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The CRB1 and adherens junction complex proteins in retinal development and maintenance

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ABSTRACT

The early developing retinal neuroepithelium is composed of multipotent retinal progenitor cells that differentiate in a time specific manner, giving rise to six major types of neuronal and one type of glial cells. These cells migrate and organize in three distinct nuclear layers divided by two plexiform layers. Apical and adherens junction complexes have a crucial role in this process by the establishment of polarity and adhesion. Changes in these complexes disturb the spatiotemporal aspects of retinogenesis, leading to retinal degeneration resulting in mild or severe impairment of retinal function and vision.

In this review, we summarize the mouse models for the different members of the apical and adherens junction protein complexes and describe the main features of their retinal phenotypes. The knowledge acquired from the different mutant animals for these proteins corroborate their importance in retina development and maintenance of normal retinal structure and function. More recently, several studies have tried to unravel the connection between the apical proteins, important cellular signaling pathways and their relation in retina development. Still, the mechanisms by which these proteins function remain largely unknown. Here, we hypothesize how the mammalian apical CRB1 complex might control retinogenesis and prevents onset of Leber congenital amaurosis or retinitis pigmentosa.

Contents

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1. Introduction

1.1. Apical polarity complex proteins and development of the retinal neuroepithelium

The retinal neuroepithelium is made as an outgrowth from the neural tube. The outgrowth or optic vesicle invaginates to form a double layered cup-like structure consisting of an outer single layered retinal pigment epithelium and an inner single layered pseudostratified retinal neuroepithelium. The progenitor cells of the retinal neuroepithelium proliferate and form a multilayered structure. Despite the wide range of nuclear positions and multilayered appearance, all progenitor cells remain attached to the basal and apical surface of the epithelium. During development of the retinal neuroepithelium, newborn progenitors remain anchored to the apical surface of the epithelium via adherens junctions (AJs) (Fig. 1). The newborn progenitors elongate along the apical basal axis forming long apical and basal processes, and then interkinetic nuclear migration takes place within the cell (Baye and Link, 2007). Neuroepithelial cells are connected by AJs at the outer limiting membrane, which separate the apical plasma membrane from the basolateral domains. These belt-like structures are linked to the actin cytoskeleton and are composed of proteins such as cadherins and catenins (Randlett et al., 2011). Apically to the AJs reside two apical complexes, the Crumbs-homologue (CRB) and partitioning defective (PAR) complexes, which act as cell polarity regulators (Fig. 2). The core CRB complex is formed by the transmembrane protein CRB, the associated cytoplasmic proteins Protein Associated with Lin Seven 1 (PALS1; also known as Membrane Protein Palmitoylated 5 or MPP5) and PALS1-associated tight junction protein (PATJ) or the Multi-PDZ Domain Protein 1 (MUPP1) (Assemat et al., 2013; Bulgakova et al., 2008; Michel et al., 2005). The PAR complex comprises PAR3, PAR6, atypical protein C (aPKC) and cell division control 42 (CDC42) (Martin-Belmonte and Perez-Moreno, 2011). Upon mutation or changes in levels of any of these components, the developing retinal epithelium loses polarity and adhesion, dividing cells detach from the apical lamina, and many of such detached progenitors exhibit ectopic mitoses. Consequently, the correct spatiotemporal aspects of retinogenesis are perturbed, leading to retinal degeneration resulting in mild or severe impairment of retinal function and vision. In this review, we focus

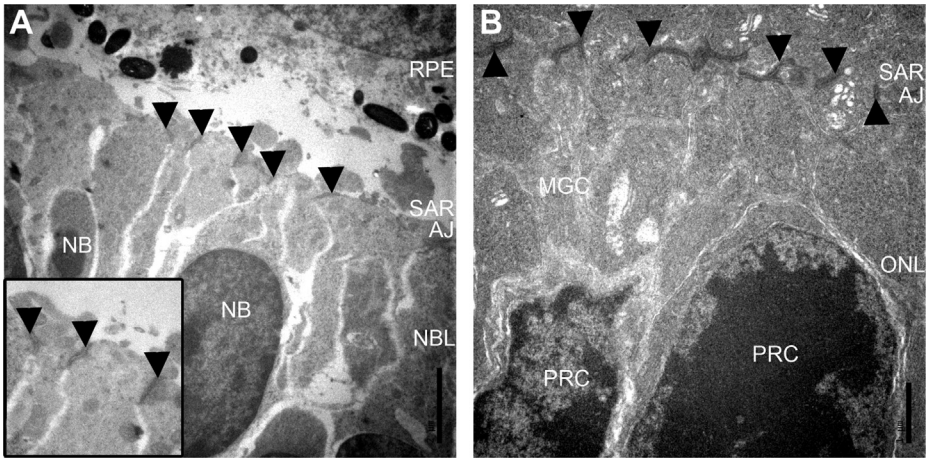

Fig. 1. Adherens junctions in developing and adult mouse retinas. Electron microscopic pictures of electron dense adherens junctions (black arrowheads) between retinal progenitor cells at E17 (A) and between photoreceptor cells or photoreceptor and Müller glial cells in 1 M old retinas (B). Legends: AJ, Adherens junctions; MGC, Müller glial cell; NB, neuroblast; NBL, neuroblast layer; ONL, outer nuclear layer; PRC, photoreceptor cells; RPE, Retinal pigmented epithelium; SAR, subapical region. Scale bar, 2 μm (A); 1 μM (B).