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Review

# Retinal remodeling in human retinitis pigmentosa

B.W. Jones [a, *], R.L. Pfeiffer [a], W.D. Ferrell [a], C.B. Watt [a], M. Marmor [b], R.E. Marc [a]

[a] Dept. Ophthalmology, Moran Eye Center, University of Utah, USA
[b] Dept. Ophthalmology, Stanford University, USA

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ABSTRACT

Retinitis Pigmentosa (RP) in the human is a progressive, currently irreversible neural degenerative disease usually caused by gene defects that disrupt the function or architecture of the photoreceptors. While RP can initially be a disease of photoreceptors, there is increasing evidence that the inner retina becomes progressively disorganized as the outer retina degenerates. These alterations have been extensively described in animal models, but remodeling in humans has not been as well characterized. This study, using computational molecular phenotyping (CMP) seeks to advance our understanding of the retinal remodeling process in humans. We describe cone mediated preservation of overall topology, retinal reprogramming in the earliest stages of the disease in retinal bipolar cells, and alterations in both small molecule and protein signatures of neurons and glia. Furthermore, while Müller glia appear to be some of the last cells left in the degenerate retina, they are also one of the first cell classes in the neural retina to respond to stress which may reveal mechanisms related to remodeling and cell death in other retinal cell classes. Also fundamentally important is the finding that retinal network topologies are altered. Our results suggest interventions that presume substantial preservation of the neural retina will likely fail in late stages of the disease. Even early intervention offers no guarantee that the interventions will be immune to progressive remodeling. Fundamental work in the biology and mechanisms of disease progression are needed to support vision rescue strategies.



**Contents**



*Abbreviations:* RP, retinitis pigmentosa; RPE, retinal pigment epithelium; GS, glutamine synthetase; GABA, γ-aminobutyric acid; CRALBP, cellular retinaldehyde binding protein 1; EM, electron microscopy; RGB, red green blue; ONL, outer nuclear layer; ISODATA, Iterative Self-Organizing Data Analysis Technique; CMP, Computational Molecular Phenotyping.

* Corresponding author. University of Utah, Moran Eye Center, 65 Mario Capecchi Dr., Salt Lake City, 84132, UT, USA.
*E-mail address:* bryan.jones@m.cc.utah.edu (B.W. Jones).

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## 1. Introduction

Animal models of retinitis pigmentosa (RP) have been extensively studied. However, with a couple of exceptions (Li et al., 1995; Fariss et al., 2000; Marc et al., 2007), detailed documentation of retinal remodeling in humans has not been coherently summarized. Our goal was to assess human RP retinas in advanced stages of remodeling and evaluate how they compare with animal models in terms of cellular metabolism, rewiring and cell survival. We examined the dependence of phase III (late stage) retinal remodeling on cone survival and document alterations in glutamine synthetase (GS) expression in human RP.

RP is a collection of progressive degenerative diseases with tissue-wide defects at the molecular and cellular level in natural (Baehr and Frederick, 2009) and engineered models of retinal degeneration (Jones et al., 2003). As of October 1st, 2015, there are 238 genes and 278 separate loci involved in retinal degenerations (RetNet, http://www.sph.uth.tmc.edu/RetNet/). RP presents in different forms with varying etiologies including genetic abnormalities in the retinal pigment epithelium (RPE) (Gu et al., 1997; Morimura et al., 1998), ABCR gene and ATP binding cassette defects (Allikmets et al., 1997a, 1997b; Cremers et al., 1998; Allikmets, 2000; Molday et al., 2000), defects in tyrosine kinase receptors (D'Cruz et al., 2000; Duncan et al., 2003), a number of cilliopathies and transport defects (Li et al., 2004; Yen et al., 2006), transducin and arrestin abnormalities (Dryja et al., 1993; Sommer and Farrens, 2006; Sommer et al., 2005, 2006, 2007; Zeitz et al., 2008), mutations in the machinery of rhodopsin processing and trafficking including peripherin defects (Clarke et al., 2000), defects in rod cGMP phosphodiesterase (McLaughlin et al., 1993, 1995; Huang et al., 1995), defects in metabotropic glutamate receptors (mGluRs) (Dryja et al., 2005; Zeitz et al., 2005), synthetic enzymatic defects (Vasireddy et al., 2007), and defects in genes associated with signaling (Chen et al., 2000; Hu and Wensel, 2002, 2004; Hu et al., 2003; Hu and Wensel, 2004; Wensel, 2008).

It is still commonly and incorrectly held that retinal degenerative diseases affect only the sensory retina, leaving the neural retina relatively unscathed. This position overlooks remodeling, a series of changes to retinal organization that extend beyond the photoreceptor layer. Loss of sensory rod and cone input to the neural retina constitutes deafferentation and the neural retina responds in the same manner as deafferented brain (Marc and Jones, 2003; Jones et al., 2003).

Neural retinal deafferentation results in remodeling at the cellular level and reprogramming at the molecular level and progressive neural degeneration becomes unavoidable (Li et al., 1995; de Raad et al., 1996; Fletcher and Kalloniatis, 1996; Fariss et al., 2000; Machida et al., 2000; Strettoi and Pignatelli, 2000; Strettoi et al., 2002; Jones et al., 2003; Marc and Jones, 2003; Marc et al., 2003a, 2003b; Strettoi et al., 2003; Cuenca et al., 2004; Jones and Marc, 2005; Jones et al., 2005, 2006; Marc et al., 2005a; Jones et al., 2006; Pu et al., 2006; Aleman et al., 2007; Marc et al., 2007, 2008; Jones et al., 2011, Jones et al., 2012). Remodeling consists of three major phases. Phase I is the pre-degeneration period characterized primarily by early markers of photoreceptor stress. Phase II is the period of photoreceptor loss accompanied by glial remodeling of the outer nuclear layer, leaving a glial seal (not a scar) between the remnant neural retina and the remnant RPE/choroid. Phase III is a protracted, life-long period of neural, glial and vascular remodeling of the survivor retina involving over thirty different modifications (Marc et al., 2003a), including neuronal cell death, neuronal morphologic change and migration, *de novo* neuritogenesis, microneuroma formation, network rewiring, altered glial metabolism and form, and RPE invasion of the neural retina.

RP remodeling progresses differently depending on the degree of cone survival. In cone decimating RP the phase II → III transition is marked by aggressive remodeling of the neural retina, including neuronal cell death. In cone sparing RP, islands of survivor cones somehow delay remodeling and cell death (Marc et al., 2003b; Jones et al., 2003), even the though the survivor cones may lack opsin expression and appear unresponsive to light (Marc et al., 2007). However, it appears that cone sparing RP itself may be a sub-phase that can devolve to cone decimated forms.

It should also be noted that retinal degeneration and remodeling can result from retinal detachment (Chang et al., 1995; Lewis et al., 1998), AMD (Sullivan et al., 2003; Marc et al., 2008; Jones et al., 2012) or any other situation where photoreceptors are lost, especially cones. Photoreceptor loss triggers a series of phased negatively "plastic" revisions to the neural retina called retinal remodeling. In detail, remodeling events are similar to neurodegenerative events in CNS including trauma and epilepsy (Prince et al., 2009). Fundamentally, regardless of the initiating event