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Integration of tight junctions and claudins with the barrier functions of the retinal pigment epithelium

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ABSTRACT

The retinal pigment epithelium (RPE) forms the outer blood-retinal barrier by regulating the movement of solutes between the fenestrated capillaries of the choroid and the photoreceptor layer of the retina. Blood-tissue barriers use various mechanisms to accomplish their tasks including membrane pumps, transporters, and channels, transcytosis, metabolic alteration of solutes in transit, and passive but selective diffusion. The last category includes tight junctions, which regulate transepithelial diffusion through the spaces between neighboring cells of the monolayer. Tight junctions are extraordinarily complex structures that are dynamically regulated. Claudins are a family of tight junctional proteins that lend tissue specificity and selectivity to tight junctions. This review discusses how the claudins and tight junctions of the RPE differ from other epithelia and how its functions are modulated by the neural retina. Studies of RPE-retinal interactions during development lend insight into this modulation. Notably, the characteristics of RPE junctions, such as claudin composition, vary among species, which suggests the physiology of the outer retina may also vary. Comparative studies of barrier functions among species should deepen our understanding of how homeostasis is maintained in the outer retina. Stem cells provide a way to extend these studies of RPE-retinal interactions to human RPE.

Contents

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1. Introduction

The retinal pigment epithelium (RPE) forms the outer blood-retinal barrier by separating the outer retina from the choroidal capillary bed. It is an active barrier that supports the neural retina in many ways. RPE supplies trophic factors for the retina, phagocytizes disc membranes that are shed daily by the photoreceptors, recycles retinoids to sustain the visual cycle, and regulates the composition and volume of the subretinal space. Dysfunction of RPE can lead to retinal edema, detachment or degeneration. Disruption of the RPE/retina interface can lead to scar formation or RPE proliferation (Marmor and Wolfensberger, 1998).

The cornerstone of any epithelial barrier is the tight junction. Tight junctions form a belt that completely encircles cells of the epithelial monolayer, partially occluding the space that lies between them. By retarding diffusion through these paracellular spaces, epithelia can regulate transport between the tissues and spaces that lie on either side of it. RPE tight junctions are disrupted in a variety of retinal diseases such as macular edema and uveitis (Vinores et al., 1999; de Smet and Okada, 2010; Scholl et al., 2010). These descriptive studies do not address how tight junctions might contribute or respond to the pathophysiology of these diseases. The structure and unique functions of RPE tight junctions are only beginning to be unraveled.

1.1. Overview of epithelia and tight junctions

Historically, epithelia have been classified as leaky or tight based upon how readily ions could cross the epithelium via the paracellular space relative to transport across the cells themselves. The urinary bladder lies at one extreme where the paracellular path is virtually blocked by the tight junction; epithelia of the intestine or proximal kidney tubule lie at the other extreme. Most epithelia, including RPE of various vertebrate species, fall somewhere along this continuum. In these epithelia, the “tight” junctions are leaky to certain solutes more than others.

Transepithelial transport for tight epithelia can be modeled by considering the apical and basolateral plasma membranes as two electrically-coupled membranes arranged in series. Models of leaky and intermediate epithelia include the paracellular pathway, which lies in parallel. This parallel pathway also electrically couples the apical and basolateral membranes (Reuss, 1997). Accordingly, this coupling offers a point where transport across the membranes can be modulated. Therefore, a complete picture of transepithelial transport requires an understanding of the tight junctions that span the paracellular space. Until recently, studies of membrane transport have far out-paced those of tight junctions, but the last decade has witnessed astonishing progress in studies of model epithelia *in vitro* and non-ocular epithelia *in vivo*. By comparison, relatively little is known about RPE tight junctions. Except for those who closely follow this rapidly evolving field, many misperceptions about tight junctions persist among vision researchers. This review will attempt to bridge this gap by summarizing data from many epithelia and placing studies on RPE tight junctions within this broader context.

1.2. How is RPE defined in vivo and in culture?

A pigmented epithelium is observed before any retinal neurons or glia *in vivo* (Stroeva and Mitashov, 1983), but is this a mature RPE or will the choroid and neural retina direct its future development? In fact, RPE can redifferentiate *in vitro* without direction from a choroid or neural retina (Hu and Bok, 2001; Maminishkis et al., 2006; Gamm et al., 2008). Nonetheless, retinal secretions can effect the maturation of chick RPE in culture (Sun et al., 2008). RPE is very plastic. Depending on culture conditions, RPE can transdifferentiate, undergo epithelial-mesenchymal-like transitions that resemble proliferative retinopathy, or display many mixtures of immature and mature RPE phenotypes (Zhao et al., 1997; Ganti et al., 2007; Burke, 2008; Pratt et al., 2008). Tissue engineering experiments that recreate elements of the native environment should reveal important interactions between RPE and its neighbors, but only if there is an adequate definition of RPE and its stages of maturation.

A definition of RPE is complicated, because proteins are integrated into interwoven networks of signaling and regulatory pathways. When RPE first appears during development, it expresses many RPE-specific markers. Nonetheless, the early RPE cell is only partially differentiated. In chick embryos, we demonstrated that RPE would undergo many transformations as the neural retina differentiates (Rahner et al., 2004; Rizzolo, 2007). Many of these changes affect the relative amounts of different proteins, including RPE-specific proteins, and are regulated by secretions of the neural retina (Sun et al., 2008). In some ways, culture is like a disease state where a degenerate neural retina no longer sends RPE the signals that modulate key functions. One outcome of our collective studies on chick RPE is that barrier function, the ability to regulate transepithelial transport, is among the last RPE functions to fully differentiate and is influenced by interactions with the neural retina.

Intriguing as chick embryology is, our studies raise several questions. Are these chick data relevant to human biology and pathology? Does RPE from different species function the same way? This review will develop the theme that the definition of RPE maturity and function is species-dependent and region-dependent. Further, vertebrate species vary in the mechanisms that regulate the outer blood-retinal barrier.

2. What is a blood-tissue barrier?

2.1. Barrier or gatekeeper? The paracellular and transcellular paths

In the early 1900s, Erhlich and Goldman reported the first evidence of a blood-tissue barrier. They observed that dye injected into the vasculature found its way into all the tissues except the brain,