Published in final edited form as:

Brain Res Bull. 2010 February 15; 81(2-3): 229–235. doi:10.1016/j.brainresbull.2009.08.024.

Growth factors and corneal epithelial wound healing

Fu-Shin X. Yu^{*}, Jia Yin, Keping Xu, and Jenny Huang

Kresge Eye Institute, Departments of Ophthalmology and Anatomy and Cell Biology, Wayne State University School of Medicine, 4717 St. Antoine Blvd., Detroit, MI, 48201, United States

Abstract

In this article, we briefly review recent findings in the effects of growth factors including the EGF family, KGF, HGF, IGF, insulin, and TGF- β on corneal epithelial wound healing. We discuss the essential role of EGFR in inter-receptor cross-talk in response to wounding in corneal epithelium and bring forward a concept of “alarmins” to the field of wound healing research.

Keywords

Cornea; Wound healing; Growth factors; Signal transduction

1. Introduction

The avascular cornea serves two specialized functions: it forms a protective barrier and serves as the main refractive element of the visual system. The cornea is arranged in three cell layers: epithelial cells, stromal cells and endothelial cells. Additionally, it contains Descemet's membrane, a thick basement membrane between the stroma and endothelium, and in humans Bowman's layer, a thickened acellular collagenous zone between the epithelium and stroma [104]. The corneal epithelium, like other epithelial barriers in the human body, is subjected continuously to physical, chemical, and biological insults, often resulting in a wound and loss of barrier functions. Proper healing of corneal wounds is vital for maintaining a clear, healthy cornea and for preserving vision. Corneal epithelium responds rapidly to injury, healing a wound by migrating as a sheet to cover the defect and to reestablish its barrier function [74]. Successful wound healing involves a number of processes including cell migration, cell proliferation, re-stratification, as well as matrix deposition and tissue remodeling [78]. Particularly critical are cell migration and proliferation, which are driven by growth factors released coordinately into the injury sites. In wounded cornea, epithelium plays a central role, not only as a key cell type in repairing the cornea, but also as the source of a number of growth factors. As in other tissues, a variety of growth factors are suggested to play a role in the regulation of corneal epithelial function and wound healing (for recent reviews, see [45,74]). This review will summarize the major growth factors involved in corneal wound healing with focus on the role of the epidermal growth factor (EGF) receptor (EGFR) in inter-receptor cross-talk in response to wounding and other various stimulants.

© 2009 Published by Elsevier Inc.

^{*} Corresponding author at: Kresge Eye Institute, Wayne State University School of Medicine, 4717 St. Antoine Blvd, Detroit, MI, 48201. Tel.: +1 313 577 1657; fax: +1 313 577 7781. fyu@med.wayne.edu (F.-S.X. Yu)..

Conflict of interest
None.

2. The epidermal growth factor (EGF) family

The EGF family is composed of up to 13 members and the main members involved in epithelial wound healing include EGF [16], transforming growth factor- α (TGF- α) [19], and heparin-binding EGF-like growth factor (HB-EGF) [34]. All members of the EGFR ligand family are synthesized as membrane-anchored forms, which are then processed to give bioactive soluble factors. These factors act via the stimulation of specific cell-surface receptors [10,42]. Four related receptor tyrosine kinases have been identified (reviewed by [44,97]). These are EGFR/erbB1/HER1, erbB2/HER2/neu, erbB3/HER3 and erbB4/HER4 [42], all of which have been detected in corneal epithelium [73,124,153]. The EGF ligands bind to the erbBs with a degree of specificity. EGF and TGF- α bind exclusively to erbB1 while HB-EGF and epiregulin bind to both erbB1 and erbB4 [20,97]. ErbB2, a potent oncogene, functions by serving as a preferred heterodimerization partner for other members of the EGFR family and is often believed to be ligandless [43]. However, it is recently hypothesized that MUC4, a member of transmembrane mucin family, can interact with and activate ErbB2 [15]. Heterodimerization of EGF receptor tyrosine kinases results in the transactivation of receptors, expanding the signaling potential of the EGF-like ligands. An analysis of EGFR-deficient mice revealed that the cell types most affected by the absence of EGFR are epithelial and glial cells, the same cell types where EGFR is found to be over-expressed in human tumors [80,118]. Thus, the level of EGFR and its activity are major determinant factors for the state of an epithelial cell in tissues and organs. Echoing this concept is the finding that targeting EGFR with cetuximab (an EGFR monoclonal antibody) and Gefitinib (an EGFR kinase inhibitor) for cancer treatments resulted in ocular abnormalities in patients, including diffuse punctate keratitis and corneal erosion [23,115,121]. Thus, maintaining a proper level of EGFR signaling is critical for corneal homeostasis.

EGF is secreted by platelets, macrophages, and fibroblasts and acts in a paracrine fashion on epithelial cells [114]. In wounded corneas, the expression of HB-EGF and TGF- α is up-regulated while the levels of EGF mRNA remain unchanged [130,153], suggesting that EGF may not be directly involved in stimulating epithelial wound closure. Clinical trials and animal studies for wound therapeutics showed that the addition of topical EGF increased epithelial wound closure and shortened healing time in diabetic corneas [29,100,113]. Therefore, EGF may still be useful to accelerate the delayed wound healing if delivered in a controlled release fashion, such as biodegradable hydrogel [39].

Another member of this family, TGF- α , is a constant component of human tear fluid [132]. *In vitro* studies demonstrate that TGF- α , similar to EGF and HB-EGF, has the ability to increase corneal epithelial migration, and proliferation, and inhibit the expression of the differentiation-related marker keratin K3 [136]. TGF- α is also involved in the progress of eyelid closure, and acts synergistically with HB-EGF for leading edge extension in epithelial sheet migration during eyelid closure [81]. Interestingly, corneal wound closure after alkali burns in TGF- α -deficient mice was not impaired, indicating that it may be dispensable in wound healing *in vivo* [75,77].

Recent studies from several laboratories including ours have shown that HB-EGF is the endogenous ligand for wound-induced EGFR activation and is essential for epithelial wound closure [6,9,142]. HB-EGF is synthesized as a type-1 transmembrane protein that can be shed enzymatically to release a soluble 14–20 kDa growth factor; a process termed ectodomain shedding [26,28,102]. While the transmembrane form of HB-EGF acts in a juxtacrine manner to signal neighboring cells [36], the soluble form of HB-EGF is a potent mitogen and chemo-attractant for many cell types, including keratinocytes and epithelial cells [47,103]. In addition to the up-regulation *in vivo* at mRNA levels in the cornea,

elevated release of HB-EGF was reported in the cultured human CECs [9]. Analysis of HB-EGF-null mice has shown that HB-EGF is a crucial factor for proper heart development and function [49], for skin wound healing [6], and for eyelid development [81]. In cell specific knockout study, HB-EGF was shown to be involved in epithelialization in skin wound healing *in vivo* and to function by accelerating keratinocyte migration, rather than proliferation [117]. Compared to TGF- α and EGF, two unique properties of HB-EGF, heparin-binding which may increase its retention at the injured ocular surface and binding to erbB4 which plays a role in the generation of protrusions and directing cell migration [112], suggest HB-EGF may be a more suitable therapeutic to treat defects in epithelial wound healing.

