retinal fibrosis, the retina exhibits the activation of the TGF-β/SMAD2/3 pathway. According to a study in vitro, it found overexpression of ECM proteins in TGF-β-induced Müller cells. Simultaneously, the treatment of TGFβ1 in Müller cells also led to an elevation in the production of TGFβ1 and upregulation of p-SMAD3 [75]. In studies in very low-density lipoprotein receptor (VLDLR)−/− mice (a model of subretinal fibrosis), protein levels of p-SMAD2/3 and α-SMA were significantly increased compared to the control group, indicating the possible roles of TGF-β/SMAD2/3 signaling in subretinal fibrosis [76, 77].

Diabetic retinopathy (DR), a common and serious complication of diabetes, has become the leading cause of blindness worldwide. The experimental results revealed that pSMAD2/3 levels were elevated in retinal capillary endothe-

lial cells (RCECs) under high glucose conditions [78]. The study also found that angiotensin-converting enzyme(ACE) mediates retinal barrier damage by activating latent TGF-β.Specifically, dual intervention with high glucose and ACE induced a more pronounced upregulation of pSMAD2/378.

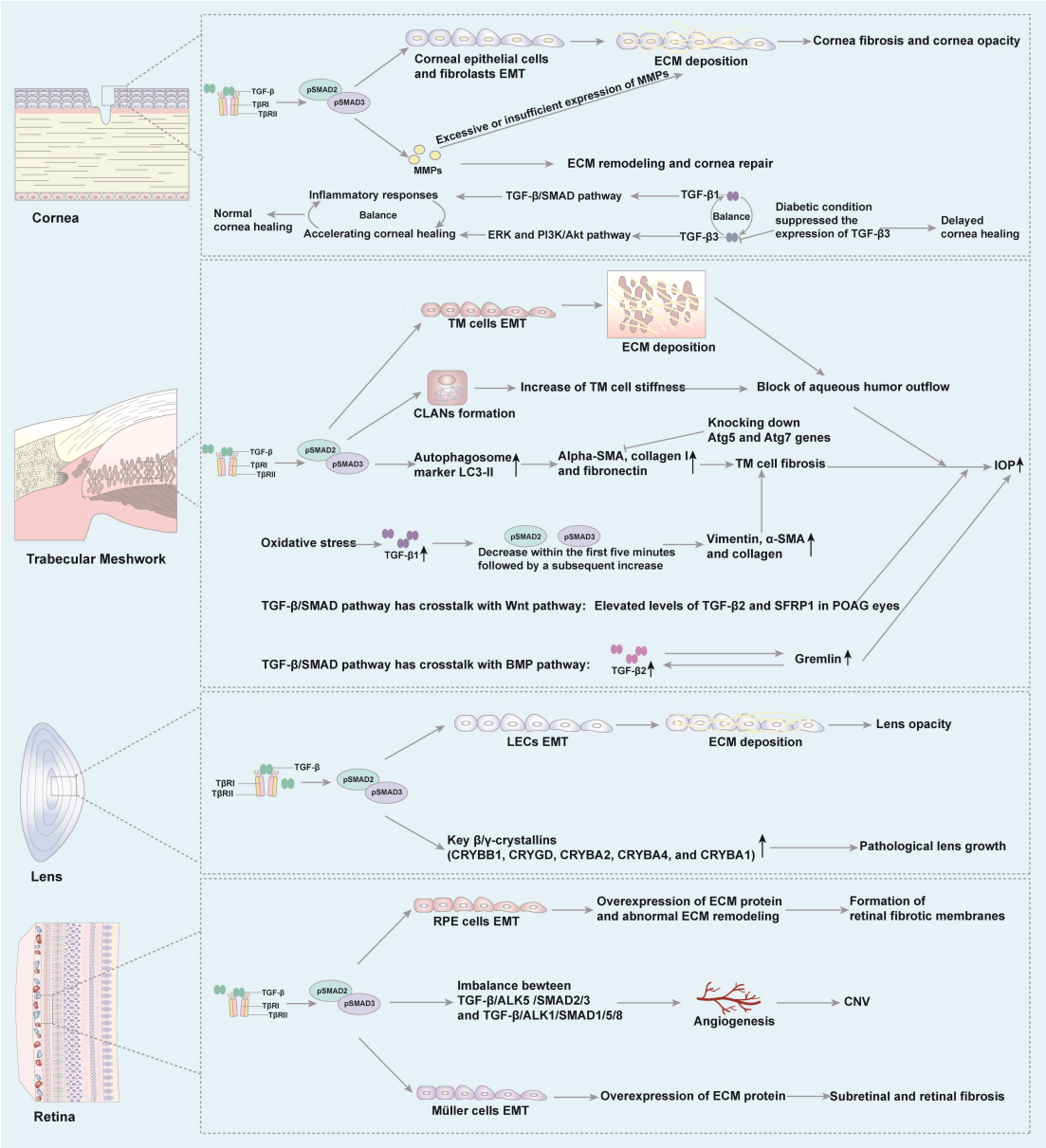

Figure 3: Schematic illustration of TGF-β/SMAD pathway in ocular diseases

The figure illustrates the role of the TGF-β/SMAD pathway in the pathogenesis of corneal fibrosis, glaucoma, lens and retinal diseases. Abbreviated words: ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; MMPs, matrix metalloproteinases; TM, trabecular meshwork; CLANs, cross-linked actin networks; Atg, autophagy-related gene; POAG, primary open-angle glaucoma; SFRP1, secreted frizzled-related protein 1; BMP, bone morphogenetic protein; LECs, lens epithelial cells.

