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Nanoparticles for retinal gene therapy

Shannon M. Conley, Muna I. Naash*

University of Oklahoma Health Sciences Center, Department of Cell Biology, BMSB 781, 940 Stanton L. Young Blvd, Oklahoma City, OK 73104, USA

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A B S T R A C T

Ocular gene therapy is becoming a well-established field. Viral gene therapies for the treatment of Leber's congentinal amaurosis (LCA) are in clinical trials, and many other gene therapy approaches are being rapidly developed for application to diverse ophthalmic pathologies. Of late, development of non-viral gene therapies has been an area of intense focus and one technology, polymer-compacted DNA nanoparticles, is especially promising. However, development of pharmaceutically and clinically viable therapeutics depends not only on having an effective and safe vector but also on a practical treatment strategy. Inherited retinal pathologies are caused by mutations in over 220 genes, some of which contain over 200 individual disease-causing mutations, which are individually very rare. This review will focus on both the progress and future of nanoparticles and also on what will be required to make them relevant ocular pharmaceutics.

Contents

* Corresponding author. Tel.: +1 405 271 8001x47969; fax: +1 405 271 3548.
E-mail address: muna-naash@ouhsc.edu (M.I. Naash).

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1. Introduction

Chronic, degenerative diseases of the retina lack curative treatments, and their blinding effects can seriously limit the quality of life. Among these diseases are several for which causative genes have been clearly identified including retinitis pigmentosa (RP), Leber's congential amaurosis (LCA), some forms of macular degeneration (MD), and ciliopathies such as Bardet–Biedl syndrome (BBS). Other diseases have both genetic and environmental components including age-related macular degeneration (ARMD) and glaucoma.

Treatments for chronic retinal diseases have historically been limited by several factors. Many drugs cannot pass through the cornea/sclera when administered topically, and the eye is protected from the bloodstream by the blood-retina barrier so that ocular bioavailability after systemic administration is typically quite low. Some exceptions do exist; notable examples include intraocular pressure lowering drugs (administered topically) for the treatment of glaucoma and vitamin A (administered systemically) for the treatment of visual defects associated with chromophore deficiencies. As a result of these limitations, alternative administration procedures have been sought to deliver drugs to the inside of the eye and advancements have been made in the use of intravitreal or subretinal injections; however, these methods are quite invasive and repeated treatments for a chronic disease are difficult and undesirable. Finally, for many retinal diseases, the onset of phenotype often follows the onset of degeneration, making regeneration a requisite for curative treatments.

Advancements in drug delivery, the generation of controlled/sustained release drugs, and an improved understanding of the pathogenesis of many degenerative retinal diseases have helped to significantly advance the field. Recently developed drugs include peptide-based, antibody-based, and small molecule therapeutics. Virally delivered gene therapeutics are in clinical trials (Bainbridge et al., 2008; Cideciyan et al., 2008; Bressler, 2009). Research into genetic therapies in particular is expanding and maturing. Herein we discuss the development and application of safe, effective, non-viral (primarily nanoparticle) – based gene therapies for ocular use. In addition, we provide thoughts and strategies to help translate those vectors into clinical use.

1.1. Ocular gene therapy

The eye is an excellent target for the development of genetic therapies. One obvious advantage is that therapy on the genetic level addresses the source of the problem, not just the symptoms, and the option for local delivery may improve effectiveness without systemic toxicity. Many debilitating monogenic retinal diseases are well characterized, with identified genes and mutations. Animal models containing loss-of-function and gain-of-function mutations are available, as are models containing mutations in structural, functional, and developmental genes, and models for testing the effects of genetic therapies on wound healing and surgical interventions enabling researchers to test therapies designed to target a variety of disease categories (Nour et al., 2003; Wilson and Wensel, 2003; Mohan et al., 2005; Chang et al., 2006; Farjo et al., 2006; den Hollander et al., 2008; Baehr and Frederick, 2009; Farjo and Naash, 2006). The same barriers that make ocular administration difficult also make the eye relatively immune-privileged. Intraocularly-delivered drugs are far less likely to induce severe immune responses than their systemically-delivered counterparts, and intraocularly administered drugs usually have low systemic bioavailability and low volume of distribution (Andrieu-Soler et al., 2006a,b). Ideally, gene therapy vectors are taken into the target cells of interest where the genetic material is protected in the nucleus and can continually express its gene product without