Epiregulin is another member of the EGF family that was found to be expressed at mRNA levels in cultured human CECs and enhance CEC proliferation *in vitro* [83]. It is interesting to note that epiregulin was strongly detected in the limbal, but not central corneal, epithelial basal cells in mice, suggesting a role of epiregulin in maintaining the proliferative capacity of limbal basal cells [83,152]. Its auto-induction and cross-induction with other EGF family members suggest that it may act in concert with other growth factors in corneal homeostasis [83].

3. Keratinocyte growth factor (KGF)

Keratinocyte growth factor (KGF), a 28 kDa polypeptide, is a member of the fibroblast growth factor (FGF) family (also known as FGF-7) [110]. KGF is produced by cells of mesenchymal origin and is a potent mitogen for epithelial cells, which express a subset of FGF receptor isoforms (the FGFR2b isoforms) [22,110].

Messenger RNA coding for KGF was detected in human corneal stromal fibroblasts and endothelial cells, but not or at very low levels in epithelial cells [120,140]. Conversely, KGF receptor mRNA was detected in corneal epithelial cells, but not keratocytes [120], indicating that KGF may be produced by stromal cells and act on epithelial cells in a paracrine manner in the cornea. The quantity of KGF and KGF receptor transcripts was highest in limbal fibroblasts and epithelial cells, respectively [138], suggesting it may preferentially modulate stem cell functions. KGF enhances the growth and proliferation of cultured corneal epithelial cells, but does not significantly affect motility [120,136,138]. There have been conflicting reports on the effects of KGF on epithelial differentiation and keratocytes proliferation [13,120,136,140].

Following corneal epithelial wounding, KGF mRNAs in keratocytes and lacrimal gland, and KGF receptor mRNA in epithelium were markedly up-regulated [137,139]. Topical application of KGF accelerated corneal epithelial wound healing in an organ culture model [14] and *in vivo* by increasing cell proliferation in the limbal epithelium of the regenerating cornea [119]. KGF protects human corneal epithelial cells from hypoxia-induced disruption of barrier function [125]. It activates Ras-MAPK and PI3K/p70 S6 pathways [14,46], but does not activate the Jak-STAT cascade in corneal epithelial cells [46,71].

4. Hepatocyte growth factor (HGF)

HGF, or scatter factor, consists of a 69 kDa α -chain and a 34 kDa β -chain [93] and is mainly produced by mesenchymal cells [109]. In addition to inducing scattering of colonies of cultured epithelial cells and promoting hepatocyte growth, HGF carries out multiple functions including facilitating the growth, motility, and morpho-genesis of various types of cells [33]. HGF functions are mediated by stimulating the tyrosine activity of its high-affinity receptor, c-Met, a proto-oncogene product expressed in epithelial cells [8,94].

Similar to KGF, HGF is believed to be produced mainly by fibroblasts, and acts on the epithelium in a paracrine manner in the cornea [138]. Contrary to KGF, the expression of HGF and its receptor is higher in central cornea than in the limbus [69], indicative of a regional specificity of these two growth factors.

HGF facilitates corneal epithelial cell migration [17,79], proliferation [138,145] and inhibits apoptosis [57,145]. The effects of HGF on keratocytes proliferation are inconclusive [13,138]. Following epithelial scrape wounds, HGF mRNA in keratocytes [137] and lacrimal gland [70,139], and the expression of HGF receptor mRNA in the corneal epithelium were markedly up-regulated [137]. Although Chandrasekher et al. reported that HGF promoted epithelial wound closure in a corneal organ culture model [14], studies by Carrington et al. demonstrated delayed epithelial coverage in the presence of HGF [13]. *In vivo* study is needed to elucidate the role of HGF in corneal epithelial wound healing.

HGF activates Ras-MAPK pathways in human corneal epithelial cells via the receptor-Grb2/Sos complex to the Ras pathway or through protein kinase C [71]. PI3K/AKT and p70 S6K are also important transducers for HGF signaling [14]. More recently, HGF has been shown to induce cell motility through transactivating EGFR [122].

5. Insulin-like growth factor-I (IGF-I) and insulin

IGF-I is a multifunctional regulatory peptide that shares structural homology with proinsulin [101]. IGF-I, via binding to IGF-I receptors, regulates cell proliferation, differentiation, and survival [133]. IGF-I and its receptors are expressed by both epithelial cells and fibroblasts in human corneas [68].

IGF-I has been shown to induce cell migration through activation of the PI3K/AKT pathway [66,92], enhance proliferation, and inhibit apoptosis in human corneal epithelial cells [145]. IGF-I stimulates DNA synthesis [48] and increases chemotaxis in corneal fibroblasts [1], but does not affect keratocytes migration [2].

Although the administration of IGF-I alone did not affect corneal epithelial wound healing *ex vivo* or *in vivo* [87,96], the combination of substance P (SP) and IGF-I has been shown to synergistically enhance corneal epithelial wound closure in organ culture and *in vivo* [87,96], especially in diabetic rats [88] and in a rat model of neurotrophic keratopathy [86,89]. In addition, the combination of SP and IGF-I increased activation of FAK and paxillin [90], and up-regulated integrin $\alpha 5$ expression in CECs [91]. Interestingly, IGF, but not EGF or FGF, was found to be the mediator released from CECs to up-regulate the expression of connexin43 in corneal fibroblasts, suggesting that CECs are important for the maintenance of gap junction-mediated communication in corneal fibroblasts [65].

Insulin, a key regulator of metabolic process, is closely related to IGF and implicated in wound repair. Insulin is present in human tear film, and its receptors have been detected in corneal epithelial, keratocytes, and conjunctival cells [84,108]. *In vitro*, insulin promotes cell proliferation, inhibits apoptosis [145], and facilitates wound closure through the activation of ERK and PI3K in CECs [116]. Moreover, its wound healing promoting property was reported to be mediated via EGFR transactivation [76]. In cultured keratocytes, insulin promotes cell proliferation, maintains their phenotype, and prevents proteoglycan degradation [84]. Importantly, both systematic [150] and topical [149] application of insulin was found to ameliorate impaired corneal re-epithelialization in diabetic rats.

6. Transforming growth factor- β (TGF- β)

The TGF- β family consists of three members, TGF- β 1, TGF- β 2, and TGF- β 3 in mammals [62]. TGF- β s are secreted with a dimeric latency-associated peptide (LAP) in an inactive form called small latent complex (SLC), and dissociation from LAP releases the approximately 25 kDa mature polypeptides [63]. Latent TGF- β binding proteins (LTBPs) are a family of fibrillin-like molecules that are covalently linked to SLC. In addition to acting as matrix components, LTBPs regulate TGF- β bioavailability and activity by facilitating latent TGF- β secretion, mediating latent TGF- β targeting to the ECM and regulating latent TGF- β activation [106,111,128]. TGF- β isoforms regulate multiple biological processes including cell proliferation, extracellular matrix synthesis, angiogenesis, immune response, apoptosis, and differentiation [107].

