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Leber congenital amaurosis due to *RPE65* mutations and its treatment with gene therapy

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A B S T R A C T

Leber congenital amaurosis (LCA) is a rare hereditary retinal degeneration caused by mutations in more than a dozen genes. *RPE65*, one of these mutated genes, is highly expressed in the retinal pigment epithelium where it encodes the retinoid isomerase enzyme essential for the production of chromophore which forms the visual pigment in rod and cone photoreceptors of the retina. Congenital loss of chromophore production due to RPE65-deficiency together with progressive photoreceptor degeneration cause severe and progressive loss of vision. *RPE65*-associated LCA recently gained recognition outside of specialty ophthalmic circles due to early success achieved by three clinical trials of gene therapy using recombinant adeno-associated virus (AAV) vectors. The trials were built on multitude of basic, preclinical and clinical research defining the pathophysiology of the disease in human subjects and animal models, and demonstrating the proof-of-concept of gene (augmentation) therapy. Substantial gains in visual function of clinical trial participants provided evidence for physiologically relevant biological activity resulting from a newly introduced gene. This article reviews the current knowledge on retinal degeneration and visual dysfunction in animal models and human patients with RPE65 disease, and examines the consequences of gene therapy in terms of improvement of vision reported.

Contents

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1. Introduction

A critical mass of knowledge reached after decades of basic, pre-clinical and clinical research recently culminated in three independent clinical trials of ocular gene therapy in patients with a rare hereditary blindness caused by mutations in the *RPE65* gene (NCT00481546, NCT00516477, NCT00643747, clinicaltrials.gov). Results so far attest not only to the safety of the procedure but also detectable improvements in vision (Bainbridge et al., 2008; Cideciyan et al., 2008, 2009a,b; Hauswirth et al., 2008; Maguire et al., 2008, 2009; Simonelli et al., 2010). Although there have been previous attempts of gene therapy in human ocular disease (Campochiaro et al., 2006; Chévez-Barrios et al., 2005), recent *RPE65* gene therapy trials provide exciting evidence of biological activity resulting from a newly introduced gene in human patients. The expression of the new gene was physiologically relevant causing up to 4.8 log unit improvement in vision corresponding to the retinal location of gene introduction, was detectable by 30 days, and lasted unabated for at least 1 year (Cideciyan et al., 2008, 2009a). These findings bode well for current and future plans of gene therapy approaches to many other rare hereditary retinal conditions as well as more common ocular diseases.

This review summarizes the literature on the retinal disease caused by *RPE65* mutations in murine and canine models as well as human patients with particular emphasis on the resulting degeneration of retinal cells and loss of function. Also reviewed are the improvements of the visual function achieved with gene therapy in pre-clinical experiments as well as results of the human clinical trials. The reader is directed to other recent reviews for in depth coverage of phototransduction, retinoid cycle of vision and RPE65 biology (Cai et al., 2009; McBee et al., 2001; Lamb and Pugh, 2004; Rando, 2001; Redmond, 2009; Travis et al., 2007), Leber congenital amaurosis and related retinal degenerative conditions (Henderson et al., 2006; Koenekoop, 2007; den Hollander et al., 2008; Moradi and Moore, 2007; Stone, 2007; Wright et al., 2010), treatment strategies for retinal degenerative diseases (Stone, 2009; Thomson and Lotery, 2009), and ocular gene therapy (Alexander and Hauswirth, 2008; Chung et al., 2009; Colella et al., 2009; Conley et al., 2008; Rex, 2007; Smith et al., 2009). Not covered in this review are the studies demonstrating the successful use of substitute chromophores in RPE65-deficiency (Moise et al., 2007; Travis et al., 2007; Van Hooser et al., 2000) which have led to the recent initiation of a clinical trial (NCT01014052, clinicaltrials.gov).

2. Biology of RPE65

Vertebrate vision is signaled by the activation of the phototransduction cascade in rod and cone photoreceptor cells of the retina when light quanta are absorbed by the ubiquitous chromophore 11-*cis*-retinal and converted to its all-*trans* isomer. Continued function of photoreceptors requires removal of the all-*trans*-retinal and resupply with chromophore. Sources of 11-*cis* retinoids are provided by two visual (retinoid) cycles of vision taking place in cells neighboring photoreceptors: the retinal pigment epithelium (RPE) and the Muller glia (Bok, 1993; Lamb and Pugh, 2004; McBee et al., 2001; Rando, 2001; Travis et al., 2007; Wang and Kefalov, 2009). The canonical (classical) visual cycle takes place in the RPE and uses a key enzyme, termed retinoid isomerase, to produce 11-*cis*-retinal for both rod and cone photoreceptors using all-*trans* retinoid substrates either recycled from photoreceptors as vision byproducts or originating from the choroidal blood supply and ultimately from dietary vitamin A. The alternative (retinal) visual cycle involves the Muller glial cells to regenerate chromophore for the cones (Travis et al., 2007; Wang and Kefalov, 2009). RPE65 is the indispensible retinoid isomerase of the canonical RPE visual cycle (Jin et al., 2005; Moiseyev et al., 2005; Redmond et al., 2005, 2010) and it is highly and preferentially expressed in the RPE cells (Redmond, 2009). Crystal structure of the RPE65 molecule has recently been solved (Kiser et al., 2009). The isomerase of the alternative visual cycle is not yet known.