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Review

Looking into the future: Using induced pluripotent stem cells to build two and three dimensional ocular tissue for cell therapy and disease modeling

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ABSTRACT

Retinal degenerative diseases are the leading cause of irreversible vision loss in developed countries. In many cases the diseases originate in the homeostatic unit in the back of the eye that contains the retina, retinal pigment epithelium (RPE) and the choriocapillaris. RPE is a central and a critical component of this homeostatic unit, maintaining photoreceptor function and survival on the apical side and choriocapillaris health on the basal side. In diseases like age-related macular degeneration (AMD), it is thought that RPE dysfunctions cause disease-initiating events and as the RPE degenerates photoreceptors begin to die and patients start loosing vision. Patient-specific induced pluripotent stem (iPS) cell-derived RPE provides direct access to a patient's genetics and allow the possibility of identifying the initiating events of RPE-associated degenerative diseases. Furthermore, iPS cell-derived RPE cells are being tested as a potential cell replacement in disease stages with RPE atrophy. In this article we summarize the recent progress in the field of iPS cell-derived RPE "disease modeling" and cell therapies and also discuss the possibilities of developing a model of the entire homeostatic unit to aid in studying disease processes in the future.

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1. Introduction

1.1. *Need for in vitro models of the ocular homeostatic unit*

The functional light-sensing unit in the back of the eye consists of a neurosensory retina, the retinal pigment epithelium (RPE), the proteinaceous Bruch's membrane, and the endothelial cells that line the choriocapillaris. Photoreceptors of the retina are the main light-sensing cells of this unit, whereas the RPE along with the structural support from the Bruch's membrane, and endothelial cells form the outer blood retina barrier (BRB) for this unit. Together, these cell types are also called the homeostatic unit in the back of the eye (Fig. 1A) (Bharti et al., 2011). The RPE is strategically located in between the neurosensory retinal layer and Bruch's membrane and is critical for maintaining the health and integrity of this entire homeostatic unit (Fig. 1A). The RPE performs several functions that are critical for photoreceptor and choriocapillaris survival and health, including: (1) transport of nutrients such as glucose, O_2, and vitamin A from the choriocapillaris to the photoreceptors that are not in direct contact with any blood supply; (2) phagocytosis of photoreceptor outer segments that have been damaged by photooxidation; (3) maintenance of the visual cycle-as light hits photoreceptors, opsin-bound visual pigment 11-cis retinal is isomerized to all-trans retinal and released from opsin, and then the RPE re-isomerizes it back to the functional form11-cis retinal; (4) maintenance of the chemical composition of the sub-retinal space by regulating the K^+ concentration to physiological levels of 5 mM and by removing CO_2 from the sub-retinal space produced during photoreceptor respiratory cycle; (5) controlling the volume of the subretinal space and the choroid by transporting water from the sub-retinal space to choriocapillaris; and (6) constitutively secreting cytokines in a polarized fashion towards the retina and the choroid to regulate their development, function, and pathophysiology (Adijanto et al., 2009; Bharti et al., 2011; Li et al., 2009, 2011; Maminishkis et al., 2006; Maminishkis and Miller, 2010; Shi et al., 2008; Strauss, 2005). Functional defects in the RPE lead to physiological defects in the entire homeostatic unit and are the hallmark features in several degenerative retinal diseases, both monogenic (e.g. Stargardt and Sorsby's fundus dystrophy) and polygenic (e.g. age-related macular degeneration (AMD) (Ambati and Fowler, 2012; Ambati et al., 2013; Langton et al., 2005; Zhong and Molday, 2010). Discovery and elucidation of early initiating events in these diseases that originate in the RPE could allow development of clinical interventions so that the homeostasis of the entire unit could be rescued. Sorsby's fundus dystrophy and AMD are typical examples of diseases where the primary functional defect originates in RPE cells, but disease processes that follow spread across the entire homeostatic unit.

Sorsby's fundus dystrophy is a rare and genetically dominant disease caused by mutation in a matrix metalloproteinase inhibitor gene *TIMP3* (Weber et al., 1994). The *TIMP3* gene is highly expressed in the RPE and the protein is located on the basal side of RPE in the Bruch's membrane (Strunnikova et al., 2010; Weber et al., 2002). Studies performed in human cell lines and mouse models suggest that mutant TIMP3 protein degrades slower compared to the wild type protein, and likely because of this slower degradation it accumulates in RPE cells and in the Bruch's membrane (Weber et al., 2002; Langton et al., 2005). The consequence of mutant TIMP3 accumulation, however, is not clear. One study suggests that mutant protein is weaker at suppressing matrix metalloproteinases (MMPs). Increased MMP activity can enhance angiogenesis in choriocapillaris (Qi et al., 2002). Another study suggests that accumulation of mutant TIMP3 or its reduced activity changes the hydraulic conductivity of Bruch's membrane. This results in a reduced flow of nutrients and oxygen from the choriocapillaris towards the RPE and the photoreceptors (Booij et al., 2010; Langton et al., 2005). Reduced oxygen absorption can cause hypoxia in the back of the eye, increase the secretion of angiogenic factor VEGF, and lead to hemorrhage and leakage in choriocapillaris. Part of the reason why it has not been feasible to understand the initiating events of such a complex disease is because there are no good human models to study the intersection of RPE, Bruch's membrane, and choriocapillaris.

Similar to Sorsby's fundus dystrophy, AMD affects all the three cell types in the back of the eye. But, unlike Sorsby's fundus dystrophy that affects the whole retina, AMD is more restricted to the center of the eye (the macula). It has two phenotypically distinct advanced stages, the “dry” stage or geographic atrophy (GA) and the “wet” stage or choroidal neovascularization (CNV) (Fig. 1). Clinically GA is defined as a stage with atrophy of RPE cells (Ambati et al., 2013; Zarbin et al., 2014). RPE cell death in GA is tightly coupled with accumulated oxidative and metabolic insult ensued by photoreceptors and is associated with a corresponding loss of choroidal blood vessels (Fig. 1B and C) (Ambati et al., 2013; Arjamaa et al., 2009; Kinnunen et al., 2012). In comparison, CNV is associated with abnormal growth of choroidal blood vessels (Fig. 1D). At the cellular level, it is widely accepted that increased basal VEGF secretion by RPE induces CNV. This increase in VEGF secretion is likely caused by intracellular inflammation and hypoxia in the RPE, likely through the activation of HIF-1 alpha, NRF2, and NF-kB pathways (Arjamaa et al., 2009; Wang et al., 2014). There are no good animal models that can recapitulate all the clinical hallmarks of an early to advanced AMD stages. The iPS cell technology has recently provided a simple two-dimensional model of patient-derived RPE to study specific stages of AMD pathogenesis (Yang et al., 2014). It is hoped that in the future this technology can be extended to develop complex 3-dimensional models of the back of the eye.