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Peptide therapies for ocular surface disturbances based on fibronectin–integrin interactions☆

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ABSTRACT

The condition of the corneal epithelium is a critical determinant of corneal transparency and clear vision. The corneal epithelium serves as a barrier to protect the eye from external insults, with its smooth surface being essential for its optical properties. Disorders of the corneal epithelium include superficial punctate keratopathy, corneal erosion, and persistent epithelial defects (PEDs). The prompt resolution of these disorders is important for minimization of further damage to the cornea. Currently available treatment modalities for corneal epithelial disorders are based on protection of the ocular surface in order to allow natural healing to proceed. PEDs remain among the most difficult corneal conditions to treat, however. On the basis of characterization of the pathobiology of PEDs at the cell and molecular biological levels, we have strived to develop new modes of treatment for these defects. These treatments rely on two key concepts: provision of a substrate, such as the adhesive glycoprotein fibronectin, for the attachment and migration of corneal epithelial cells, and activation of these cells by biological agents such as the combination of substance P and insulin-like growth factor-1 (IGF-1). Central to both approaches is the role of the fibronectin–integrin system in corneal epithelial wound healing. Determination of the minimum amino acid sequences required for the promotion of corneal epithelial wound closure by fibronectin (PHSRN) and by substance P (FGLM-amide) plus IGF-1 (SSSR) has led to the development of peptide eyedrops for the treatment of PEDs that are free of adverse effects of the parent molecules.

Contents

Abbreviations: EGF, epidermal growth factor; FGF, fibroblast growth factor; IGF, insulin-like growth factor; SPK, superficial punctate keratopathy; PED, persistent epithelial defect; ECM, extracellular matrix; u-PA, urokinase-type plasminogen activator; HCE, simian virus 40-transformed human corneal epithelial cell; IL, interleukin; PKC, protein kinase C; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; JNK, c-Jun NH_2-terminal kinase; ZO, zonula occludens; CGRP, calcitonin gene-related peptide.

☆ All clinical research of the authors presented in this review was performed with approval of the appropriate ethics committee and with informed consent of the subjects.

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1. Introduction

Both the structure and function of the cornea are rather simple compared with those of other tissues and organs. The cornea nevertheless plays a key role in vision as a result of its transparency and refractive power. It is thus necessary for the cornea to be clear and transparent for it to allow external light to enter through the pupil and lens and to reach the retina. The smooth surface of the cornea and its stable shape with appropriate refractive power are also essential for the focusing of external light and formation of clear images on the retina.

The human cornea contains a stratified epithelium at its external surface with a thickness of ~50 μm, which accounts for ~10% of the total thickness of the cornea. This epithelium comprises five or six layers of epithelial cells, including basal cells, wing cells, and superficial cells. Only basal cells have mitogenic activity, and they differentiate consecutively into wing cells and superficial cells. The superficial cells undergo desquamation as a result either of the mechanical friction associated with blinking (Lemp and Mathers, 1989; Mathers and Lemp, 1992; Pfister, 1973) or of apoptosis (Glaso et al., 1993; Kinoshita et al., 2001; Ren and Wilson, 1996, 1997; Wilson et al., 1996). The mechanisms of cell-to-cell and cell-to-matrix interaction differ among the cell layers of the epithelium. Integrins, which serve as receptors for extracellular matrix (ECM) proteins, are expressed predominantly in the basal epithelial cells and mediate the tight adherence of these cells to the basement membrane. Gap junctions composed of connexin 43 are present only in basal cells and subserve intercellular communication between these cells. On the other hand, tight junctions, consisting of proteins such as zonula occludens (ZO)-1 and occludin, are present mainly in the superficial cells and confer barrier properties on the entire epithelium. A well-layered structure and orderly differentiation process are essential for the maintenance of corneal transparency and clarity (Nishida and Saika, 2011; Suzuki et al., 2003).

The body has acquired passive protective and active repair mechanisms through the process of evolution in order to survive environmental insults. These mechanisms maintain the normal structure and function of the body as well as repair injured components to restore their structure and function. Epithelia form the boundary of the body with the external environment, covering its entire surface and protecting the internal milieu from outside insults. Damage to or disorders of epithelia often result in inflammation or the activation of fibroblasts and other cell types that are normally isolated from the external environment. Epithelial wound healing is thus an important biological process for restoration of the normal structure and function of tissues and organs subjected to mechanical, chemical, or biological insults. Otherwise, a loss of or break in tissue continuity would persist and tissue dysfunction would proceed.

The ocular surface is covered by the corneal and conjunctival epithelia, with the transition between these two epithelia being located at the limbus. Stem cells for the corneal epithelium are located at the limbus (Dua and Azuara-Blanco, 2000; Osei-Bempong et al., 2013; O'Sullivan and Clynes, 2007; Yoon et al., 2014).

The conjunctival epithelium is folded to form the bulbar conjunctiva and palpebral conjunctiva. The anatomic characteristics of the corneal and conjunctival epithelia are distinct (Fukuda and Nishida, 2010b; Kinoshita et al., 2001). Whereas both face the external environment, the corneal epithelium forms a tight barrier but the conjunctival epithelium does not. The cornea is also an avascular tissue, whereas the conjunctiva has an extensive vascular system. Furthermore, immune cells, such as mast cells, lymphocytes, and eosinophils, are abundant in the conjunctiva, but they are present in only low numbers in the cornea (Allansmith et al., 1978; Morgan et al., 1991). In addition, mucin-secreting (goblet) cells are present only in the conjunctival epithelium (Argueso and Gipson, 2001; Gipson, 2004). Given that the conjunctival and corneal epithelia are separated by tear fluid (Gipson, 2007), inflammatory reactions in the conjunctiva can spread to the cornea through tear fluid and vice verse (Nishida, 2010a).

Tear fluid is an evolutionary adaptation to life on dry land that arose to prevent desiccation of the ocular surface. In addition, tear