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Review

Using the rd1 mouse to understand functional and anatomical retinal remodelling and treatment implications in retinitis pigmentosa: A review

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ABSTRACT

Retinitis Pigmentosa (RP) reflects a range of inherited retinal disorders which involve photoreceptor degeneration and retinal pigmented epithelium dysfunction. Despite the multitude of genetic mutations being associated with the RP phenotype, the clinical and functional manifestations of the disease remain the same: nyctalopia, visual field constriction (tunnel vision), photopsias and pigment proliferation. In this review, we describe the typical clinical phenotype of human RP and review the anatomical and functional remodelling which occurs in RP determined from studies in the rd/rd (rd1) mouse. We also review studies that report a slowing down or show an acceleration of retinal degeneration and finally we provide insights on the impact retinal remodelling may have in vision restoration strategies.

Contents

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1. Introduction

Inherited retinal dystrophies are a family of hereditary diseases where mutations affecting the retinal pigment epithelium (RPE) or photoreceptors lead to photoreceptor degeneration (Hamel, 2014). Over 238 genes have been identified in retinal disease (RetNet, http://www.sph.uth.tmc.edu/RetNet/; Daiger et al., 1998), many associated retinitis pigmentosa (RP) which affects around 1:4000 individuals (Bertelsen et al., 2014; Haim, 2002). RP is usually classified clinically as an inherited retinal dystrophy where electrophysiological testing displays a greater rod deficit compared to cone function. Although RP progression rate varies, ultimately continued rod and cone degeneration leads to functional blindness (Hamel, 2014; Maugeri et al., 2000).

Anatomical remodelling in RP includes pigment proliferation, a clinical hallmark of the disease and reason from which the condition derives its name (Fig. 1A, B). With progressive photoreceptor loss, pigmented epithelial cells migrate to the inner retina (Kolb and Gouras, 1974; Li et al., 1994) displaying a bone-spicule like appearance (Fig. 1A, B). Dysfunctional retinal areas, demonstrated with visual field testing (Fig. 1D) also display reduced fundus autofluorescence reflecting RPE dysfunction (Fig. 1C). Mid-peripheral areas of vision loss (Fig. 1D) typically progress inwards and outwards with increased disease severity.

Anatomical changes in RP can also be visualised in optical coherence tomography (OCT) images. Fig. 1E demonstrates constituent layers of the retina missing in RP (photoreceptor layer: Fig. 1E). Fig. 1F demonstrates the migration of cells forming the pigmented bone-spicule like changes in retinal areas where photoreceptors have been lost for a long time (mid-periphery). Hyper-reflective areas identifying an epiretinal membrane (ERM) in the vitreal interface (asterisks identify the small hyper-reflective dots of the ERM in Fig. 1E) reflect a further example of anatomical remodelling common to RP (16%: Testa et al., 2014). Other common anatomical changes include cystoid macular oedema (20%–49%) and abnormal vitreo-retinal traction (5%: Adackapara et al., 2008; Hajali et al., 2008; Sandberg et al., 2008; Testa et al., 2014). Histopathological analysis of ERMs suggest a glial contribution (Kase et al., 2006; Schumann et al., 2011) and indicate anatomical remodelling in RP involves RPE cells and retinal glia, presaging some recent discoveries in animal models of RP. In addition to anatomical remodelling, functional changes such as photopsia are reported by almost half of patients experiencing them at the time of RP diagnosis (Bittner et al., 2009).

Overall, the anatomical and functional changes observed in human RP sufferers have implications for intervention measures and require a better understanding of the disease process at the cellular level. This review provides an overview of anatomical, neurochemical and functional changes in an animal model of RP, the rd1 mouse (Farber et al., 1994). Specifically, this review highlights anatomical changes in the rd1 mouse as revealed by cell markers, aberrant functional glutamate receptors in both bipolar and other inner retinal neurons and recent findings showing the critical role of Müller glia in late phase remodelling. We also review the impact of retinal remodelling may have on vision restoration strategies.

2. The rd1 mouse model of RP

The rd/rd ($rd^{+/+}$ or rd1) mouse is widely used as an animal model for autosomal recessive forms of RP (Carter-Dawson et al., 1978; Farber et al., 1994). It carries a mutation affecting the expression of the β subunit of phosphodiesterase 6 (PDE6) leading to accumulation of cGMP that is thought to trigger rod photoreceptor degeneration (Farber and Lolley, 1976; Ulshafer et al., 1980). Humans with autosomal recessive RP are known to carry this mutation (McLaughlin et al., 1993), and thus, the rodent models can be used to study core biological mechanisms that may provide useful insights applicable to human sufferers of the condition. In the rd1 mouse, rod degeneration begins ~P10 with progressive loss of the outer nuclear layer and cell kinesis evident in latter stages of degeneration (Fig. 2; Acosta et al., 2005; Carter-Dawson et al., 1978; Farber et al., 1994; Gibson et al., 2013; Greferath et al., 2015). All rod photoreceptors are lost by ~P25 and most cone photoreceptors degenerate by ~P100 although regional differences remain (Farber et al., 1994). Late stage retinal remodelling (phase 3), is thought to occur after ~P600 in the rd1 mouse (Jones et al., 2003).

2.1. Anatomical remodelling in the rd1 mouse

Anatomical remodelling involves morphological changes such as sprouting or pruning of cellular processes and cell kinesis and has been described in age-related macular degeneration and secondary to inherited retinal dystrophies, retinal detachment and, ischaemia/reperfusion (Fisher et al., 2005; Gargini et al., 2007; Jones et al., 2012, 2003; Marc et al., 2007; Phillips et al., 2010; Strettoi et al., 2003; Sullivan et al., 2007; Sun et al., 2007a, 2007b). A sequelae of photoreceptor death also includes death of retinal ganglion cells (the major output cell of the retina), either directly due to the pathology in primary optic nerve diseases or secondary to outer retinal disease such as rod-cone and related dystrophies (Almasieh et al., 2012; Damiani et al., 2012; Humayun et al., 1999; Newman et al., 1987; Osborne et al., 2004; Santos et al., 1997) and glial cell remodelling (Chua et al., 2013; Greferath et al., 2015; Milam et al., 1998; Strettoi and Pignatelli, 2000; Strettoi et al., 2003, 2002).

During photoreceptor degeneration in the rd1 mouse and other models of rod-cone retinal dystrophies (i.e. the chx10 and prph2 mouse and the P23H, RCS and S344ter rat), anatomical changes occur progressively in three phases (Marc et al., 2003: Table 1). Phase 1 and 2 refer to different stages of photoreceptor degeneration (rod followed by cone degeneration), and include sprouting of neurites by photoreceptors that can extend through the whole retina as far as the inner limiting membrane (Fariss et al., 2000; Kolb and Gouras, 1974; Li et al., 1994; Milam et al., 1998; Strettoi and Pignatelli, 2000; Strettoi et al., 2003, 2002). There is also concurrent dendrite retraction of bipolar cells and horizontal cells (altered calbindin labelling in the OPL: Fig. 3A) and loss of markers of glutamate release vesicular transporter in the outer retina (Fig. 3B). Amacrine and horizontal cells show neurite sprouting and