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Gene Therapy for Corneal Neovascularization

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Corneal neovascularization occurs when the balance between angiogenic and antiangiogenic factors is tilted toward angiogenic factors. It can cause corneal scarring, stromal edema, lipid deposition, and inflammation, resulting in significant visual impairment and poor prognosis after subsequent penetrating keratoplasty. Because Vascular Endothelial Growth Factor (VEGF) plays an integral role in the pathogenesis of corneal neovascularization, many studies on gene delivery to the cornea have been focused on inhibiting the VEGF signaling pathway in animal models of chemical burn-induced corneal neovascularization.

Several routes including subconjunctival, intracorneal, and topical administration have been used to deliver genes to the cornea. In addition, gene can be applied to the cornea using plasmid DNA, viral vectors, or nanoparticles.

First, subconjunctival or intracorneal injection of plasmid DNA genes which have anti-angiogenic effects has been tried in VEGF-induced experimental corneal neovascularization. Naked plasmid DNA encoding soluble VEGF receptor Flt-1 was injected directly into the corneal stroma [1]. In addition, plasmids encoding Kringle 5 of plasminogen and endostatin were effectively transferred to the cornea by subconjunctival injection [2,3]. We have previously reported that subconjunctival delivery of Brain-specific Angiogenesis Inhibitor 1 (BAI1) and GA-Binding Protein (GABP) transcription factor genes as plasmid forms could effectively reduce experimental corneal neovascularization induced by chemical and mechanical denudation [4,5]. Exogenous BAI1 and GABP gene expression was observed in the cornea until 7 days after subconjunctival injection of plasmid DNA.

Second, subconjunctival, intracorneal, or topical administration of viral vectors encoding anti-angiogenic genes has been successfully used to transfect the cornea. The major viral vectors include adenoviral vectors, lentiviral vectors, and recently, Adeno-Associated Viral (AAV) vectors. Recombinant adenovirus encoding human vasohibin-1 and retrovirus encoding murine endostatin or murine-soluble VEGF receptor-2 were injected subconjunctivally to reduce corneal neovascularization [6,7]. Subconjunctival injection of a recombinant AAV vector could deliver endostatin and angiostatin genes to the corneal epithelium directly to inhibit angiogenesis [8,9]. The delivered genes were expressed in the cornea within therapeutic levels for a prolonged period. Delivery by intracorneal injection of viral vectors could also yield good expression of genes in murine corneas. Recently, recombinant viral vectors have been applied topically to deliver genes to the cornea. Targeted decorin gene therapy which was delivered with a single topical AAV5 titer application onto the rabbit stroma effectively decreased VEGF expression and retarded corneal neovascularization [10].

Finally, subconjunctival, intracorneal, or topical gene delivery using nanoparticles or nanomaterials is a promising method to treat corneal neovascularization. Nanoparticles which can be used in gene transfer to the cornea include chitosan and gold. In a recent report, subconjunctival injection of a micellar nanovector containing a reporter gene showed prolonged gene expression with low cytotoxicity. Also, subconjunctival gene transfer by the polyplex micelles containing sflt-1 plasmid significantly inhibited murine corneal neovasularization [11]. Another study demonstrated that intrastromal injection of plasmids containing pSEC.shRNA against VEGF-A-loaded poly (lactic co-glycolic acid) nanoparticles was an effective, nonviral, nontoxic, and sustainable method of gene therapy for corneal neovascularization [12].

However, there are several shortcomings in gene therapy, which can be limited in the clinical utility. Injection into the corneal stroma has the risk of complications associated with the procedure. For topical gene application, the corneal epithelium should be removed extensively. On the other hand, subconjunctival injection of genes may be relatively safe and simple procedure compared with other approaches.

In summary, gene therapy by subconjunctival, intracorneal, or topical delivery of anti-angiogenic genes using plasmids, viral vectors, or nanoparticles is a simple, safe, and effective treatment modality which can lead to sustained, high levels of gene expression to inhibit experimental corneal neovascularization by inhibiting the VEGF signaling pathway. Gene therapy could be potentially useful for the treatment of patients with corneal neovascularization.

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