TGF- β 1 and - β 2 have been localized in corneal epithelium and stroma, and tear fluid with TGF- β 2 being expressed at higher levels [95]. Although TGF- β 3 mRNA was detected in rat corneas after excimer laser photorefractive keratectomy (PRK), no immunoreactivity of TGF- β 3 was detected in the anterior segment of the human eye [99]. The TGF- β receptors RI and RII are located in epithelial, stromal, and endothelial layers of the cornea. The nonsignaling TGF- β RIII receptor has been located on both the epithelium and endothelium, but appears to be absent in keratocytes *in vivo* [55].

While TGF- β 1 and TGF- β 2 inhibit CEC proliferation [82,98,145], contradictory effects of TGF- β on keratocytes have been reported. Kay et al. and Andresen et al. reported that TGF- β significantly stimulates corneal stromal fibroblast proliferation [2,60], while Pancholi et al. showed a decrease in keratocyte proliferation by TGF- β 1 [98]. TGF- β was found to stimulate cell chemotactic migration in corneal epithelial, fibroblast, and endothelial cells in Boyden chambers [32], but it strongly inhibited keratocyte migration in collagen gel [2]. In addition, TGF- β 1 induces the activation and myofibroblast transformation of corneal keratocytes [51]. Inhibition of TGF- β reduces corneal fibrosis and stromal haze after PRK *in vivo* [52,85,126]. It is worth noting that connective tissue growth factor (CTGF) is up-regulated by TGF- β in corneal fibroblasts and may play an important role in TGF- β -induced myofibroblast differentiation [24,25], and collagen synthesis by fibroblasts and scar formation [4]. Similarly, TGF- β -induced keratocyte proliferation and myofibroblast differentiation are believed to be through the activation of platelet-derived growth factor (PDGF) autocrine loop [53,54,59].

In an organ cultural corneal wound healing setting, TGF- β 1 delayed re-epithelialization, increased keratocyte proliferation and promoted myofibroblast differentiation, while TGF- β 2 and TGF- β 3 had little effect on re-epithelialization [12]. In an *in vivo* rabbit model, topical TGF- β 2 facilitated corneal epithelial wound healing [21]. The actions of TGF- β during corneal epithelial wound healing have to be considered in the context of other growth factors. For examples, TGF- β has been shown to antagonize EGF-induced CEC proliferation, adhesion, and migration [82] and both TGF- β 1 and - β 2 inhibited corneal epithelial cell proliferation promoted by KGF and HGF, and weakly inhibited cell proliferation promoted by EGF [38], and TGF- β 1 was found to enhance the growth promoting effect of EGF in the keratocytes [37].

7. Epithelial–stromal interaction during corneal epithelial injury

The cornea serves an excellent organ for studying epithelial–stromal interaction, since these two tissues are connected both anatomically and functionally without few confounding factors. Due to the limited scope of the current review, we will briefly discuss the interaction and network of growth factors between the epithelium and stroma following an epithelial wound (Fig. 1).

As mentioned previously, HGF and KGF proteins are mainly expressed and highly up-regulated following epithelial injury in keratocytes, while their respective receptors are expressed highest in the epithelium. Therefore, it is believed that both growth factors are released by the stroma to regulate corneal epithelial cell differentiation, proliferation, and motility after injury [136]. However, while the quantity of KGF and KGF receptor transcripts was highest in limbal fibroblasts and epithelial cells, respectively [68], the expression of HGF and its receptor is higher in central cornea [69], suggesting a regional specificity of these two growth factors.

On the other direction, epithelium also releases factors to influence keratocyte behaviors. For instance, interleukin (IL)-1 is highly expressed in the epithelium, while little is detected in the stroma [135,140]. Keratocytes express IL-1 receptor and undergo apoptosis in response to IL-1, a mechanism hypothesized to be responsible for keratocyte death after epithelial injury [134]. Similarly, PDGF is expressed by corneal epithelial cells and modulates proliferation, migration, and differentiation of keratocytes, which express PDGF receptors [1,18,58]. Another interesting phenomenon is that IGF seems to be the mediator released by the epithelium to maintain gap junction-mediated communication in corneal fibroblasts [65].

8. EGFR transactivation, growth factor cross-talk and the concept of “alarmins”

More recently, using a variety of molecular reagents, our group and others have shown EGFR is a central mediator that converges multiple extracellular signals generated in response to cell injury to intracellular signaling pathways, particularly ERK and PI3K, and regulates corneal epithelial wound healing [6,7,9,142,145] (Fig. 2). Wounding caused rapid activation of EGFR and erbB2 through proteolytic release of transmembrane HB-EGF by ectodomain shedding [6,7,9,142,146] (for review, see [5,35]). Blocking EGFR kinase with chorological reagents such as AG1478 or neutralizing antibodies inhibits wound-induced EGFR phosphorylation and blocks the healing process including cell migration and proliferation *in vitro* and *ex vivo* (corneal organ culture). Studies also demonstrated that two major EGFR-mediated signaling pathways, ERK and PI3K/AKT, are essential for transducing EGFR signaling to cellular activities including cell migration, adhesion, proliferation, and cytoskeletal rearrangement [147,148], and are required for wound healing [141].

Several non-EGF family growth factors known to stimulate corneal epithelial wound healing including insulin [76], IGF (Yu and Yin, unpublished results), and HGF [122] are also shown to activate ERK and PI3K pathways in CECs. Using the inhibitors and neutralizing antibodies to HB-EGF and EGFR, these studies have shown that HB-EGF ectodomain shedding and EGFR transactivation, contribute at least in part, to the activation of ERK and PI3K pathways. We propose that although these non-EGFR ligands can directly elicit ERK and PI3K signaling pathways, EGFR transactivation may enhance intracellular signaling by increasing the intensity or the duration of these receptor-mediated signals, leading to synergistic effects on corneal epithelial cells.

In addition to growth factors, a multitude of chemical signals is produced when a wound occurs [31]. Injury and its associated tissue damage would result in the release of cellular proteins that, through receptors on the surface of surrounding cells, provoke a very complex response intended to close, and eventually heal, the wound [31]. Recently, a concept of “alarmins” was proposed to characterize these proteins including high mobility group box 1 and heat shock proteins [3]. Antimicrobial peptides (AMPs), including defensins, cathelicidin, eosinophil-derived neurotoxin, are another group of alarmins that are induced

by injury in cells surrounding the injured site [123,144]. AMPs possess broad-spectrum antimicrobial activity against bacteria, fungi, and enveloped viruses. Antimicrobial peptides also act as multifunctional immune effectors by stimulating cytokine and chemokine production, angiogenesis, and wound healing [56,151]. In the cornea, LL-37 has been shown to kill *Pseudomonas aeruginosa*, to induce cytokine and chemokine expression, and to enhance epithelial proliferation and in vitro wound healing [30,40,41]. Importantly, the chemotactic and healing promoting activities of LL-37 are mediated through G-protein-coupled receptor (GPCR) which in turn transactivates EGFR [11,40,129].

While cellular proteins are recognized as alarmins, we propose that several non-protein components, adenosine nucleotides, lysophosphatidic acid (LPA), and lipid autacoids, released from injured cells, may also function as alarmins to alert cells of potential further damage such as infection when a wound occurs.