Inhibitors of TGF-β/SMAD Pathway in Ocular Diseases

Inhibitor of TGF-β/SMAD Pathway in Corneal and Conjunctival Diseases

Many experiments on inhibitors which enable to block the TGF-β induced signaling cascades. Suberoylanilide hydroxamic acid (SAHA), valproic acid (VPA) and trichostatin A (TSA) are first generation histone deacetylase inhibitor (HDACi) (Fig. 4). HDAC deacetylates SMAD7,

and inhibiting HDAC disrupts the balance between deacetylation and acetylation of SMAD7. Acetylation of SMAD7 prevents its degradation, thereby affecting TGF-β-mediated gene expression [79, 80]. Topical TSA treatment inhibited the increase of α-SMA in a rat trabeculectomy model, demonstrating its therapeutic efficacy in attenuating conjunctival fibrosis. Furthermore, the increase of TGF-β1 expression and pSMAD2/3 levels after trabeculectomy was significantly decreased in 1μmol/L TSA groups [81]. VPA has demonstrated significant therapeutic efficacy both *in vitro* and *in vivo* experiment. Mechanistically, VPA inhibits collagen I expression in primary conjunctival fibroblasts, involving the downregulation of SMAD2, SMAD3 and SMAD4 and the induction of SMAD6 [82]. In a study in canine corneal fibroblast, SAHA attenuated TGF-β1-induced phosphorylation of SMAD2/3 and affected the expression of MMP-9, indicating the anti-fibrotic effects of SAHA [30]. MMP-9 plays an important role in ECM remodeling of wounded cornea surface [28]. But overexpression of MMP-9 has been linked to the disruption of cornea integrity and transparency [83]. Doxycycline has been demonstrated to effectively suppress TGF-β1-induced MMP-9 production by modulating the TGF-β/SMAD signaling pathway and exhibits the potential efficacy in treating ocular surface diseases [84]. Additionally, ITF2357 (Givinostat), a second generation synthetic pan-HDACi with HDAC type I and type II inhibitory action, exhibits functional similarities to TSA,VPA and SAHA [85].

Sphingosine kinase inhibitor II (SphK I2) is a selective inhibitor of SphK1(Sphingosine Kinase 1) which catalyzes the formation of Sphingosine 1-phosphate (Fig. 4) [86], has been implicated the in modulating TGF-β signaling during corneal fibrogenesis [87]. Mechanistic investigations revealed that SphK I2 treatment demonstrated significant inhibitory effects on key components of the TGF-β signaling pathway, markedly suppressing the expression of TβRI and TβRII, along with downstream effector SMAD2. Furthermore, this intervention could attenuate corneal fibrosis progression as evidenced by the downregulation of fibrosis markers such as α-SMA and collagen III [88].

In conjunctival fibrosis, Triarylmethane-34 (TRAM34), TSA and VPA have been reported to effectively ameliorate fibrosis progression (Fig. 4). The mechanism underlying TSA and VPA's antifibrotic action has been mentioned above. TRAM34, a selective inhibitor of the calcium activated potassium channel (KCa3.1) [89], effectively suppresses TGF-β1-induced SMAD2/3 nuclear translocation. This inhibition attenuates TGF-β-mediated transcriptional regulation of downstream target genes and consequently reduces the expression of fibrosis-related proteins [90] (Fig. 4).

For more details, see the Table 1.

Table 1: Inhibitor of TGF-β/SMAD pathway in corneal and conjunctival diseases

Author	Inhibitor	Model	Target	Effects	Conclusion
[30]	SAHA*	Canine corneal fibroblast	HDAC (-)	pSMAD2/3↓	The corneal anti-fibrotic effects of SAHA in the canine cornea functioned through inhibiting phosphorylation of SMAD2/3.
[84]	Doxycycline*	HCECs	SMAD2(-)	pSMAD2↓, MMP-9↓	Doxycycline inhibits TGF-β1-induced MMP-9 production and activity in MMP-9-mediated ocular surface diseases.
[34]	Celastrol*	RCFs	YAP/TAZ (-)	pSMAD2/3↓, TβRII↓, YAP↓, TAZ↓, TEAD1↓	Celastrol may exert its antifibrotic effects in the cornea via TGF-β/SMAD pathway.

