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Review

Biomechanical relationships between the corneal endothelium and Descemet's membrane

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ABSTRACT

The posterior face of the cornea consists of the corneal endothelium, a monolayer of cuboidal cells that secrete and attach to Descemet's membrane, an exaggerated basement membrane. Dysfunction of the endothelium compromises the barrier and pump functions of this layer that maintain corneal deturgesence. A large number of corneal endothelial dystrophies feature irregularities in Descemet's membrane, suggesting that cells create and respond to the biophysical signals offered by their underlying matrix. This review provides an overview of the bidirectional relationship between Descemet's membrane and the corneal endothelium. Several experimental methods have characterized a richly topographic and compliant biophysical microenvironment presented by the posterior surface of Descemet's membrane, as well as the ultrastructure and composition of the membrane as it builds during a lifetime. We highlight the signaling pathways involved in the mechanotransduction of biophysical cues that influence cell behavior. We present the specific example of Fuchs' corneal endothelial dystrophy as a condition in which a dysregulated Descemet's membrane may influence the progression of disease. Finally, we discuss some disease models and regenerative strategies that may facilitate improved treatments for corneal dystrophies.

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Abbreviations: CEnC, corneal endothelial cells; ECM, extracellular matrix; DM, Descemet's membrane; FCED, Fuchs' corneal endothelial dystrophy; AFM, atomic force microscopy; SEM, scanning electron microscopy; TEM, transmission electron microscopy; ABL, anterior banded layer; PNBL, posterior non-banded layer; TGF-β, transforming growth factor β; Wnt, Wingless/int; YAP, Yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; EMT, epithelial-mesenchymal transition; PI3K, Phosphoinositide 3-kinase; FGF-2, fibroblastic growth factor-2; PCL, posterior collagenous layer; ICE, Iridocorneal endothelial syndrome.

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The endothelium is the most posterior layer of the cornea and plays a critical role in maintaining corneal transparency, regulating deturgescence by providing both barrier and transport functions (Srinivas, 2010). A monolayer of corneal endothelial cells (CEnCs) maintains a barrier through tight junctions and adherens junctions (Srinivas, 2010; Ramachandran and Srinivas, 2010; Hartsock and Nelson, 2008; Noske et al., 1994). Osmotic pressure drives water from the anterior segment into the corneal tissues, and the endothelial layer maintains deturgescence through active fluid transport, energetically maintained by Na^{+}/K^{+}-ATPases (Bonanno, 2012; Fischbarg, 2003; Hatou et al., 2009). Corneal endothelial cells also produce a specialized basement membrane known as Descemet's membrane (DM) (Kabosova et al., 2007). Anterior to DM is the stroma, which constitutes the bulk of the cornea (Reinstein et al., 2009). Bowman's layer (Gordon et al., 1994), a specialized acellular extracellular matrix (ECM), separates the stroma from the anterior corneal epithelium in humans, but is absent in all domestic animals (Adler and Hart, 1992). A stratified squamous nonkeratinized epithelium makes up the anterior face of the cornea, with basal columnar cells that are anchored to the underlying anterior basement membrane (Adler and Hart, 1992).