Adenosine triphosphate (ATP) and other nucleotides (ADP, UTP and UDP) function as extracellular signaling molecules, like those released by neuronal cells as a neurotransmitter in the central and peripheral nervous systems [61]. Several purinoceptors have been found in corneal epithelial cells and inhibition of these receptors attenuated epithelial wound healing in vitro [64]. Recently, we and others showed that extracellular ATP released from the injured cells can reach high enough concentration to activate P2Y receptors and that ATP-mediated P2Y activation resulted in EGFR transactivation and acceleration of epithelial wound healing in cultured CECs and porcine corneas [9,146]. Since injury of epithelial cells is likely to cause the release of cellular ATP, the released ATP can act as a 'cell (or tissue)-damage' signal to trigger cell signaling events including Ca^{2+} waves and GPCR activation, both of which transactivate EGFR and its downstream signaling pathways [146].

LPA, a growth factor-like lipid, is an important serum component that affects cell adhesion, migration, proliferation, and survival [50,127]. LPA is also released by epithelial cells, platelets, or fibroblasts at sites of injury and inflammation [27,131]. LPA has been detected in aqueous humor and lacrimal gland fluid, and corneal injury results in a significant increase in the concentration of LPA [72]. Recently, we reported that LPA promotes corneal epithelial wound healing via transactivating EGFR [143]. Since receptors for LPA belong to the GPCR family, a cross-talk between GPCR and EGFR represents a critical event during corneal wound healing.

Acknowledgments

This work was supported by NIH/NEI grant EY010869. We thank our laboratory members Dr. Ashok Kumar and Gi Sang Yoon who contributed to discussions. We regret that not all related and important references are cited due to space limitations.

References

1. Andresen JL, Ehlers N. Chemotaxis of human keratocytes is increased by platelet-derived growth factor-BB, epidermal growth factor, transforming growth factor- α , acidic fibroblast growth factor, insulin-like growth factor-I, and transforming growth factor- β . *Curr. Eye Res* 1998;17(1): 79–87. [PubMed: 9472475]
2. Andresen JL, Ledet T, Ehlers N. Keratocyte migration and peptide growth factors: the effect of PDGF, bFGF, EGF, IGF-I, aFGF and TGF- β on human keratocyte migration in a collagen gel. *Curr. Eye Res* 1997;16(6):605–613. [PubMed: 9192171]
3. Bianchi ME. DAMPs, PAMPs and alarmins: all we need to know about danger. *J. Leukoc. Biol* 2007;81(1):1–5. [PubMed: 17032697]

4. Blalock TD, et al. Connective tissue growth factor expression and action in human corneal fibroblast cultures and rat corneas after photorefractive keratectomy. *Invest. Ophthalmol. Vis. Sci* 2003;44(5): 1879–1887. [PubMed: 12714619]
5. Blobel CP. ADAMs: key components in EGFR signalling and development. *Nat. Rev. Mol. Cell Biol* 2005;6(1):32–43. [PubMed: 15688065]
6. Block ER, et al. Wounding induces motility in sheets of corneal epithelial cells through loss of spatial constraints: role of heparin-binding epidermal growth factor-like growth factor signaling. *J. Biol. Chem* 2004;279(23):24307–24312. [PubMed: 15039441]
7. Block ER, Klarlund JK. Wounding sheets of epithelial cells activates the epidermal growth factor receptor through distinct short- and long-range mechanisms. *Mol. Biol. Cell* 2008;19(11):4909–4917. [PubMed: 18799627]
8. Bottaro DP, et al. Identification of the hepatocyte growth factor receptor as the c-met proto-oncogene product. *Science* 1991;251(4995):802–804. [PubMed: 1846706]
9. Boucher I, et al. Injury and nucleotides induce phosphorylation of epidermal growth factor receptor: MMP and HB-EGF dependent pathway. *Exp. Eye Res* 2007;85(1):130–141. [PubMed: 17490650]
10. Carpenter, G.; Wahl, M. The epidermal growth factor family. In: Sporn, M.; AB, R., editors. *Peptides, Growth Factors and their Receptors I*. Springer Verlag; New York: 1991. p. 69-171.
11. Carretero M, et al. In vitro and in vivo wound healing-promoting activities of human cathelicidin LL-37. *J. Invest. Dermatol* 2008;128(1):223–236. [PubMed: 17805349]
12. Carrington LM, et al. Differential regulation of key stages in early corneal wound healing by TGF-beta isoforms and their inhibitors. *Invest. Ophthalmol. Vis. Sci* 2006;47(5):1886–1894. [PubMed: 16638995]
13. Carrington LM, Boulton M. Hepatocyte growth factor and keratinocyte growth factor regulation of epithelial and stromal corneal wound healing. *J. Cataract Refract. Surg* 2005;31(2):412–423. [PubMed: 15767167]
14. Chandrasekhar G, Kakazu AH, Bazan HE. HGF- and KGF-induced activation of PI-3K/p70 s6 kinase pathway in corneal epithelial cells: its relevance in wound healing. *Exp. Eye Res* 2001;73(2):191–202. [PubMed: 11446769]
15. Chaturvedi P, Singh AP, Batra SK. Structure, evolution, and biology of the MUC4 mucin. *FASEB J* 2008;22(4):966–981. [PubMed: 18024835]
16. Cohen, S. Isolation and Biological Effects of an Epidermal Growth-stimulating Protein. Vol. 13. National Cancer Institute Monograph; Bethesda, MD: 1964. p. 13-27.
17. Daniels JT, et al. Human corneal epithelial cells require MMP-1 for HGF-mediated migration on collagen I. *Invest. Ophthalmol. Vis. Sci* 2003;44(3):1048–1055. [PubMed: 12601028]
18. Denk PO, Knorr M. The in vitro effect of platelet-derived growth factor isoforms on the proliferation of bovine corneal stromal fibroblasts depends on cell density. *Graefes Arch. Clin. Exp. Ophthalmol* 1997;235(8):530–534. [PubMed: 9285224]
19. Derynck R, et al. Human transforming growth factor- β : precursor structure and expression in *E. coli*. *Cell* 1984;38:287–297. [PubMed: 6088071]
20. Elenius K, et al. A novel juxtamembrane domain isoform of HER4/ErbB4. Isoform-specific tissue distribution and differential processing in response to phorbol ester. *J. Biol. Chem* 1997;272(42): 26761–26768. [PubMed: 9334263]
21. Er H, Uzmez E. Effects of transforming growth factor-beta 2, interleukin 6 and fibronectin on corneal epithelial wound healing. *Eur. J. Ophthalmol* 1998;8(4):224–229. [PubMed: 9891893]
22. Finch PW, et al. Human KGF is FGF-related with properties of a paracrine effector of epithelial cell growth. *Science* 1989;245(4919):752–755. [PubMed: 2475908]
23. Foerster CG, Cursiefen C, Kruse FE. Persisting corneal erosion under cetuximab (Erbix) treatment (epidermal growth factor receptor antibody). *Cornea* 2008;27(5):612–614. [PubMed: 18520515]
24. Folger PA, et al. Transforming growth factor-beta-stimulated connective tissue growth factor expression during corneal myofibroblast differentiation. *Invest. Ophthalmol. Vis. Sci* 2001;42(11): 2534–2541. [PubMed: 11581194]