[87, 88].	SphK I2*	HCFs.	SphK1(-)	pSMAD4↓, pSMAD2/3↓, TGF-βRI↓, TGF-βRII↓, α-SMA↓, Col III↓	SphK I2 treatment inhibited the TGF-β/SMAD pathways and resulted in reduced corneal fibrosis.
[85]	ITF2357*	pHCSFs and New Zealand White rabbits	HDAC (-)	pSMAD2/3↓, pSMAD4↓, α-SMA↓, Col I↓, Col IV↓, fibronectin↓	ITF2357 reduced clinical haze in a rabbit model of corneal fibrosis and inhibits myofibroblast formation and irregular ECM proteins in pHCSFs.
Rosa et al.,2022.	BAY 41-2272*	HCK	sGC (-)	pSMAD3↓, α-SMA↓, Col I ↓, vimentin↓, N-cadherin↓	BAY 41-2272 reduced TGFβ1-induced invasiveness of HCK.
Nguyen et al.,2022.	SB505124†	WJ-MSCs and CECs	TβRI (-)	pSMAD2/3↓	SB505124 downregulated the TGF-β signaling pathway via reducing phosphorylation of Smad2/3 which helps WJ-MSCs transdifferentiate into CECs.
[90]	TRAM34‡	Conjunctival fibroblasts	KCa3.1(-)	Nuclear SMAD2/3↓, α-SMA↓, fibronectin↓, Col I↓, Col IV↓	TRAM34 treatment attenuated TGFβ1-induced fibrosis *in vitro*.
[82]	VPA‡	NIH3T3/BL6 mice and conjunctival fibroblasts from C57BL6/J mice	HDAC (-)	pSMAD2/3↓, SMAD4↓, Col I↓	VPA reduced collagen accumulation in conjunctival fibrosis.
[81]	TSA‡	Sprague-Dawley rats	HDAC (-)	pSMAD2/3↓, α-SMA↓	TSA treatment attenuated conjunctival fibrosis in a rat trabeculectomy model.

*Represents the research is mainly about ameliorating corneal fibrosis.

†Represents the research is mainly about ameliorating limbal stem cell deficiency.

‡Represents the research is mainly about ameliorating conjunctival fibrosis.

↓Represents the expression of this protein decreased.

Abbreviated words: SAHA, suberoylanilide hydroxamic acid; HDAC, histone deacetylase; HCECs, human corneal epithelial cells; RCFs, rabbit corneal fibroblasts; HCFs, human corneal fibroblasts; pHCSFs, primary cultures of human corneal fibroblasts; WJ-MSCs, human Wharton's jelly derived mesenchymal stem cells; CECs, corneal epithelial cells; HCK, human corneal keratocytes; sGC, soluble guanylate cyclase; TRAM34, Triarylmethane-34; VPA, valproic acid; TSA, trichostatin A; Col I/III/IV, collagen I/III/IV.

Inhibitors of TGF-β/SMAD Pathway in Glaucoma

Oxidative stress, implicated in the pathology of several neurodegenerative diseases, also plays a prominent early role in the pathophysiology of POAG. Increased in ROS production associated with POAG may arise as a consequence of age-associated mitochondrial dysfunction. XJB-5-131 and MitoQ are mitochondrial-targeted antioxidants (Fig. 4). As reported in an *in vitro* research, mitochondrial-targeted antioxidants attenuate TGF-β2–mediated

changes in SMAD-dependent transcriptional activity, including marked reductions in connective tissue growth factor (CTGF) and collagen protein expression [91].

Six-bromoindirubin-3-oxime (BIO), SB216763, and CHIR99021 are glycogen synthase kinase 3 beta (GSK3β) inhibitor (Fig. 4). As activators of the canonical Wnt pathway, GSK3β inhibitors can crosstalk with the TGF-β/SMAD pathway by reducing SMAD3 phosphorylation, thereby decreasing ECM deposition in the TM and suppressing the formation of CLANs in TM cells. This mechanism ultimately helps prevent elevated intraocular pressure [92]. There is also crosstalk between the canonical TGF-β pathway and the MAPK pathway. SB203580 is a p38 MAPK inhibitor. Consequently, SB203580 can indirectly inhibit the TGF-β/SMAD pathway by partially suppressing the phosphorylation of SMAD2/3, thereby reducing ECM deposition in the TM [93].

For more details, see the Table 2.

Table 2: Inhibitors of TGF-β/SMAD pathway in glaucoma

Author	Inhibitor	Model	Target	Effects	Conclusion
[91]	XJB-5-131*	HTM cells	Mitochondria (-)	pSMAD2/3↓, CTGF↓, COL1A1↓, COL4A1 ↓	XJB-5-131 attenuated TGF-b2–mediated changes via TGF β/SMAD pathway.
[91]	MitoQ*	HTM cells	Mitochondria (-)	pSMAD2/3↓, CTGF↓, COL1A1↓, COL4A1↓	MitoQ attenuated TGF-b2–mediated changes via TGF β/SMAD pathway.
[92]	BIO*	GTM3 cells and primary HTM cells	GSK3β (-)	pSMAD3↓, fibronectin↓, Col 1↓	GSK3β inhibitors inhibited TGFβ2-induced ECM proteins and CLAN formation.
[92]	SB216763*	GTM3 cells and primary HTM cells	GSK3β (-)	pSMAD3↓, fibronectin↓, Col 1↓	GSK3β inhibitors inhibited TGFβ2-induced ECM proteins and CLAN formation.
[92]	CHIR99021*	GTM3 cells and primary HTM cells	GSK3β (-)	pSMAD3↓, fibronectin↓, Col 1↓	GSK3β inhibitors inhibited TGFβ2-induced ECM proteins and CLAN formation.
[93].	SB203580†	HTM cells	SMAD2(-)	pSMAD2↓, Col I↓	TGF-β2–induced production of type 1 collagen in HTM cells is suppressed by SB203580.

