Available online at www.sciencedirect.com
ScienceDirect
Advanced Drug Delivery Reviews 58 (2006) 1243–1257
Advanced DRUG DELIVERY Reviews
www.elsevier.com/locate/addr

Current status of gene delivery and gene therapy in lacrimal gland using viral vectors ☆

Shivaram Selvam [a,b], Padmaja B. Thomas [b], Sarah F. Hamm-Alvarez [c,d,e], Joel E. Schechter [b,f], Douglas Stevenson [b], Austin K. Mircheff [d,e], Melvin D. Trousdale [b,e,*]

[a] *Mork Family Department of Chemical Engineering and Materials Science, Viterbi School of Engineering, University of Southern California, Los Angeles, CA 90089, USA*
[b] *Ocular Surface Center, Doheny Eye Institute, Los Angeles, CA 90033, USA*
[c] *Department of Pharmaceutical Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA*
[d] *Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA*
[e] *Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA*
[f] *Department of Cell and Neurobiology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA*

Received 12 June 2006; accepted 31 July 2006
Available online 15 September 2006

Abstract

Gene delivery is one of the biggest challenges in the field of gene therapy. It involves the efficient transfer of transgenes into somatic cells for therapeutic purposes. A few major drawbacks in gene delivery include inefficient gene transfer and lack of sustained transgene expression. However, the classical method of using viral vectors for gene transfer has circumvented some of these issues. Several kinds of viruses, including retrovirus, adenovirus, adeno-associated virus, and herpes simplex virus, have been manipulated for use in gene transfer and gene therapy applications. The transfer of genetic material into lacrimal epithelial cells and tissues, both in vitro and in vivo, has been critical for the study of tear secretory mechanisms and autoimmunity of the lacrimal gland. These studies will help in the development of therapeutic interventions for autoimmune disorders such as Sjögren's syndrome and dry eye syndromes which are associated with lacrimal dysfunction. These studies are also critical for future endeavors which utilize the lacrimal gland as a reservoir for the production of therapeutic factors which can be released in tears, providing treatment for diseases of the cornea and posterior segment. This review will discuss the developments related to gene delivery and gene therapy in the lacrimal gland using several viral vector systems.

Keywords: Viral vectors; Lacrimal gland; Gene therapy; Gene delivery; Sjögren's syndrome; Exocytosis

Abbreviations: Ad, adenovirus; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; β-gal, β-galactosidase.

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Ocular Drug Delivery", Vol. 11, 2006.

* Corresponding author. Doheny Eye Institute, 1450 San Pablo Street, #204, Los Angeles, CA, 90033 USA. Tel.: +1 323 442 6610; fax: +1 323 442 6688.
E-mail address: mtrousdale@doheny.org (M.D. Trousdale).

0169-409X/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.addr.2006.07.021

Contents

1. Introduction . . . 1244
2. Gene delivery by viral vectors in primary cultures of lacrimal gland tissue . . . 1244
3. Ad-mediated gene therapy. . . . 1245
3.1. Dry eye syndrome . . . 1245
3.2. Autoimmune dacryoadenitis in animal models. . . . 1245
3.3. Prophylactic effect of IL-10 in vivo . . . 1246
3.4. Prophylactic effect of TNF-α in vivo . . . 1247
4. Ad-mediated gene transfer: in the study of lacrimal gland physiology. . . . 1249
4.1. Androgen responses in primary cultures of lacrimal epithelial cells . . . 1249
4.2. Role of cytoplasmic dynein in apical secretory traffic in lacrimal acini . . . 1249
4.3. Role of PKC-α and PKC-ε on apical exocytosis of lacrimal acini . . . 1249
4.4. Role of actin and non-muscle myosin II in apical exocytosis of tear proteins . . . 1250
5. Ad-mediated gene transfer: modulation of secretory functions by Adv capsids in lacrimal epithelia . . . 1250
6. Retroviral-mediated gene transfer: immortalization of rabbit lacrimal gland epithelial cells . . . 1251
7. Conclusions and future directions . . . 1252
References . . . 1252

1. Introduction

Gene transfer and gene therapy in principle involve the development of efficient means for delivering gene (s) to the nuclei of somatic cells to replace a defective gene with a functionally normal one. This approach offers the hope of cures for various genetic and autoimmune diseases, including sickle cell disease [1], X-linked severe combined immunodeficiency disorder [2], Sjögren's syndrome [3], rheumatoid arthritis [4], type I diabetes [5], multiple sclerosis [6], cystic fibrosis [7], and hemophilia [8]. Additionally, it also provides hope for long-term therapeutic benefits in contrast to the transient relief provided by conventional drug therapy.

One of the basic methods of gene transfer is to modify viruses into genetic shuttles which will deliver the gene of interest into the target cells. Much progress in gene delivery and therapy has been achieved with viral vectors due to their high transduction efficiency in cells in vivo. Viral vector systems, including retroviruses, lentiviruses, adenoviruses, and adeno-associated viruses, currently offer the best choice for efficient gene delivery [9,10]. The most commonly used DNA viral vectors are adenoviruses (Ad) and adeno-associated viruses. These vectors have been extensively used in gene therapy of the eye [11]. They have been successfully used to mediate gene transfer for ocular neovascularization [12,13], age-related macular degeneration [14], uveitis [15], diabetic retinopathy [16] corneal wound healing [17] and experimental autoimmune lacrimal gland disease [18,19]. In this review, we discuss the viral gene delivery approaches performed in the lacrimal gland to understand and modulate lacrimal gland functions for therapeutic purposes.

2. Gene delivery by viral vectors in primary cultures of lacrimal gland tissue

Genes can also be introduced into cells to produce beneficial substances for therapeutic purposes. The lacrimal gland is responsible for the production and regulated release of tear proteins into ocular surface fluid. These proteins include nutrient factors which nurture the cornea, as well as factors which protect the ocular surface from pathogens. Delivery of genes for necessary products the lacrimal gland would chronically secrete could be a potential therapeutic approach for patients suffering from various diseases of the eye, including, glaucoma, dry eye, keratitis, and uveitis. Currently, these diseases require long-term administration of therapeutic preparations in the form of topical eye drops and eye ointments. Although this approach has the advantage in minimizing systemic side effects, the major drawback is the short residence time of the