25. Garrett Q, et al. Involvement of CTGF in TGF-beta1-stimulation of myofibroblast differentiation and collagen matrix contraction in the presence of mechanical stress. *Invest. Ophthalmol. Vis. Sci* 2004;45(4):1109–1116. [PubMed: 15037576]
26. Gechtman Z, et al. The shedding of membrane-anchored heparin-binding epidermal-like growth factor is regulated by the Raf/mitogen-activated protein kinase cascade and by cell adhesion and spreading. *J. Biol. Chem* 1999;274(40):28828–28835. [PubMed: 10497257]
27. Goetzl EJ, An S. Diversity of cellular receptors and functions for the lysophospholipid growth factors lysophosphatidic acid and sphingosine 1-phosphate. *FASEB J* 1998;12(15):1589–1598. [PubMed: 9837849]
28. Goishi K, et al. Phorbol ester induces the rapid processing of cell surface heparin-binding EGF-like growth factor: conversion from juxtacrine to paracrine growth factor activity. *Mol. Biol. Cell* 1995;6(8):967–980. [PubMed: 7579712]
29. Gonul B, et al. Effect of EGF on the corneal wound healing of alloxan diabetic mice. *Exp. Eye Res* 1992;54(4):519–524. [PubMed: 1623938]
30. Gordon YJ, et al. Human cathelicidin (LL-37), a multifunctional peptide, is expressed by ocular surface epithelia and has potent antibacterial and antiviral activity. *Curr. Eye Res* 2005;30(5):385–394. [PubMed: 16020269]
31. Gov NS. Collective cell migration patterns: follow the leader. *Proc. Natl. Acad. Sci. U.S.A* 2007;104(41):15970–15971. [PubMed: 17913874]
32. Grant MB, et al. Effects of epidermal growth factor, fibroblast growth factor, and transforming growth factor-beta on corneal cell chemotaxis. *Invest. Ophthalmol. Vis. Sci* 1992;33(12):3292–3301. [PubMed: 1428704]
33. Grierson I, et al. Hepatocyte growth factor/scatter factor in the eye. *Prog. Retin. Eye Res* 2000;19(6):779–802. [PubMed: 11029554]
34. Higashiyama S, et al. A heparin-binding growth factor secreted by macrophage-like cells that is related to EGF. *Science* 1991;251:936–939. [PubMed: 1840698]
35. Higashiyama S, et al. Membrane-anchored growth factors, the epidermal growth factor family: beyond receptor ligands. *Cancer Sci* 2008;99(2):214–220. [PubMed: 18271917]
36. Higashiyama S, et al. The membrane protein CD9/DRAP 27 potentiates the juxtacrine growth factor activity of the membrane-anchored heparin-binding EGF-like growth factor. *J. Cell Biol* 1995;128(5):929–938. [PubMed: 7876316]
37. Hongo M, et al. Distribution of epidermal growth factor (EGF) receptors in rabbit corneal epithelial cells, keratocytes and endothelial cells, and the changes induced by transforming growth factor-beta 1. *Exp. Eye Res* 1992;54(1):9–16. [PubMed: 1541345]
38. Honma Y, et al. Effect of transforming growth factor-beta1 and -beta2 on in vitro rabbit corneal epithelial cell proliferation promoted by epidermal growth factor, keratinocyte growth factor, or hepatocyte growth factor. *Exp. Eye Res* 1997;65(3):391–396. [PubMed: 9299175]
39. Hori K, et al. Controlled-release of epidermal growth factor from cationized gelatin hydrogel enhances corneal epithelial wound healing. *J. Control. Release* 2007;118(2):169–176. [PubMed: 17289206]
40. Huang LC, et al. Multifunctional roles of human cathelicidin (LL-37) at the ocular surface. *Invest. Ophthalmol. Vis. Sci* 2006;47(6):2369–2380. [PubMed: 16723446]
41. Huang LC, et al. Ocular surface expression and in vitro activity of antimicrobial peptides. *Curr. Eye Res* 2007;32(7–8):595–609. [PubMed: 17852183]
42. Hynes NE, et al. The ErbB receptor tyrosine family as signal integrators. *Endocr. Relat. Cancer* 2001;8(3):151–159. [PubMed: 11566606]
43. Hynes NE, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. *Nat. Rev. Cancer* 2005;5(5):341–354. [PubMed: 15864276]
44. Hynes NE, Stern DF. The biology of erbB-2/neu/HER-2 and its role in cancer. *Biochim. Biophys. Acta* 1994;1198(2–3):165–184. [PubMed: 7819273]
45. Imanishi J, et al. Growth factors: importance in wound healing and maintenance of transparency of the cornea. *Prog. Retin. Eye Res* 2000;19(1):113–129. [PubMed: 10614683]
46. Imayasu M, Shimada S. Phosphorylation of MAP kinase in corneal epithelial cells during wound healing. *Curr. Eye Res* 2003;27(3):133–141. [PubMed: 14562178]