*Represents the research is mainly about ameliorating POAG.

†Represents the research is mainly about ameliorating glaucoma.

↓Represents the expression of this protein decreased.

Abbreviated words: HTM, human trabecular meshwork; CTGF, connective tissue growth factor; GTM3, transformed human glaucomatous trabecular meshwork; GSK3β, glycogen synthase kinase 3 beta; COL1A1, collagen type I alpha 1 chain; COL4A1, collagen type IV alpha 1 chain.

Inhibitors of TGF-β/SMAD Pathway in Fibrotic Cataracts

Natural compounds such as curcumin and celastrol have been extensively investigated for their diverse biological effects (Fig. 4). Curcumin has been shown to counteract TGF-β2-induced increase of EMT markers, encompassing fibronectin, collagen I, collagen IV and α-SMA. Further-

more, curcumin demonstrates significant inhibition of SMAD2/3 phosphorylation, suggesting its mechanism of action involves block of canonical TGF-β signaling transduction [58]. Similar to curcumin, celastrol derived from the Chinese medicinal plant *Tripterygium wilfordi* also demonstrates inhibitory effects on TGF-β signaling. Celastrol suppresses the upregulation of EMT-associated cytokines while concurrently reducing SMAD2/3 phosphorylation. Notably, *in vivo* experiment reveals that intracapsular injection of celastrol markedly attenuates PCO progression in rabbit models [94].

SMAD7, a well-characterized negative regulator of TGF-β signaling, was strategically engineered into a therapeutic fusion protein designated as Tat-SMAD7(203-426)-HA. In primary lens epithelial cell cultures, Tat-SMAD7(203-426)-HA effectively attenuated TGF-β2-induced expression of α-SMA. More importantly, in an experimental cataract surgery model using intraocular injection in mice, it also significantly ameliorated α-SMA expression[7]. Integrin is also an important component of TGF-β/SMAD pathway. ADWA-11 is an antibody of αVβ8 integrin, which antagonizes LAP binding to αVβ8 integrin (αVβ8-IBA) (Fig. 4), thus blocking TGF-β activation. The results shows that the blocking of αVβ8 integrin substantially reduces the EMT and progression of fibrosis after cataract surgery [53].

3-methyladenine (3-MA), chloroquine (CQ) and bafilomycin A1 (Baf A1) are autophagy inhibitors (Fig. 4). Autophagy inhibition suppresses EMT induced by TGF-β2 in LECs. The expression of fibronectin and α-SMA in autophagy-treated group are significantly reduced compared to the TGF-β2 group. Moreover, western blot analysis and quantification showed the phosphorylation of Smad2 and Smad3 reduced after culturing with autophagy inhibitors, suggesting the effect on EMT might attenuate TGF-β2 pathway through suppression of Smad2/3 phosphorylation [95].

For more details, see the Table 3.

Table 3: Inhibitors of TGF-β/SMAD pathway in fibrotic cataracts

Author	Inhibitor	Model	Target	Effects	Conclusion
[7]	Tat-SMAD7(203-426)-HA*	AR-Tg mice and LECs from AR-Tg mice	SMAD2/3(-)	α-SMA↓, fibronectin↓	Tat-Smad7(203-426)-HA treatment reduced expression of EMT marker both *in vitro* and *in vivo*.
[53]	ADWA-11*	Itgb5^{tm1Des} [C57BL/6J 129/Sv] mice, Itgb6^{tm1Des} 129/Sv, β8ITG-cKO mice and β8ITG-cKO LCs	αVβ8 integrin (-)	pSMAD2/3↓, α-SMA↓, tenascin C↓, fibronectin↓, Col I↓	ADWA-11 ameliorated post cataract surgery fibrosis.
[57, 58]	Curcumin*	HLECs-SRA 01/04	SMAD2/3(-)	pSMAD2/3↓, pERK1/2↓, fibronectin↓, Col I↓, Col IV↓	Curcumin inhibited the proliferation and TGF-β2-Induced EMT of LECs.
[56]	Mefunidone*	Eight-week-old male mice and HLECs-SRA 01/04	SMAD2/3(-)	pSMAD2/3↓, pERK1/2↓, fibronectin↓, α-SMA↓, Col I↓, vimentin↓	Mefunidone repressed proliferation, migration and EMT in LECs both *in vivo* and *in vitro*.

