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Review

Retinal pigment epithelium development, plasticity, and tissue homeostasis

Sabine Fuhrmann*, ChangJiang Zou, Edward M. Levine

Department of Ophthalmology & Visual Sciences, John A. Moran Eye Center, University of Utah, 65 Mario Capecchi Drive, Salt Lake City, UT 84132, USA

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ABSTRACT

The retinal pigment epithelium (RPE) is a simple epithelium interposed between the neural retina and the choroid. Although only 1 cell-layer in thickness, the RPE is a virtual workhorse, acting in several capacities that are essential for visual function and preserving the structural and physiological integrities of neighboring tissues. Defects in RPE function, whether through chronic dysfunction or age-related decline, are associated with retinal degenerative diseases including age-related macular degeneration. As such, investigations are focused on developing techniques to replace RPE through stem cell-based methods, motivated primarily because of the seemingly limited regeneration or self-repair properties of mature RPE. Despite this, RPE cells have an unusual capacity to transdifferentiate into various cell types, with the particular fate choices being highly context-dependent. In this review, we describe recent findings elucidating the mechanisms and steps of RPE development and propose a developmental framework for understanding the apparent contradiction in the capacity for low self-repair versus high transdifferentiation.

1. Overview of early eye development and RPE specification

To truly understand RPE development, it is important to begin at the steps leading to the formation of the eye field. Like the neural retina, the RPE is a derivative of the optic neuroepithelium, which is initially specified as a patch of cells, the “eye field”, in the anterior neuroectoderm. Some progress has been made on resolving the mechanistic underpinnings of these early developmental steps, in large part because they provide insight into how the forebrain is initially organized. In the following subsections, we describe the recent findings describing the mechanisms and steps leading to the specification and early differentiation of the RPE.

1.1. Regulation of anterior neuroectodermal fate

Eye development is initiated by the formation of a single eye field in the anterior neural plate, comprised of neuroepithelial cells that give rise to the optic stalk, retina and RPE. The eye field arises within the future forebrain region that develops into telencephalon and diencephalon but it is unclear how its formation is initiated. FGF, BMP, Wnt and retinoic acid signaling exert multiple roles during gastrulation and early neural development; however, the complex morphogenetic movements make it challenging to examine the exact role of these pathways in specification of the anterior neural plate, including the eye field.

Observations from different model systems suggest that anterior neuroectodermal fate is a ubiquitous state, and that specification of posterior neuroectoderm requires additional signals to prevent spreading of anterior fate across the neural plate. Wnt/β-catenin signaling is one such signal, acting at different threshold requirements to elicit distinct morphogenetic responses in different brain regions (for reviews, see (Andoniadou and Martinez-Barbera, 2013; Beccari et al., 2013; Fuhrmann, 2008; Wilson and Houart, 2004). In rostral regions, several mechanisms exist to maintain anterior fate, such as the presence of antagonists of the Wnt/β-catenin pathway (e.g. Dkk1, sFRP) or direct suppressors of Wnt ligand transcription (e.g. the homeodomain transcription factor Six3 in the eye field). Consequently, loss of Wnt/β-catenin inhibition leads to suppression of forebrain development, resulting in eyeless or headless embryos in the most severe cases (Kim et al., 2000; Lagutin et al., 2003). Studies in sea urchins suggest a potential mechanism by which non-canonical Wnt signaling through the receptors Frizzled-1/-2/-7 and JNK induces the Wnt/β-catenin antagonist Dkk1 and is required for expression of Six3 in the anterior neural plate (Range et al., 2013). Consistent with this, non-canonical Wnt signaling is required for repression of Wnt/β-

* Corresponding author. Tel.: +1 801 581 4684.
E-mail addresses: sabine.fuhrmann@hsc.utah.edu (S. Fuhrmann), changjiang.zou@hci.utah.edu (C. Zou), ed.levine@utah.edu (E.M. Levine).

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catenin signaling and for promoting expression of eye-specific genes during eye field formation in frog and zebrafish (Fig.1; (Cavodeassi et al., 2005; Kibardin et al., 2006; Maurus et al., 2005; Rasmussen et al., 2001); for review, see (Fuhrmann, 2008). Thus, it is possible that the anterior neural fate is specified as a "default state" with an initially more widespread expression of Six3 and the paired transcription factor Rx in the rostral forebrain (Mathers et al., 1997; Muranishi et al., 2012; Oliver et al., 1995).

Further fine-tuning of the forebrain into different territories requires additional signaling centers or organizers. During establishment of the eye field in zebrafish, BMP acts as an instructive signal to pattern the anterior-most part of the neural plate into telencephalon and represses Rx3 inhibiting eye field formation (Fig.1; (Bielen and Houart, 2012). BMP may be also provided from the paraxial rostral mesoderm to restrict the eye field; experimental and functional manipulations in chick embryos demonstrate that BMP signaling mediates the inhibitory effect of the paraxial rostral mesoderm on optic vesicle formation, potentially through differential modulation of distinct Wnt pathways (Teraoka et al., 2009).

