Communication between corneal epithelial cells and keratocytes is likely to contribute to normal maintenance, wound healing, corneal tissue organization, and the pathophysiology of corneal disease. Interactions between these cells are mediated via cytokines, growth factors, and their receptors. Other mechanisms of communication may also occur.

Hepatocyte growth factor (HGF) and keratinocyte growth factor (KGF) are classical paracrine mediators produced by the keratocytes that regulate the proliferation, motility, and differentiation of corneal epithelial cells via the HGF receptor and KGF receptor (stromal to epithelial interactions). HGF is also produced by the lacrimal gland and is a component in the tear film. After corneal wounding, however, HGF protein and HGF and KGF mRNA production is stimulated in keratocyte cells. Upregulation of HGF and KGF production in the keratocyte cells is likely mediated by the release of IL-1 from the injured epithelial cells. Thus, IL-1 serves as a molecular transducer that signals keratocytes that the epithelium has been injured and stimulates the stromal cells to increase production of HGF and KGF to modulate corneal epithelial wound healing.

Epithelial to stromal interactions are also important in the cornea. It has recently been demonstrated that the disappearance of anterior keratocytes following corneal epithelial injury is mediated via programmed cell death (apoptosis) characterized by chromatin condensation, nucleosomal fragmentation, the formation of apoptotic bodies, and DNA fragmentation. Our data suggest that IL-1, and possibly soluble Fas ligand, released from corneal epithelial cells by injury, trigger apoptosis in the keratocytes via IL-1 receptor and Fas, respectively, expressed by the stromal cells.

It is hypothesized this system is physiologically activated by infection of corneal epithelial cells by viral pathogens such as herpes simplex virus and that death of the anterior keratocytes functions to limit the extension of virus. Injury to the epithelium during refractive surgical procedures such as photorefractive keratectomy (PRK) could be perceived by the cornea as a massive viral infection of the epithelium that results in apoptosis.
of the anterior keratocytes. Keratocyte apoptosis may be the initiating event in the subsequent wound healing response and a promising site for interventions to control wound healing following refractive surgery. These observations provide a physiologic explanation for the difference that has been noted in wound healing response between surface ablation procedures (i.e., PRK) where the central corneal epithelium is injured and procedures such as LASIK in which the central corneal epithelium is maintained. This epithelial-stromal interactive system also provides a working hypothesis for the pathogenesis of ectatic diseases such as keratoconus where various abnormalities that might shift the balance between keratocyte proliferation and apoptosis could lead to a slow loss of the total number of keratocytes and, therefore, to stromal thinning.

Clinicians and scientists have long speculated regarding the importance of communications occurring between corneal epithelial and stromal cells (stromal-epithelial interactions) and the significance of these interactions in maintenance of normal corneal structure and function, pathophysiology of corneal disease, and corneal wound healing. Over the past few years specific growth factor/cytokine-receptor systems have been detected in corneal cells in vivo and in vitro and some of their functions identified. This paper will review what is currently known about these corneal modulators of stromal-epithelial interactions and some of the processes they regulate.

**Hepatocyte Growth Factor (HGF), Keratinocyte Growth Factor (KGF), and Their Receptors: Stromal-Epithelial Interactions in the Cornea**

HGF and KGF have been characterized as classical mediators of stromal-epithelial interactions that function in many tissues. HGF and KGF are heparin-binding paracrine mediators secreted by fibroblast cells to regulate the functions of epithelial cells. For example, HGF and KGF modulate proliferation and other functions in skin keratinocytes. HGF has been shown to be identical to scatter factor, a fibroblast-derived factor that disperses cohesive colonies of epithelial cells. HGF, KGF, and their receptor messenger RNAs (mRNA) have been detected in vitro and ex vivo in corneal cells. HGF and KGF mRNA are expressed in corneal stromal fibroblast and endothelial, but not epithelial, cells. HGF receptor and KGF receptor mRNAs are expressed in all three major cell types in the cornea. In addition, alternatively spliced mRNAs coding for a soluble form of the KGF receptor consisting only of the extracellular domain of the receptor and a HGF receptor that is truncated within the intracellular domain appear to be expressed in corneal epithelial cells. The functions of the alternative receptors thought to be coded from these mRNAs are currently under investigation (Liang Q, Weng J, Wilson SE, unpublished data, 1996). Presumably, they are expressed by the corneal epithelial cells to modulate the responses of the cells to the corresponding growth factors (KGF and HGF) or possibly, in the case of the alternative HGF receptor mRNA, to activate different signal transduction pathways in response to the growth factor.

Monoclonal antibodies that are useful for immunohistologic localization are available for HOF and HGF receptor. HGF receptor protein is expressed in all three major cell types of the human cornea, but at highest levels in epithelium (Fig. 1A). HGF protein is detectable in keratocytes (Fig. 1B) and endothelial, but not epithelial, cells. HGF production by keratocyte cells is markedly upregulated in response to mechanical corneal epithelial wounding (Fig. 1C). Interestingly, HGF can be detected in association with the ocular surface in the unwounded cornea. HGF is detectable in tears and is produced by the lacrimal gland. Therefore, it is likely that the HGF associated with the surface epithelial cells in the unwounded cornea is derived from the lacrimal gland, although other sources such as conjuncti-