Zhu et al.,2024.	Conbercept*	C57BL/6J mice and HLEC-SRA01/04	SMAD2/3(-)	pSMAD2/3↓, α-SMA↓, snail↓, fibronectin↓, Col I↓, Col IV↓	Conbercept treatment reversed TGF-β2 induced EMT in HCL-SRA01/04 via TGF-β/Smad signaling pathway.
Chang et al.,2015.	Sorbini*	C57BL/6 mice and HLE B3	AR (-)	pSMAD2/3↓, α-SMA↓, vimentin↓, AR↓	Inhibition or knockdown of AR reduces TGF-β2 Induced EMT Markers in HLE B3 cells.
Huang et al.,2020.	H-RN*	HLEC-SRA01/04	SMAD2/3(-)	pSMAD2/3↓, α-SMA↓, fibronectin↓,	H-RN inhibited TGF-β2-induced EMT
Li et al.,2022.	Naringenin*	HLEC-SRA01/04	SMAD2/3(-)	pSMAD2/3↓, α-SMA↓, vimentin↓, fibronectin↓	Naringenin suppressed TGFβ2-induced LEC EMT process
Ma et al.,2023.	Lanosterol synthase*	LECs from New Zealand White rabbits	Lanosterol (-)	pSMAD2/3↓, α-SMA↓, fibronectin↓	Lanosterol synthase treatment inhibited EMT of LECs.
Shih et al.,2022.	TSE*	HLEC-SRA01/04	SMAD3(-)	SMAD3↓, nuclear SMAD2/3↓, nuclear SMAD4↓, fibronectin↓, Col I↓	TSE reduced the expression of EMT markers in cell models mimicking PCO.
Sun et al.,2021.	3-MA*	Rabbit LECs	LC3(-)	pSMAD2/3↓, α-SMA↓, fibronectin↓	TGF-β2-induced EMT was reversed by pharmacological inhibition of autophagy.
Sun et al.,2021.	CQ*	Rabbit LECs	LC3(-)	pSMAD2/3↓, α-SMA↓, fibronectin↓	TGF-β2-induced EMT was reversed by pharmacological inhibition of autophagy.
Sun et al.,2021.	Baf A1*	Rabbit LECs	LC3(-)	pSMAD2/3↓, α-SMA↓, fibronectin↓	TGF-β2-induced EMT was reversed by pharmacological inhibition of autophagy.
[100]	Metformin*	HLE B-3	AMPK (+)	pSMAD2/3↓, Col I↓, vimentin↓, α-SMA↓, fibronectin↓	Metformin suppressed migration and EMT induced by TGF-β2 in HLECs.
[94]	Celastrol*	Female New Zealand white rabbits and rabbit LECs	SMAD2/3(-)	pSMAD2/3↓, α-SMA↓, TGF-β1↓, TβRII↓, fibronectin↓, Col I↓	Anti-PCO effects could be observed after celastrol treatment both *in vitro* and *in vivo*.

Ding et al.,2024.	Nintedanib†	Male C57BL/6J mice and HLEC-SRA01/04	SMAD2/3(-)	pSMAD2/3↓, α-SMA↓, Col I↓, fibronectin↓	Nintedanib attenuated the puncture-induced ACS progression in mice.
Ding et al.,2024.	Entrectinib†	C57BL/6 mice and HLECs-SRA 01/04	PYK2(-)	pSMAD2/3↓, α-SMA↓, Col I↓, fibronectin↓	Entrectinib ameliorated fibrotic cataract *in vitro* and *in vivo*.
[85]	Sprouty2†	HLECs-SRA 01/04	ERK1/ 2(-)	pSMAD2↓, ERK1/2↓, fibronectin↓, α-SMA↓, Col I↓, Col IV↓	Sprouty2 inhibited TGFβ-induced EMT and migration in human lens epithelial cells.

*Represents the research is mainly about ameliorating PCO.

†Represents the research is mainly about ameliorating ASC.

↓Represents the expression of this protein decreased.

Abbreviated words: HLEC, human lens epithelial cell; LECs, lens epithelial cells; H-RN, hepatocyte growth factor-derived peptide; 3--MA,3-methyladenine; LC3, microtubule-associated protein 1 light chain 3; CQ, chloroquine; Baf A1, bafilomycin A1; TSE, 2-phenyl-5-propyl-2,4-dihydro-3H-pyrazol-3-one; AMPK, AMP-activated protein kinase; AR, aldose reductase; PYK2, proline-rich tyrosine kinase 2; ERK1/2, extracellular signal-regulated kinase 1/2.

Inhibitors of TGF-β/SMAD Pathway in Retinal Diseases

Quercetin [96], resveratrol [97], curcumin, epigallocatechin gallate(EGCG) [98], silibinin [99], and artesunate [100] are all natural compounds that have demonstrated inhibitory effects on the progression of PVR in experimental studies(Fig. 4). Their mechanisms of action are associated with the TGF-β canonical signaling pathway. Specifically, SMAD2 and SMAD3 serve as common molecular target for these compounds which block signal transduction by inhibiting the formation of the SMAD2/3 complex and suppressing its phosphorylation. Additionally, quercetin and resveratrol further exert their anti-PVR effects by targeting SMAD4. Bradykinin (BK) has also been validated in *in vitro* experiments for its potential to alleviate PVR. It exerts inhibitory effects on the TGF-β/SMAD signaling pathway by reducing phosphorylated SMAD3 and elevating SMAD7 levels, while simultaneously suppressing the upregulation of α-SMA and vimentin, as well as inhibiting cell migration [68].