Another potential mechanism for regionalization of the forebrain could be that different target genes in distinct brain regions are regulated by specific stoichiometric ratios of transcriptional activators such as Six3, the orthodenticle-related transcription factor Otx2 and the high mobility group transcription factor Sox2 (Beccari et al., 2012; Danno et al., 2008). Recent studies in frog indicate that both Otx2 and Sox2 proteins can directly and synergistically interact to transactivate a conserved, non-coding sequence upstream of the Rx promoter (Danno et al., 2008). Rax may not be upregulated in the brain outside of the eye field because the ratio of Sox2 and Otx2 is too high or too low for transcriptional activation of Rx; for example, excess Sox2 can inhibit transcription cooperatively induced by Sox2 and Otx2 (Danno et al., 2008). Therefore, these and other mechanisms may tightly control gene expression levels, resulting in distinct target gene activation in different brain regions.

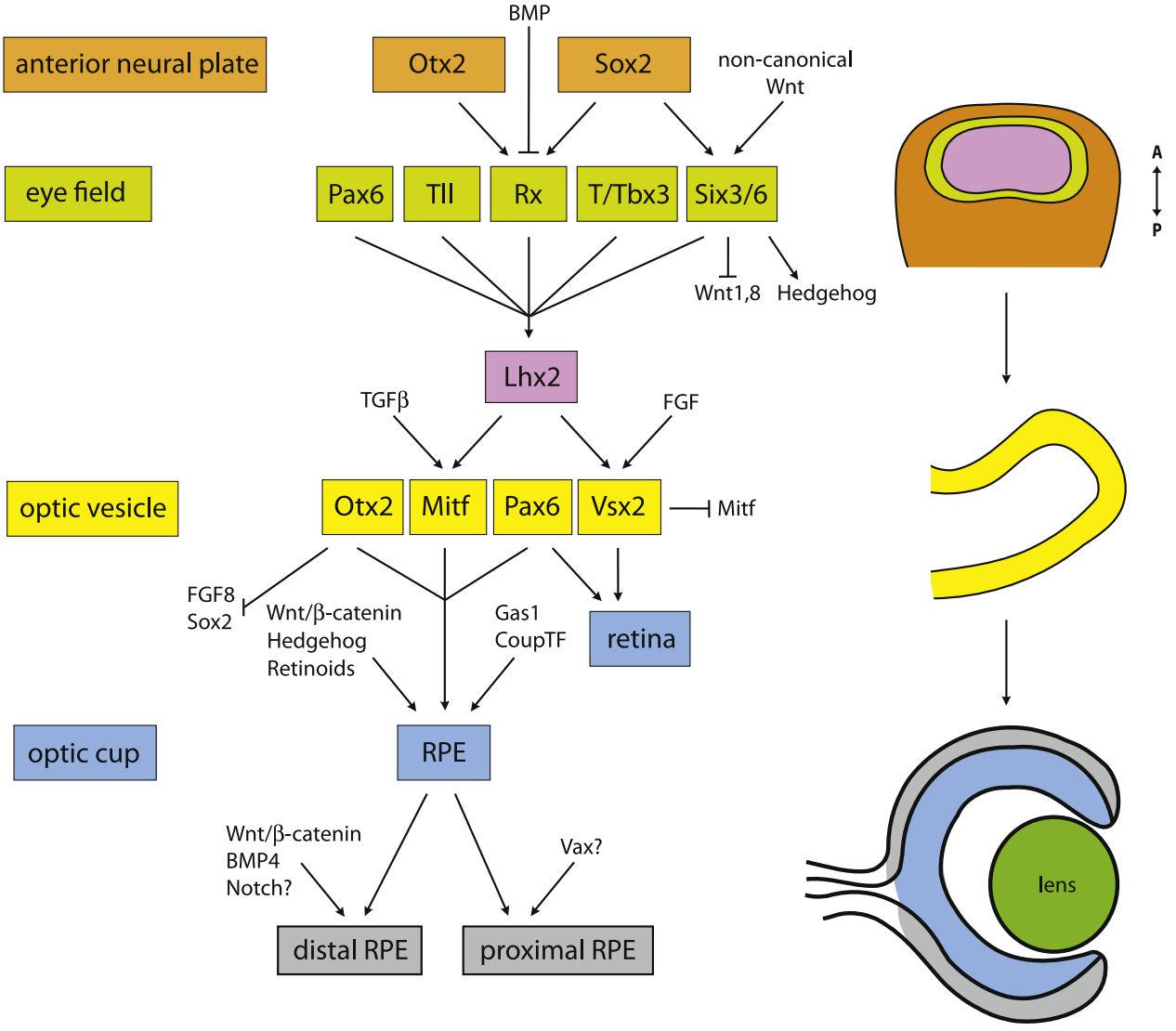

Fig. 1. Regulation of early eye and RPE development by extracellular signals and transcription factors. The eye field is initiated in the anterior neural plate by induction of eye field transcription factors: Pax6, Tll, Rx, T/Tbx3, Six3/6. Rx may be upregulated cooperatively by Otx2 and Sox2 that are broadly expressed in the anterior neural plate. Additional interaction with extracellular pathways (BMP, Wnt, sonic hedgehog) separate the eye field from other brain regions. Eye field transcription factors promote Lhx2 expression that acts as a competence factor to allow patterning of the optic vesicle. Otx2, Mitf (possibly induced by TGFb-like signals), and Pax6 are initially present throughout the optic vesicle, however Mitf is then downregulated by Vsx2 in the presumptive retina domain, which is initiated by FGF signals. Otx2 may further suppress expression of FGF and Sox2 to support RPE formation. In the optic cup, additional factors such as Wnt, hedgehog, retinoids, Gas1, CoupTFs, BMP4, Notch and Vax stabilize the RPE fate and promote differentiation into RPE subdomains. For more details, see text. A: anterior, P: posterior.