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PRPH2/RDS and ROM-1: Historical context, current views and future considerations

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ABSTRACT

Peripherin 2 (PRPH2), also known as RDS (retinal degeneration slow) is a photoreceptor specific glycoprotein which is essential for normal photoreceptor health and vision. PRPH2/RDS is necessary for the proper formation of both rod and cone photoreceptor outer segments, the organelle specialized for visual transduction. When PRPH2/RDS is defective or absent, outer segments become disorganized or fail to form entirely and the photoreceptors subsequently degenerate. Multiple *PRPH2/RDS* disease-causing mutations have been found in humans, and they are associated with various blinding diseases of the retina such as macular degeneration and retinitis pigmentosa, the vast majority of which are inherited dominantly, though recessive LCA and digenic RP have also been associated with RDS mutations. Since its initial discovery, the scientific community has dedicated a considerable amount of effort to understanding the molecular function and disease mechanisms of PRPH2/RDS. This work has led to an understanding of how the PRPH2/RDS molecule assembles into complexes and functions as a necessary part of the machinery that forms new outer segment discs, as well as leading to fundamental discoveries about the mechanisms that underlie OS biogenesis. Here we discuss PRPH2/RDS-associated research and how experimental results have driven the understanding of the PRPH2/RDS protein and its role in human disease.

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1. Introduction

Peripherin 2 (PRPH2, also known as retinal degeneration slow or RDS) is a photoreceptor-specific transmembrane glycoprotein that is necessary for the proper formation of both rod and cone photoreceptor outer segments (OS) (Cheng et al., 1997b; Connell et al., 1991; Demant et al., 1979; Hawkins et al., 1985; Molday et al., 1987; Sanyal et al., 1980; Sanyal and Jansen, 1981). Beyond its structural role in the formation of the OS, the human *PRPH2/RDS* gene has been associated with 151 individual disease-causing mutations (according to the Human Gene Mutation Database http://www.hgmd.cf.ac.uk/ac/gene.php?gene=PRPH2) with highly variable patient diagnoses ranging from retinitis pigmentosa to macular degeneration with additional disparity in severity and time of onset (Boon et al., 2008). These phenotypes are associated with degeneration of the neural retina as well as, in some cases, atrophy of the retinal pigment epithelium (RPE) and defects in the choroid. Currently no known treatment has been developed for *PRPH2/RDS*-associated disease. Additionally, while much work has been dedicated to understanding the role of PRPH2/RDS in OS formation; the details of this process remain largely a mystery, although exciting new work is leading to proposed mechanisms for PRPH2/RDS function. Given the central role of photoreceptor OSs in vision, the study of OS biogenesis in general and PRPH2/RDS specifically remains an active and controversial field of research with broad implications for the treatment of human blinding diseases. The current review will focus on a comprehensive analysis of PRPH2/RDS research to aid those interested in furthering their understanding of this critical photoreceptor protein.

In order to appreciate PRPH2/RDS and its importance, we must first establish the context within which PRPH2/RDS plays a significant role. The nomenclature in this field has been confusing, and is further discussed below in its historical context. Though the official gene name is *PRPH2,* much of the early work and work done using mouse models, has used the designation *Rds*. We will use the two forms of nomenclature judiciously, in an attempt to both minimize confusion for the reader and preserve the connection to the literature in the field. The first observation related to the *PRPH2/RDS* gene was that it was important for the survival of rod and cone photoreceptor cells of the neural retina in mice (van Nie et al., 1978). This critical importance of *PRPH2/RDS* would eventually be expanded to include the photoreceptors of all vertebrates (Conley et al., 2012b). Photoreceptors form the outermost neuronal layer in the retina and are the light sensitive cells which initiate phototransduction. The high metabolic, nutritional and environmental support that these cells require is maintained through a combination of the Müller glia and the adjacent RPE (Hoon et al., 2014; Strauss, 2005). Photoreceptors extend from the outer plexiform layer to the RPE and are polarized neuronal cells (Hoon et al., 2014). Their synapses are in the outer plexiform layer, their nuclei are in the outer nuclear layer, their cell bodies with most of the mitochondria, endosomes, and protein synthesis machinery are in the inner segment layer, and finally their sensory OSs extend toward the RPE from the inner segments (Hoon et al., 2014; LaVail, 1983; Mustafi et al., 2009; Steinberg et al., 1980; Sung and Chuang, 2010). The photoreceptor OSs are modified primary cilia which have evolved to detect incoming light and initiate a signal transduction cascade which is the first domino in the long chain of signaling and cellular communications necessary for vision (Arshavsky and Wensel, 2013; Gilliam et al., 2012; Hoon et al., 2014; Hubbell et al., 2003; Koch and Dell'Orco, 2015; Li et al., 2004; Palczewski et al., 2000; Papermaster and Dreyer, 1974; Sung and Chuang, 2010; Zhou et al., 2012).

Rod OSs are long and cylindrical consisting of approximately a thousand disc shaped membrane structures oriented perpendicular to the incoming light and covered with an outer sheath of plasma membrane (Carter-Dawson and LaVail, 1979a; Cohen, 1960; Nickell et al., 2007; Sung and Chuang, 2010). Cone OSs are generally shorter and more conical in shape than rod OS and their discs are referred to as lamellae because they are at least partially fused with the plasma membrane sheath and thus the intradiscal space is continuous with the extracellular environment (Carter-Dawson and LaVail, 1979a, b; Eckmiller, 1987; Mustafi et al., 2009). Because OSs go through a dynamic process of turnover in which the top tenth of the OS is phagocytosed by the RPE cells each day, biogenesis of new discs at the base of the OS is a constant process which requires an incredible level of coordination between various cellular components (Anderson et al., 1978; Insinna and Besharse, 2008; LaVail, 1976; Steinberg et al., 1980; Young, 1967).

The OS discs are packed with the photo-sensitive opsins (rhodopsin in rods and S-, M−, or L-wavelength opsins in cones) and other proteins that participate in the initial steps of phototransduction (Hubbell et al., 2003; Mustafi et al., 2009; Sakmar et al., 2002; Sung and Chuang, 2010), while the adjacent plasma membrane contains, among other things, cyclic nucleotide gated channels which convert the chemical phototransduction signal into an electrical one. However, a third membrane domain exists between these two regions. In both rods and cones the flattened surface of the disc is circumscribed by a rim region of membrane that makes a hairpin-like structure (Carter-Dawson and LaVail, 1979a; Nickell et al., 2007; Steinberg et al., 1980; Sung and Chuang, 2010), and this rim is the region where PRPH2/RDS plays its part. Though not a phototransduction protein, PRPH2/RDS is central to the entire process of vision because without it OSs completely fail to form (Fig. 1). Extensive research (further discussed below) has suggested that PRPH2/RDS functions differently in rods vs. cones, but that in both cell types its function depends on the formation of a wide variety of precisely tuned types of homo- and hetero-oligomers. Abnormalities in these oligomers and the difference in function in PRPH2/RDS between the two cell types is thought to underlie the vast phenotypic variation in patients with PRPH2/RDS-associated disease, and an understanding of the biochemical and cell biological function of PRPH2/RDS is critical for future development of effective therapies for patients. Here we will trace how the current understanding of PRPH2/RDS has developed over time and point the way towards exciting future developments in the field.

2. The discovery of *PRPH2/RDS*

2.1. Rds: phenotype to gene

Mouse inbred strains have provided some of the foundational understanding in almost every field of biomedical research and