Subretinal fibrosis is a common pathological feature of nAMD. Both Am580 and fenofibrate have been demonstrated to alleviate subretinal fibrosis in mouse models (Fig. 4). Am580 is a retinoic acid receptor-α (RAR-α) agonist and previous studies have shown that RA inhibits the TGF-β pathway [101]. In an experiment revealed Am580 suppressed TGF-β2-induced SMAD2 phosphorylation and significantly inhibited the expression of EMT markers in TGF-β2-induced mouse RPE cells [101]. To further validate Am580's therapeutic potential, the study administered intravitreal injections of Am580 in a subretinal fibrosis mouse model, demonstrating effective inhibition of fibrosis progression [101]. Fenofibrate, a peroxisome proliferator–activated receptor alpha (PPARα) agonist, was evaluated in a $VLDLR^{-/-}$ mouse model of subretinal fibrosis [77]. The study revealed that fenofibrate treatment downregulated the expression of TGF-β2, TβRII, and phosphorylated SMAD2/3, indicating suppression of the canonical TGF-β signaling pathway [77]. Concurrently, fenofibrate exhibited antagonistic effects against subretinal fibrosis in this model [77].

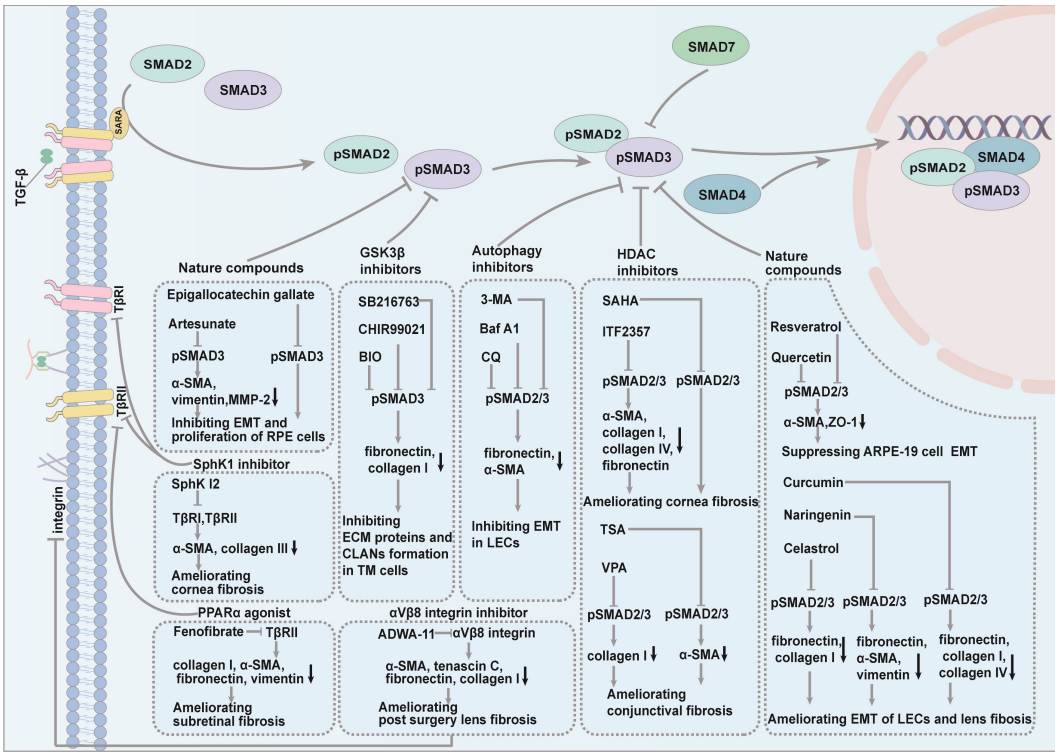

Figure 4: Schematic illustration of inhibitors TGF-β/SMAD pathway in ocular diseases

The figure describes the mechanisms of action, targets, and effects of different TGF-β/SMAD pathway inhibitors. Abbreviated words: SphK1, sphingosine kinase 1; 3-MA ,3-methyladenine; CQ, chloroquine; Baf A1, bafilomycin A1; HDAC, histone deacetylase; SAHA, suberoylanilide hydroxamic acid; TSA, trichostatin A; VPA, valproic acid; CLANs, cross-linked actin networks; PPARα, peroxisome proliferator–activated receptor alpha.

For more details, see the Table 4.