It is well-documented that biophysical cues, such as substratum topography and stiffness, intrinsic attributes of all extracellular matrices, profoundly modulate a host of fundamental cell behaviors (Hay, 1985; Hao et al., 2014; Ingber, 2003; Wang et al., 2009; Janmey and Miller, 2011; Thomasy et al., 2012; Myrna et al., 2012; Raghunathan et al., 2013a; Dreier et al., 2013). Corneal cells interact with a rich variety of *in vivo* biophysical stimuli: the stroma and basement membranes present them with a range of stiffnesses and complex topographies (Abrams et al., 2000a). Our laboratory and others have documented that the biophysical attributes of matrices represent ubiquitous and potent cellular stimuli that modulate morphology (Petroll et al., 2004; Karamichos et al., 2007; McKee et al., 2011a; Raghunathan et al., 2013b; Koo et al., 2014), adhesion (Karuri et al., 2004), motility (Dreier et al., 2012; Raghunathan et al., 2013c), proliferation (Muhammad et al., 2015), gene expression and regulation (Raghunathan et al., 2014), and cell differentiation (Myrna et al., 2012; Dreier et al., 2013; Petroll and Lakshman, 2015) in a wide array of cell types. These cues also impact how cells respond to soluble signaling molecules and therapeutic agents (Thomasy et al., 2012; Myrna et al., 2012; Dreier et al., 2013). Insights gleaned from research on biophysical stimuli in the cornea inform potential therapies for conditions including corneal wounds (Okumura et al., 2015a; Petroll and Miron-Mendoza, 2015; Gao et al., 2015), as well as to tissue-engineered corneal constructs for transplantation (Shah et al., 2008). In particular, topographical and mechanical stimuli have been introduced to CEnCs to increase proliferation (Koo et al., 2014; Muhammad et al., 2015), maintain phenotype (Palchesko et al., 2015), and produce cell sheets for transplantation (Teichmann et al., 2013; Niu et al., 2014; Teo et al., 2012). Given the evidence supporting the role of mechanical signals in the function of CEnCs, it is surprising that the roles of these signals in homeostasis and pathogenesis have not been explored more thoroughly.

In this review, we present evidence that biophysical interactions must be considered when developing a complete model of the corneal endothelium in health and disease. We begin by describing experimental methods used to explore the biophysical microenvironment of corneal cells, particularly the stiffnesses of the tissues with which these cells interact. Next, we describe the ultrastructure of DM and the variations in the ECM at different stages of an organism's lifespan. We then highlight the signaling pathways that are likely to be involved in transducing mechanical signals from the ECM to the nucleus, thereby influencing cell behavior. To illustrate the reciprocal relationship between ECM and CEnCs, we describe a proposed interaction between DM and endothelial cells, engaging biophysical stimuli in Fuchs' corneal endothelial dystrophy (FCED), a corneal endothelial disease marked by characteristic abnormalities of DM. We then highlight the existing literature on *in vitro* studies of ECM biomolecules produced by CEnCs. We conclude by discussing corneal endothelial regeneration, an active area of research in which a deeper understanding of mechanical cues could have a beneficial impact.

1. Methods for characterizing the biophysical properties of corneal tissues

To investigate biophysical cues and their impact, it is necessary to characterize the mechanical microenvironment that cells experience *in vivo*, and to represent these cues *in vitro*. Tissues are mechanically quantified by measuring the elastic or Young's modulus (Askeland et al., 2011), a property that defines the sample's stiffness or its ability to resist deformation under an applied stress (Askeland et al., 2011). The elastic moduli of many biological tissues including the cornea have been reported and, interestingly, the reported values for a single tissue type can span several orders of magnitude, largely depending on the method of sample preparation and/or measurement (McKee et al., 2011b) (Table 1). Tensile measurements tend to be of higher magnitude than indentation-based measurements, such as those acquired through atomic force microscopy (AFM) or mechanical interferometry imaging, as the former measures bulk deformations in the tissue (with contributions from the ECM, cells, fibrillar and network-like proteins, and constrained water (McKee et al., 2011b)) whereas the latter methods measure localized deformations on small length scales (McKee et al., 2011b; Yoo et al., 2011).

In thin, heterogeneous tissue samples such as the endothelium or DM, AFM is ideal for measuring the micron-scale deformations that cells and their local ECM environments experience (McKee et al., 2011b; Last et al., 2010). Our lab has extensively used AFM to characterize the stiffness of the distinct layers of the human and rabbit cornea (Last et al., 2009, 2012; Thomasy et al., 2014) (detailed in Table 2), as well as the normal human trabecular meshwork (4.0 ± 2.2 kPa (Last et al., 2011)). The properties of the ECM can vary considerably between species (Thomasy et al., 2014; Worthington et al., 2014; Danielsen, 2004) (Table 1), and each layer in the rabbit eye is consistently softer than the corresponding structure in the human eye (Thomasy et al., 2014). For further information, we direct the reader to these reviews on the nuances of stiffness measurements in ocular tissues (McKee et al., 2011b; Last et al.,

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