Available online at www.sciencedirect.com
ScienceDirect
Journal of Controlled Release 124 (2007) 107–133
journal of controlled release
www.elsevier.com/locate/jconrel

Review

Corneal gene therapy ☆

Eytan A. Klausner [a,*], Dan Peer [b], Robert L. Chapman [a], Richard F. Multack [c], Shridhar V. Andurkar [a]

[a] *Midwestern University Chicago College of Pharmacy, 555 31st Street, Downers Grove, IL 60515, United States*
[b] *CBR Institute for Biomedical Research, and Department of Anesthesia, Harvard Medical School, 200 Longwood Avenue, Boston, MA 02115, United States*
[c] *Midwestern University Chicago College of Osteopathic Medicine, 555 31st Street, Downers Grove, IL 60515, United States*

Received 15 January 2007; accepted 15 May 2007
Available online 4 July 2007

Abstract

Gene therapy to the cornea can potentially correct inherited and acquired diseases of the cornea. Factors that facilitate corneal gene delivery are the accessibility and transparency of the cornea, its stability *ex vivo* and the immune privilege of the eye. Initial corneal gene delivery studies characterized the relationship between intraocular modes of administration and location of reporter gene expression. The challenge of achieving effective topical gene transfer, presumably due to tear flow, blinking and low penetration of the vector through epithlelial tight junctions left no alternative but invasive administration to the anterior chamber and corneal stroma. DNA vaccination, RNA interference and gene transfer of cytokines, growth factors and enzymes modulated the corneal microenvironment. Positive results were obtained in preclinical studies for prevention and treatment of corneal graft rejection, neovascularization, haze and herpetic stromal keratitis. These studies, corneal gene delivery systems and modes of administration, and considerations regarding the choice of animal species used are the focus of this review. Opportunities in the field of corneal gene therapy lie in expanding the array of corneal diseases investigated and in the implementation of recent designs of safer vectors with reduced immunogenicity and longer duration of gene expression.

Keywords: Cornea; Eye; Gene therapy; Corneal graft rejection; Herpetic stromal keratitis; Corneal neovascularization

Contents

☆ This article is dedicated to the memory of Milo Gibaldi, Ph.D.

* Corresponding author. Tel.: +1 630 515 7104; fax: +1 630 515 6958.
E-mail address: eklaus@midwestern.edu (E.A. Klausner).

0168-3659/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jconrel.2007.05.041

1. Introduction

Corneal gene therapy initially emerged in 1994 when its potential in correcting acquired corneal inflammatory diseases was noted following successful transduction of corneal tissues using replication-deficient adenovirus [1]. Inherited corneal diseases such as corneal endothelial dystrophies [2] are natural candidates for corneal gene therapy [3–5]. However, most of the research has focused on modulation, including immunomodulation, of acquired medical conditions. This is feasible since control of the corneal microenvironment can be attained by induction or knock-down of proteins using corneal gene therapy.

Local corneal gene delivery has the potential to achieve low and continuous concentrations of biologically active proteins thereby improving the efficacy and safety of the treatment [6]. This methodology can be applied to the delivery of various cytokines and growth factors to the cornea thus affecting immune response, inflammation, angiogenesis and proliferation and cell differentiation. Corneal gene therapy also holds promise in obtaining local protein expression at concentrations unattainable by systemic administration of the recombinant protein [7].

While corneal gene therapy has developed as a part of the natural growth in the field of gene therapy, several advantages are apparent in making the cornea particularly attractive for gene transfer. The cornea has a well-defined anatomy [8] and is easily accessible [8–11] during ambulatory visits, as well as surgical procedures [12,13]. The cornea can be treated non-invasively [13] as the anatomic location of corneal epithelium permits direct topical instillation of the gene delivery system [14]. The perfect transparency of the cornea allows rapid and non-invasive visual observation [8,9,15] using standard ophthalmologic methods *e.g.*, slit-lamp biomicroscopy, with high magnification thus estimating the effectiveness and safety of the treatment [16].

Additional factors facilitate gene therapy to both anterior and posterior parts of the eye and are therefore relevant to corneal gene transfer. For instance, the eye is a partially immune-privileged site [17,18] thereby enabling the use of otherwise immunogenic or proinflammatory vectors [18]. In terms of experimental design, the fact that the eye is a paired organ enables the contralateral eye to serve as an internal control [19,20]. Also, the ocular tissues are easily anesthetized [16], and are treatable during trabeculectomy, cataract surgery and corneal transplantation [21]. In the same spirit, *ex vivo* gene transfer to a donor cornea prior to corneal grafting entails several advantages when compared to *ex vivo* manipulations of other grafts: The cornea can be maintained in culture for up to 1 month [8,9]; its small size enables modification of the complete tissue [18]; and the major target cell (the corneal endothelial cell) forms a monolayer on the corneal surface and is therefore perfectly accessible to gene vectors [7].

Due to the importance of corneal gene therapy and its inherent advantages, studies have been conducted throughout recent years on various types of animals to investigate new treatments for major corneal disorders such as allograft rejection following corneal transplantation, herpetic stromal keratitis (HSK), corneal neovascularization and corneal haze. The potential of corneal gene therapy in decreasing the incidence of blindness is vast, as it can enhance survival of corneal grafts as well as ameliorate corneal disorders that currently lead to the need for corneal transplantation thus obviating the need for an allograft [22]. A particular challenge in corneal gene delivery