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Review

Aberrant protein trafficking in retinal degenerations: The initial phase of retinal remodeling

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ABSTRACT

Retinal trafficking proteins are involved in molecular assemblies that govern protein transport, orchestrate cellular events involved in cilia formation, regulate signal transduction, autophagy and endocytic trafficking, all of which if not properly controlled initiate retinal degeneration. Improper function and or trafficking of these proteins and molecular networks they are involved in cause a detrimental cascade of neural retinal remodeling due to cell death, resulting as devastating blinding diseases. A universal finding in retinal degenerative diseases is the profound detection of retinal remodeling, occurring as a phased modification of neural retinal function and structure, which begins at the molecular level. Retinal remodeling instigated by aberrant trafficking of proteins encompasses many forms of retinal degenerations, such as the diverse forms of retinitis pigmentosa (RP) and disorders that resemble RP through mutations in the rhodopsin gene, retinal ciliopathies, and some forms of glaucoma and age-related macular degeneration (AMD). As a large majority of genes associated with these different retinopathies are overlapping, it is imperative to understand their underlying molecular mechanisms. This review will discuss some of the most recent discoveries in vertebrate retinal remodeling and retinal degenerations caused by protein mistrafficking.

Contents

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1. Introduction

Retinal remodeling induced by protein mistrafficking followed by photoreceptor degeneration is a concept that although has been well established, has reemerged due to technical advances in the field (Marc and Jones, 2003; Jones and Marc, 2005; Marc et al., 2007). Retinal remodeling occurs in three known phases (Marc and Jones, 2003; Jones and Marc, 2005; Jones et al., 2012). The first phase is due to an initial insult such as protein mislocalization that elicits cell stress within the photoreceptor or retinal pigmented epithelium (RPE) cells. Although the insult may be subtle, it can induce cascades of regulatory molecular and physiological pathways. These modifications provoke the second phase of retinal remodeling, in which the outer nuclear layer is remodeled due to photoreceptor death, resulting in cell apoptosis. This causes depletion of neuronal classes, leading into the third phase, extreme retinal remodeling, described by modifications of the neural retina by cell migration, new neurite and or synapse formation and neuronal death (Marc and Jones, 2003; Marc et al., 2003; Marc et al., 2007; Jones et al., 2012).

Protein trafficking within the photoreceptors must occur efficiently and at a high fidelity to maintain structural maintenance and overall retinal homeostasis. The goal of this review, while non-comprehensive, is to bring together some of the main details of what is known on a molecular level of retinal degenerative diseases and retinal remodeling in regards to improper protein trafficking. It is known that mutations occurring in genes encoding vital trafficking proteins display similar pathophysiologies, yet are associated with categorically different blinding diseases. Understanding at a molecular level what is occurring in these diseased states will provide a better explanation on a larger scale of how these molecular assemblies function and overlap.

1.1. Polarized trafficking occurs in the vertebrate outer retina

Vertebrate photoreceptors are unusual neurons that contain highly modified primary cilium (Horst et al., 1990) composed of approximately two thousand of flattened membranous disks which house all of the protein components necessary for phototransduction in the outer segment (OS) region (Fig. 1). This is separated from the inner segment (IS) region containing cellular organelles such as mitochondria and Golgi apparatus *via* a transition zone, or connecting cilium (CC). In addition to a structural role, the CC plays a critical functional role as a selective ciliary gate and transport pathway from the IS to the OS (Christensen et al., 2007; Leroux, 2007; Insinna and Besharse, 2008; Berbari et al., 2009; Emmer et al., 2010).

The movement of proteins is governed by vesicular interaction with the transition zone complexes, such as the BBSome and the intraflagellar transport (IFT) machinery (Nachury et al., 2007). In photoreceptors, proteins of the transition zone interact with IFT complexes to support movement of phototransduction components (Chuang et al., 2004; Zhao and Malicki, 2011). Ciliary targeting sequences such as the VXPX motif ensure a more efficient

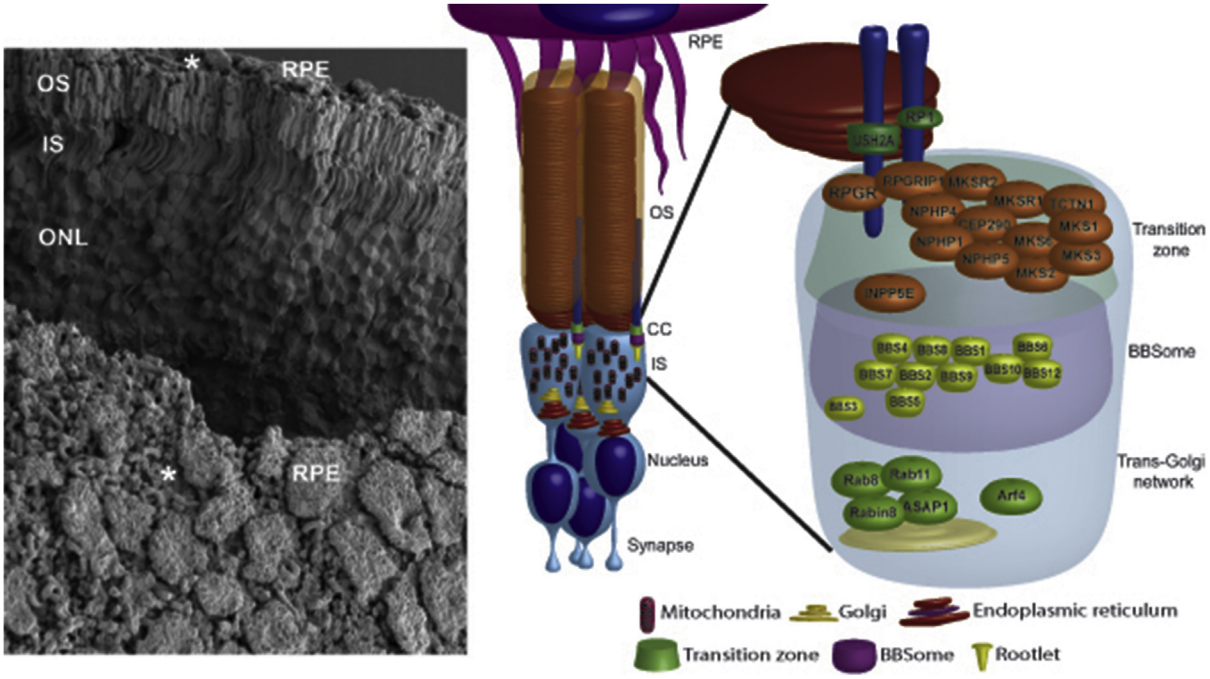

Fig. 1. The vertebrate retina and rod cell highlighting trafficking proteins. Scanning electron micrograph (SEM) of wild-type mouse reveals the precise architecture of the neural retina (left). Schematic of rod cell (middle) highlighting an outer (OS), connecting cilium (CC) and inner segment (IS). Retinal pigmented epithelial (RPE) cells lay over the photoreceptor OS. Schematic of transition zone, BBSome and trans-Golgi network showing the hypothesized order and localization of the trafficking proteins (right) discussed in this review and others. SEM taken by Alecia K. Gross and Ivan Anastassov at the Marine Biological Labs, Fundamental Issues in Vision Research course 2010. *, tips of rod OS.