Table 4: Inhibitors of TGF-β/SMAD pathway in retinal diseases

Author	Inhibitor	Model	Target	Effects	Conclusion
[96]	Quercetin*	ARPE-19	SMAD2/3(-)	pSMAD2/3↓, nuclear SMAD4↓, α-SMA↓, N-cadherin↓, ZO-1↓	Quercetin treatment suppressed TGF-β1 induced ARPE-19 cell migration and EMT.
Chen et al.,2017.	Resveratrol*	ARPE-19	SMAD2/3(-)	pSMAD2/3↓, α-SMA↓, ZO-1↓, vimentin↓,	Treatment with resveratrol suppressed TGF-β2-induced EMT and cell proliferation *in vitro*.
Chen et al.,2016.	LYTAK1*	ARPE-19	TAK 1(-)	pSMAD2↓, α-SMA↓, fibronectin↓	LYTAK1 prevents TGF-β1-induced EMT and the proliferation of RPE cells.

He et al.,2017.	HC-HA/PTX3*	ARPE-19 and primary human RPE cells	SMAD2/3(-)	pSMAD2/3↓, Col I↓, α-SMA↓	HC-HA/PTX3 prevented migration induced by TGF-β1 and collagen gel contraction induced by TGF-β1.
He et al.,2015.	5-AZA-dC*	Human fetal RPE cells	MECP 2(-)	pSMAD2/3↓, TβRII↓, α-SMA↓, fibronectin↓	5-AZA-dC inhibited cell migration and EMT in RPE.
Heffer AM et al.,2019.	Salinomycin*	ARPE-19 and human primary RPE cells	SMAD2/3(-)	pSMAD2/3↓, α-SMA↓, Col I↓	Salinomycin inhibited TGFβ-induced cell migration, EMT and contraction in RPE cells.
Hsiao et al.,2021.	TA*	RPE R-50	SMAD2(-)	pSMAD2↓, α-SMA↓, Col I↓, MMP-2↓, MMP-9↓, VEGF↓	TA suppressed TGF-β2-enhanced RPE cell contraction and EMT.
Ishikawaet al.,2015.	Resveratrol*	Human fetal RPE cells and rabbits	SMAD4(-)	Acetylated SMAD4↓, α-SMA↓, fibronectin↓	Resveratrol inhibited cell proliferation, migration and fibronectin synthesis *in vitro* and inhibited progression of PVR *in vivo* and human RPE cells
Shanmuganathan et al.,2017.	Curcumin*	ARPE-19	SMAD3(-)	pSMAD3↓, α-SMA↓, vimentin↓, MMP-2↓	Curcumin inhibited EMT and proliferation of ARPE-19 cells.
Shanmuganathan et al.,2017.	EGCG*	ARPE-19	SMAD3(-)	pSMAD3↓, α-SMA↓, vimentin↓, MMP-2↓	EGCG inhibited EMT and proliferation of ARPE-19.
Wei et al.,2018.	BK*	ARPE-19	SMAD3(-)	SMAD3↓, SMAD7↑, α-SMA↓, vimentin↓, E-cadherin↓	BK inhibited TGF-β1-induced EMT in ARPE-19.
Ma et al.,2023	Silibinin*	ARPE-19	SMAD3(-)	Nuclear SMAD3↓, COL1A1↓, MMP2↓, fibronectin1↓, N-cadherin↓	Silibinin effectively inhibited TGFβ1-induced the EMT and cell migration of RPE cells *in vitro*, and also suppressed the formation of proliferative membranes *in vivo*.
Wang et al.,2021.	Artesunate*	Rabbits and ARPE-19	SMAD3(-)	TGF-β2↓, SMAD3↓	Artesunate inhibited the TGF-β2-mediated EMT in ARPE-19 cells and attenuates the progression of PVR in rabbits.

Wang et al.,2017	LY2157299[†]	Male C57BL/6 J mice	TβRI (-)	pSMAD2/3↓, VEGF↓, TNF-α↓	TGF-β inhibition by LY2157299 reduced nAMD progression through the TGF-β/SMAD pathway.
Wang et al.,2017	Decorin[†]	Male C57BL/6 J mice	TGF-β (-)	pSMAD2/3↓, VEGF↓, TNF-α↓	TGF-β inhibition by Decorin reduced nAMD progression through the TGF-β/SMAD pathway.
Kobayashi et al.,2021.	Am580[†]	Female C57BL/6J mice and RPE cells from female C57BL/6J mice	RAR-α (-)	pSMAD2↓, α-SMA↓, Col I↓, fibronectin↓	Am580 treatment inhibited EMT induced by TGF-β2 in RPE cell and suppressed the development of nAMD in a mouse model.
Chen et al.,2020.[77]	Fenofibrate[‡]	VLDLR$^{-/-}$ mice	PPARα (-)	TGF-β2↓, TβRII↓, pSMAD2/3↓, Col I↓, α-SMA↓, fibronectin↓, vimentin↓	Fenofibrate ameliorated subretinal fibrosis in VLDLR$^{-/-}$ mice.
Fan et al.,2020.	RO4929097[§]	C57BL/6J mice and MIO-M1	γ-secretase (-)	pSMAD3↓, TβRI↓, TβRII↓	RO4929097 inhibited TGF-β signaling in retinas damaged by NaIO3 and overexpression of ECM proteins in Müller cells
Da Silva et al.,2023.	Galunisertib[‖]	MIO-M1	SMAD2/3(-)	pSMAD2 /3↓, α-SMA↓	Galunisertib attenuated glial-mesenchymal transition in MIO-M1.
Jang HY et al.,2023.	α-Klotho[#]	Male C57BL/6 J mice and ARPE19	TGF-β/ TβRII interaction (-)	TβRII↓, α-SMA↓, ZO-1↓, vimentin↓	Alpha-Kloth inhibited TGF-β2-induced EMT and attenuated age-related degenerative changes without causing toxicity *in vivo* and prevents TGF-β2-induced EMT in RPE cells.