47. Iwamoto R, Mekada E. Heparin-binding EGF-like growth factor: a juxtacrine growth factor. *Cytokine Growth Factor Rev* 2000;11(4):335–344. [PubMed: 10959080]
48. Izumi K, et al. Involvement of insulin-like growth factor-I and insulin-like growth factor binding protein-3 in corneal fibroblasts during corneal wound healing. *Invest. Ophthalmol. Vis. Sci* 2006;47(2):591–598. [PubMed: 16431955]
49. Jackson LF, et al. Defective valvulogenesis in HB-EGF and TACE-null mice is associated with aberrant BMP signaling. *EMBO J* 2003;22(11):2704–2716. [PubMed: 12773386]
50. Jalink K, Hordijk PL, Moolenaar WH. Growth factor-like effects of lysophosphatidic acid, a novel lipid mediator. *Biochim. Biophys. Acta (BBA)—Rev. Cancer* 1994;1198(2–3):185–196.
51. Jester JV, et al. Induction of alpha-smooth muscle actin expression and myofibroblast transformation in cultured corneal keratocytes. *Cornea* 1996;15(5):505–516. [PubMed: 8862928]
52. Jester JV, et al. Inhibition of corneal fibrosis by topical application of blocking antibodies to TGF beta in the rabbit. *Cornea* 1997;16(2):177–187. [PubMed: 9071531]
53. Jester JV, et al. TGFbeta induced myofibroblast differentiation of rabbit keratocytes requires synergistic TGFbeta, PDGF and integrin signaling. *Exp. Eye Res* 2002;75(6):645–657. [PubMed: 12470966]
54. Jester JV, et al. Myofibroblast differentiation of normal human keratocytes and hTERT, extended-life human corneal fibroblasts. *Invest. Ophthalmol. Vis. Sci* 2003;44(5):1850–1858. [PubMed: 12714615]
55. Joyce N, Zieske J. Transforming growth factor-beta receptor expression in human cornea. *Invest. Ophthalmol. Vis. Sci* 1997;38:1922–1928. [PubMed: 9331255]
56. Kai-Larsen Y, Agerberth B. The role of the multifunctional peptide LL-37 in host defense. *Front. Biosci* 2008;13:3760–3767. [PubMed: 18508470]
57. Kakazu A, Chandrasekhar G, Bazan HE. HGF protects corneal epithelial cells from apoptosis by the PI-3K/Akt-1/Bad- but not the ERK1/2-mediated signaling pathway. *Invest. Ophthalmol. Vis. Sci* 2004;45(10):3485–3492. [PubMed: 15452053]
58. Kamiyama K, et al. Effects of PDGF on the migration of rabbit corneal fibroblasts and epithelial cells. *Cornea* 1998;17(3):315–325. [PubMed: 9603389]
59. Kaur H, et al. Corneal stroma PDGF blockade and myofibroblast development. *Exp. Eye Res* 2009;88(5):960–965. [PubMed: 19133260]
60. Kay EP, et al. TGF-beta s stimulate cell proliferation via an autocrine production of FGF-2 in corneal stromal fibroblasts. *Curr. Eye Res* 1998;17(3):286–293. [PubMed: 9543637]
61. Khakh BS. Molecular physiology of P2X receptors and ATP signalling at synapses. *Nat. Rev. Neurosci* 2001;2(3):165–174. [PubMed: 11256077]
62. Kinoshita S, et al. Characteristics of the human ocular surface epithelium. *Prog. Retin. Eye Res* 2001;20(5):639–673. [PubMed: 11470454]
63. Klenkler B, Sheardown H. Growth factors in the anterior segment: role in tissue maintenance, wound healing and ocular pathology. *Exp. Eye Res* 2004;79(5):677–688. [PubMed: 15500826]
64. Klepeis VE, et al. P2Y receptors play a critical role in epithelial cell communication and migration. *J. Cell Biochem* 2004;93(6):1115–1133. [PubMed: 15449317]
65. Ko JA, et al. Up-regulation of connexin43 expression in corneal fibroblasts by corneal epithelial cells. *Invest. Ophthalmol. Vis. Sci.* 2008
66. Lee HK, et al. Insulin-like growth factor-1 induces migration and expression of laminin-5 in cultured human corneal epithelial cells. *Invest. Ophthalmol. Vis. Sci* 2006;47(3):873–882. [PubMed: 16505019]
68. Li DQ, Tseng SC. Three patterns of cytokine expression potentially involved in epithelial-fibroblast interactions of human ocular surface. *J. Cell. Physiol* 1995;163(1):61–79. [PubMed: 7896901]
69. Li DQ, Tseng SC. Differential regulation of keratinocyte growth factor and hepatocyte growth factor/scatter factor by different cytokines in human corneal and limbal fibroblasts. *J. Cell. Physiol* 1997;172(3):361–372. [PubMed: 9284956]
70. Li Q, et al. Hepatocyte growth factor and hepatocyte growth factor receptor in the lacrimal gland, tears, and cornea. *Invest. Ophthalmol. Vis. Sci* 1996;37:727–739. [PubMed: 8603858]

71. Liang Q, et al. Signaling by HGF and KGF in corneal epithelial cells: Ras/MAP kinase and Jak-STAT pathways. *Invest. Ophthalmol. Vis. Sci* 1998;39(8):1329–1338. [PubMed: 9660480]
72. Liliom K, et al. Growth factor-like phospholipids generated after corneal injury. *Am. J. Physiol* 1998;274(4, Pt 1):C1065–C1074. [PubMed: 9575804]
73. Liu Z, et al. Expression of the receptor tyrosine kinases, epidermal growth factor receptor, ErbB2, and ErbB3, in human ocular surface epithelia. *Cornea* 2001;20(1):81–85. [PubMed: 11189010]
74. Lu L, Reinach PS, Kao WW. Corneal epithelial wound healing. *Exp. Biol. Med* 2001;226(7):653–664.
75. Luetke NC, et al. TGF alpha deficiency results in hair follicle and eye abnormalities in targeted and waved-1 mice. *Cell* 1993;73(2):263–278. [PubMed: 8477445]
76. Lyu J, Lee KS, Joo CK. Transactivation of EGFR mediates insulin-stimulated ERK1/2 activation and enhanced cell migration in human corneal epithelial cells. *Mol. Vis* 2006;12:1403–1410. [PubMed: 17149366]
77. Mann GB, et al. Mice with a null mutation of the TGF alpha gene have abnormal skin architecture, wavy hair, and curly whiskers and often develop corneal inflammation. *Cell* 1993;73(2):249–261. [PubMed: 8477444]
78. Martin P. Wound healing—aiming for perfect skin regeneration. *Science* 1997;276(5309):75–81. [PubMed: 9082989]
79. McBain VA, Forrester JV, McCaig CD. HGF, MAPK, and a small physiological electric field interact during corneal epithelial cell migration. *Invest. Ophthalmol. Vis. Sci* 2003;44(2):540–547. [PubMed: 12556381]
80. Miettinen PJ, et al. Epithelial immaturity and multiorgan failure in mice lacking epidermal growth factor receptor. *Nature* 1995;376(6538):337–341. [PubMed: 7630400]
81. Mine N, Iwamoto R, Mekada E. HB-EGF promotes epithelial cell migration in eyelid development. *Development* 2005;132(19):4317–4326. [PubMed: 16141218]
82. Mishima H, et al. Transforming growth factor-beta modulates effects of epidermal growth factor on corneal epithelial cells. *Curr. Eye Res* 1992;11:691–696. [PubMed: 1521469]
83. Morita S, et al. Human corneal epithelial cell proliferation by epiregulin and its cross-induction by other EGF family members. *Mol. Vis* 2007;13:2119–2128. [PubMed: 18079685]
84. Musselmann K, et al. Maintenance of the keratocyte phenotype during cell proliferation stimulated by insulin. *J. Biol. Chem* 2005;280(38):32634–32639. [PubMed: 16169858]
85. Myers JS, et al. Effect of transforming growth factor beta 1 on stromal haze following excimer laser photorefractive keratectomy in rabbits. *J. Refract. Surg* 1997;13(4):356–361. [PubMed: 9268935]
86. Nagano T, et al. Effects of substance P and IGF-1 in corneal epithelial barrier function and wound healing in a rat model of neurotrophic keratopathy. *Invest. Ophthalmol. Vis. Sci* 2003;44(9):3810–3815. [PubMed: 12939296]
87. Nakamura M, et al. Combined effects of substance P and insulin-like growth factor-1 on corneal epithelial wound closure of rabbit in vivo. *Curr. Eye Res* 1997;16(3):275–278. [PubMed: 9088746]
88. Nakamura M, et al. Promotion of corneal epithelial wound healing in diabetic rats by the combination of a substance P-derived peptide (FGLM-NH2) and insulin-like growth factor-1. *Diabetologia* 2003;46(6):839–842. [PubMed: 12764579]
89. Nakamura M, et al. Restoration of corneal epithelial barrier function and wound healing by substance P and IGF-1 in rats with capsaicin-induced neurotrophic keratopathy. *Invest. Ophthalmol. Vis. Sci* 2003;44(7):2937–2940. [PubMed: 12824234]
90. Nakamura M, et al. Up-regulation of phosphorylation of focal adhesion kinase and paxillin by combination of substance P and IGF-1 in SV-40 transformed human corneal epithelial cells. *Biochem. Biophys. Res. Commun* 1998;242(1):16–20. [PubMed: 9439602]
91. Nakamura M, Chikama T, Nishida T. Up-regulation of integrin alpha 5 expression by combination of substance P and insulin-like growth factor-1 in rabbit corneal epithelial cells. *Biochem. Biophys. Res. Commun* 1998;246(3):777–782. [PubMed: 9618288]
92. Nakamura M, Chikama TI, Nishida T. Characterization of insulin-like growth factor-1 receptors in rabbit corneal epithelial cells. *Exp. Eye Res* 2000;70(2):199–204. [PubMed: 10655145]

93. Nakamura T, et al. Molecular cloning and expression of human hepatocyte growth factor. *Nature* 1989;342(6248):440–443. [PubMed: 2531289]
94. Naldini L, et al. Hepatocyte growth factor (HGF) stimulates the tyrosine kinase activity of the receptor encoded by the proto-oncogene c-MET. *Oncogene* 1991;6:501–504. [PubMed: 1827664]
95. Nishida K, et al. Immunohistochemical localization of transforming growth factor-beta 1, -beta 2, and -beta 3 latency-associated peptide in human cornea. *Invest. Ophthalmol. Vis. Sci* 1994;35:3289–3294. [PubMed: 8045718]
96. Nishida T, et al. Synergistic effects of substance P with insulin-like growth factor-1 on epithelial migration of the cornea. *J. Cell. Physiol* 1996;169(1):159–166. [PubMed: 8841432]
97. Olayioye M, et al. The ErbB signaling network: receptor heterodimerization in development and cancer. *EMBO J* 2000;19:3159–3167. [PubMed: 10880430]
98. Pancholi S, et al. The effects of growth factors and conditioned media on the proliferation of human corneal epithelial cells and keratocytes. *Graefes Arch. Clin. Exp. Ophthalmol* 1998;236(1):1–8. [PubMed: 9457509]
99. Pasquale L, et al. Immunolocalization of TGF-beta 1, TGF-beta 2, and TGF-beta 3 in the anterior segment of the human eye. *Invest. Ophthalmol. Vis. Sci* 1993;34:23–30. [PubMed: 8425829]
100. Pastor JC, Calonge M. Epidermal growth factor and corneal wound healing. A multicenter study. *Cornea* 1992;11(4):311–314. [PubMed: 1424650]
101. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. *Nat. Rev. Cancer* 2008;8(12):915–928. [PubMed: 19029956]
102. Raab G, et al. Biosynthesis and processing by phorbol ester of the cells surface-associated precursor form of heparin-binding EGF-like growth factor. *Biochem. Biophys. Res. Commun* 1994;204(2):592–597. [PubMed: 7980519]
103. Raab G, Klagsbrun M. Heparin-binding EGF-like growth factor. *Biochim. Biophys. Acta* 1997;1333(3):F179–F199. [PubMed: 9426203]
104. Rajan MS, et al. In vitro human corneal model to investigate stromal epithelial interactions following refractive surgery. *J. Cataract Refract. Surg* 2005;31(9):1789–1801. [PubMed: 16246786]
106. Rifkin DB. Latent transforming growth factor-beta (TGF-beta) binding proteins: orchestrators of TGF-beta availability. *J. Biol. Chem* 2005;280(9):7409–7412. [PubMed: 15611103]
107. Roberts AB. The ever-increasing complexity of TGF-beta signaling. *Cytokine Growth Factor Rev* 2002;13(1):3–5. [PubMed: 11750874]
108. Rocha EM, et al. Identification of insulin in the tear film and insulin receptor and IGF-1 receptor on the human ocular surface. *Invest. Ophthalmol. Vis. Sci* 2002;43(4):963–967. [PubMed: 11923235]
109. Rosen EM, Nigam SK, Goldberg ID. Scatter factor and the c-met receptor: a paradigm for mesenchymal/epithelial interaction. *J. Cell Biol* 1994;127(6, Pt 2):1783–1787. [PubMed: 7806559]
110. Rubin JS, et al. Purification and characterization of a newly identified growth factor specific for epithelial cells. *Proc. Natl. Acad. Sci. U.S.A* 1989;86(3):802–806. [PubMed: 2915979]
111. Saharinen J, et al. Latent transforming growth factor-beta binding proteins (LTBPs)—structural extracellular matrix proteins for targeting TGF-beta action. *Cytokine Growth Factor Rev* 1999;10(2):99–117. [PubMed: 10743502]
112. Sakakibara A, Horwitz AF. Mechanism of polarized protrusion formation on neuronal precursors migrating in the developing chicken cerebellum. *J. Cell. Sci* 2006;119(Pt 17):3583–3592. [PubMed: 16912080]
113. Scardovi C, De FG, Gazzaniga A. Epidermal growth factor in the topical treatment of traumatic corneal ulcers. *Ophthalmologica* 1993;206(3):119–124. [PubMed: 8272333]
114. Schultz G, Rotatori DS, Clark W. EGF and TGF-alpha in wound healing and repair. *J. Cell. Biochem* 1991;45(4):346–352. [PubMed: 2045428]
115. Shah NT, et al. Practical management of patients with non-small-cell lung cancer treated with gefitinib. *J. Clin. Oncol* 2005;23(1):165–174. [PubMed: 15557594]