*Represents the research is mainly about ameliorating PVR.

[†]Represents the research is mainly about ameliorating nAMD.

[‡]Represents the research is mainly about ameliorating subretinal fibrosis.

[‖]Represents the research is mainly about ameliorating epiretinal membrane.

[#]Represents the research is mainly about ameliorating dry-AMD.

↓Represents the expression of this protein decreased.

Abbreviated words: VLDLR, very low-density lipoprotein receptor; TAK, TGF-β1-activated kinase; HC-HA/PTX3, heavy chain-hyaluronic acid/pentraxin 3; 5-AZA-dC, 5-aza-20-deoxycytidine; TA, triamcinolone acetonide; EGCG, epigallocatechin gallate; BK, Bradykinin; PPARα, peroxisome proliferator–activated receptor alpha; RAR-α, retinoic acid receptor-α; MECP2, Methyl-CpG Binding Protein 2.

Conclusion

The TGF-β/SMAD pathway plays a crucial role in the pathogenesis of various ocular diseases, including lens diseases, retinal diseases, glaucoma, and corneal diseases. A wide range of inhibitors targeting the TGF-β/SMAD signaling pathway in ocular diseases have been extensively characterized through both *in vitro* and *in vivo* studies, as comprehensively detailed in preceding sections. Meanwhile, emerging therapeutic targets inhibiting TGF-β/SMAD signaling have garnered significant attention. In corneal epithelial cells, Krüppel-like factor 4 (KLF4) suppresses cell cycle progression by inhibiting canonical TGF-β signaling, demonstrating potential in mitigating ocular surface squamous neoplasia progression [102]. The long non-coding RNA H19 plays a critical role in maintaining lens transparency. Upregulation of H19 suppresses lens EMT, thereby attenuating lens fibrosis [103]. Methyl-CpG-binding protein 2 (MeCP2), particularly its phosphorylated isoform P-MeCP2-421, has been implicated in PVR pathogenesis. Experimental evidence demonstrates that either MeCP2 silence or exogenous MeCP2 inhibitor treatment significantly alleviates EMT in ARPE-19 [104]. Concurrently, microRNA studies have unveiled critical regulatory roles in ocular pathology. Let-7a-5p upregulation effectively counteracts TGF-β2-induced pathological changes in LEC by targeting SMAD2 [57]. MiR-200a-3p overexpression ameliorates neovascularization and inflammation in diabetic retinopathy rat models [105]. MiR-302d elevation attenuates EMT in human retinal pigment epithelial cells through TβRII downregulation [106]. MiR-1285 upregulation suppresses EMT in PVR rabbit models via SMAD4-dependent mechanisms [107].

However, despite these promising results, several challenges remain. First, the translation of these inhibitors from pre-clinical studies to clinical applications is still a long-way off. The safety and efficacy of these inhibitors need to be further evaluated in large-scale clinical trials. Side effects observed in animal models may not fully represent what could occur in humans, and the long - term effects of these inhibitors on ocular and systemic health are yet to be determined. Second, the optimal dosing and treatment duration for these inhibitors are still unclear.

Future research should focus on improving the delivery methods of these inhibitors to enhance their bioavailability in the eye. Novel drug delivery systems, such as nanoparticle-based carriers or gene-therapy-mediated delivery, could be explored to ensure that the inhibitors reach the target cells more effectively. Additionally, combination therapies that target multiple pathways involved in ocular diseases may be more effective than single-pathway inhibitors. For example, combining TGF-β/SMAD pathway inhibitors with anti-VEGF agent may provide a new direction for the treatment of nAMD. Finally, understanding the long-term effects of these inhibitors on ocular function and overall health through more in-depth pre-clinical and clinical studies is essential for their successful translation into clinical practice.

In conclusion, the TGF-β/SMAD pathway is deeply involved in ocular diseases and its inhibitors show great potential in treating ocular diseases. However, further research is needed to overcome the existing challenges and fully realize their therapeutic benefits.

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Author Contributions

Yang Liu: Conceptualization, Writing-review and editing, Supervision **Wenxuan Duan:** Conceptualization, Writing-original draft, Writing-review and editing **Linghan Gao:** Data curation, Supervision **Yurong Shi:** Data curation, Supervision **Ju Zhang:** Data curation, Supervision.

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Conflicts of Interest

None

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