116. Shanley LJ, et al. Insulin, not leptin, promotes in vitro cell migration to heal monolayer wounds in human corneal epithelium. *Invest. Ophthalmol. Vis. Sci* 2004;45(4):1088–1094. [PubMed: 15037573]
117. Shirakata Y, et al. Heparin-binding EGF-like growth factor accelerates keratinocyte migration and skin wound healing. *J. Cell Sci* 2005;118(Pt 11):2363–2370. [PubMed: 15923649]
118. Sibilio M, et al. The epidermal growth factor receptor: from development to tumorigenesis. *Differentiation* 2007;75(9):770–787. [PubMed: 17999740]
119. Sotozono C, et al. Keratinocyte growth factor accelerates corneal epithelial wound healing in vivo. *Invest. Ophthalmol. Vis. Sci* 1995;36(8):1524–1529. [PubMed: 7601632]
120. Sotozono C, et al. Paracrine role of keratinocyte growth factor in rabbit corneal epithelial cell growth. *Exp. Eye Res* 1994;59(4):385–391. [PubMed: 7859813]
121. Specenier P, Koppen C, Vermorken JB. Diffuse punctate keratitis in a patient treated with cetuximab as monotherapy. *Ann. Oncol* 2007;18(5):961–962. [PubMed: 17442661]
122. Spix JK, et al. Hepatocyte growth factor induces epithelial cell motility through transactivation of the epidermal growth factor receptor. *Exp. Cell Res* 2007;313(15):3319–3325. [PubMed: 17643426]
123. Steinstraesser L, et al. Host defense peptides in wound healing. *Mol. Med* 2008;14(7–8):528–537. [PubMed: 18385817]
124. Swan JS, et al. An ErbB2-Muc4 complex in rat ocular surface epithelia. *Curr. Eye Res* 2002;24(5):397–402. [PubMed: 12434309]
125. Teranishi S, et al. Protection of human corneal epithelial cells from hypoxia-induced disruption of barrier function by keratinocyte growth factor. *Invest. Ophthalmol. Vis. Sci* 2008;49(6):2432–2437. [PubMed: 18362114]
126. Thom SB, et al. Effect of topical anti-transforming growth factor-beta on corneal stromal haze after photorefractive keratectomy in rabbits. *J. Cataract Refract. Surg* 1997;23(9):1324–1330. [PubMed: 9423903]
127. Tigyi G. Physiological responses to lysophosphatidic acid and related glycerophospholipids. *Prostaglandins Other Lipid Mediat* 2001;64(1–4):47–62. [PubMed: 11324707]
128. Todorovic V, et al. Latent TGF-beta binding proteins. *Int. J. Biochem. Cell Biol* 2005;37(1):38–41. [PubMed: 15381147]
129. Tokumaru S, et al. Induction of keratinocyte migration via transactivation of the epidermal growth factor receptor by the antimicrobial peptide LL-37. *J. Immunol* 2005;175(7):4662–4668. [PubMed: 16177113]
130. Tuli SS, et al. Immunohistochemical localization of EGF, TGF-alpha, TGF-beta, and their receptors in rat corneas during healing of excimer laser ablation. *Curr. Eye Res* 2006;31(9):709–719. [PubMed: 16966143]
131. van Leeuwen FN, et al. Lysophosphatidic acid: mitogen and motility factor. *Biochem. Soc. Trans* 2003;31(Pt 6):1209–1212. [PubMed: 14641027]
132. van Setten G, Schultz G. Transforming growth factor-alpha is a constant component of human tear fluid. *Graefes Arch. Clin. Exp. Ophthalmol* 1994;32(9):523–526. [PubMed: 7959090]
133. Werner H, Weinstein D, Bentov I. Similarities and differences between insulin and IGF-I: structures, receptors, and signalling pathways. *Arch. Physiol. Biochem* 2008;114(1):17–22. [PubMed: 18465355]
134. Wilson SE, et al. Epithelial injury induces keratocyte apoptosis: hypothesized role for the interleukin-1 system in the modulation of corneal tissue organization and wound healing. *Exp. Eye Res* 1996;62(4):325–327. [PubMed: 8795451]
135. Wilson SE, et al. The corneal wound healing response: cytokine-mediated interaction of the epithelium, stroma, and inflammatory cells. *Prog. Retin. Eye Res* 2001;20(5):625–637. [PubMed: 11470453]
136. Wilson SE, et al. Effect of epidermal growth factor, hepatocyte growth factor, and keratinocyte growth factor, on proliferation, motility and differentiation of human corneal epithelial cells. *Exp. Eye Res* 1994;59(6):665–678. [PubMed: 7698260]
137. Wilson SE, et al. Expression of HGF, KGF and EGF and receptor messenger RNAs following corneal epithelial wounding. *Exp. Eye Res* 1999;68(4):377–397. [PubMed: 10192796]

138. Wilson SE, et al. Hepatocyte growth factor, keratinocyte growth factor, their receptors, fibroblast growth factor receptor-2, and the cells of the cornea. *Invest. Ophthalmol. Vis. Sci* 1993;34(8): 2544–2561. [PubMed: 8392040]
139. Wilson SE, Liang Q, Kim WJ. Lacrimal gland HGF, KGF, and EGF mRNA levels increase after corneal epithelial wounding. *Invest. Ophthalmol. Vis. Sci* 1999;40(10):2185–2190. [PubMed: 10476782]
140. Wilson SE, Liu JJ, Mohan RR. Stromal-epithelial interactions in the cornea. *Prog. Retin. Eye Res* 1999;18(3):293–309. [PubMed: 10192515]
141. Xu KP, et al. Role of ErbB2 in corneal epithelial wound healing. *Invest. Ophthalmol. Vis. Sci* 2004;45(12):4277–4283. [PubMed: 15557433]
142. Xu KP, et al. Wound-induced HB-EGF ectodomain shedding and EGFR activation in corneal epithelial cells. *Invest. Ophthalmol. Vis. Sci* 2004;45(3):813–820. [PubMed: 14985295]
143. Xu KP, Yin J, Yu FS. Lysophosphatidic acid promoting corneal epithelial wound healing by transactivation of epidermal growth factor receptor. *Invest. Ophthalmol. Vis. Sci* 2007;48(2): 636–643. [PubMed: 17251460]
144. Yamasaki K, Gallo RL. Antimicrobial peptides in human skin disease. *Eur. J. Dermatol* 2008;18(1):11–21. [PubMed: 18086583]
145. Yanai R, et al. Correlation of proliferative and anti-apoptotic effects of HGF, insulin, IGF-1, IGF-2, and EGF in SV40-transformed human corneal epithelial cells. *Exp. Eye Res* 2006;83(1): 76–83. [PubMed: 16530761]
146. Yin J, et al. Wound-induced ATP release and EGF receptor activation in epithelial cells. *J. Cell Sci* 2007;120(Pt 5):815–825. [PubMed: 17284517]
147. Yin J, Yu FS. Rho kinases regulate corneal epithelial wound healing. *Am. J. Physiol. Cell Physiol* 2008;295(2):C378–C387. [PubMed: 18495812]
148. Yin J, Lu J, et al. Role of small GTPase Rho in regulating corneal epithelial wound healing. *Invest. Ophthalmol. Vis. Sci* 2008;49(3):900–909. [PubMed: 18326710]
149. Zagon IS, et al. Use of topical insulin to normalize corneal epithelial healing in diabetes mellitus. *Arch. Ophthalmol* 2007;125(8):1082–1088. [PubMed: 17698755]
150. Zagon IS, Sassani JW, McLaughlin PJ. Insulin treatment ameliorates impaired corneal reepithelialization in diabetic rats. *Diabetes* 2006;55(4):1141–1147. [PubMed: 16567540]
151. Zaiou M. Multifunctional antimicrobial peptides: therapeutic targets in several human diseases. *J. Mol. Med* 2007;85(4):317–329. [PubMed: 17216206]
152. Zhou M, Li XM, Lavker RM. Transcriptional profiling of enriched populations of stem cells versus transient amplifying cells. A comparison of limbal and corneal epithelial basal cells. *J. Biol. Chem* 2006;281(28):19600–19609. [PubMed: 16675456]
153. Zieske JD, et al. Activation of epidermal growth factor receptor during corneal epithelial migration. *Invest. Ophthalmol. Vis. Sci* 2000;41(6):1346–1355. [PubMed: 10798649]

Fig. 1.

A multitude of growth factors and cytokines is released following an epithelial injury in the cornea. These factors play essential roles in epithelial–stromal interaction and in the successful healing of a wound. KGF and HGF are believed to be produced by keratocytes to influence epithelial behaviors, while IL-1 and PDGF may be master mediators secreted by the epithelium to modulate stromal response to injury. Others such as the EGF family, IGF, and TGF- β regulate both epithelium and stroma, and the cross-talk among various growth factors determines the outcome of an epithelial wound.

Fig. 2.

EGFR is a central mediator that converges multiple extracellular signals generated in response to cell injury to intracellular signaling pathways, particularly ERK and PI3K, and regulates corneal epithelial wound healing. Several non-EGF family growth factors such as insulin, IGF, and HGF, are known to transactivate EGFR. Cellular components, such as ATP and LPA, released from injured cells, act as “alarmins” to initiate cell response by transactivating EGFR and to signal potential further damage to the cornea such as infection. Hence, EGFR represents a pivotal point of cell signaling accessible to a variety of stimuli in response to pathophysiological challenge in human corneas.