Gene Therapy Using Neuroprotective Factors in Glaucoma

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Adeno-associated virus (AAV) vectors are considered optimal vectors for gene transfer into the retina because of their stable long-term gene expression and safety. In ocular gene therapy, the route of vector administration to the retina is exceedingly important. For inherited retinal diseases that affect the photoreceptors and the retinal pigment epithelium (RPE), vectors are typically administered via the subretinal route. Via this route, AAV-mediated gene therapy has been used to deliver the RPE 65 gene to the RPE in patients with Leber's congenital amaurosis, an inherited blinding disease[1,2]. In contrast to subretinal administration, which has a high transduction efficiency, intravitreal injection has a low and insufficient transduction efficiency[3]. However, because subretinal injection for iatrogenic retinal detachment may cause decreased visual acuity, intravitreal injection is a better choice when the macula is involved.

There are 12 subtypes of AAV vector with various tissue specificities. Our group has investigated their specificity in muscles[4] and the nervous system[5]. In addition, transduction efficiency into intraocular tissues has been shown to vary greatly depending on the cell type. So far, gene transfer via the intravitreal route has been performed with AAV vectors of types 2, 5, and 8[3]. We have found that the AAV type 8 vector has a high transduction efficiency into the retina[6]. Furthermore, serial measurement of gene expression with an in vivo imaging system has shown that transduction efficiency comparable to that with the subretinal route can be achieved with the intravitreal route, with effects lasting for 1 year[7]. We predict that gene therapy studies using intravitreal administration will be performed for disorders of the inner retina.

High transduction efficiency in the retina has been demonstrated with the intravitreal injection of tyrosine-mutant AAV vectors[8]. These vectors are mutant viral vectors in which a tyrosine residue in the outer envelope has been replaced by phenylalanine. Because this replacement inhibits self-degradation of the vector via the ubiquitin-proteasome system, transduction efficiency is 30 times as high as with the wild-type vector. We also have created tyrosine-mutant AAV vectors that express neuroprotective factors, such as ciliary neurotrophic factor and brain-derived neurotrophic factor. We are planning a gene therapy study aimed at establishing neuroprotection in a glaucoma model.

References

1. Hauswirth WW, Aleman TS, Kaushal S, et al.: Treatment of leber congenital amaurosis due to RPE65 mutations by ocular subretinal injection of adeno-associated virus gene vector: short-term results of a phase I trial. Human gene therapy 2008; 19: 979–990.
2. Maguire AM, Simonelli F, Pierce EA, et al.: Safety and efficacy of gene transfer for Leber's congenital amaurosis. The New England journal of medicine 2008; 358: 2240–2248.
3. Lebherz C, Maguire A, Tang W, Bennett J, Wilson JM: Novel AAV serotypes for improved ocular gene transfer. The journal of gene medicine 2008; 10: 375–382.
4. Isotani M, Miyake K, Miyake N, Hirai Y, Shimada T: Direct comparison of four adeno-associated virus serotypes in mediating the production of antiangiogenic proteins in mouse muscle. Cancer investigation 2011; 29: 353–359.
5. Miyake N, Miyake K, Yamamoto M, Hirai Y, Shimada T: Global gene transfer into the CNS across the BBB after neonatal systemic delivery of single-stranded AAV vectors. Brain research 2011; 1389: 19–26.

6. Igarashi T, Miyake K, Masuda I, Takahashi H, Shimada T: Adeno-associated vector (type 8)-mediated expression of soluble Flt-1 efficiently inhibits neovascularization in a murine choroidal neovascularization model. Human gene therapy 2010; 21: 631–637.
7. Igarashi T, Miyake K, Asakawa N, Miyake N, Shimada T, Takahashi H: Direct comparison of administration routes for AAV8-mediated ocular gene therapy. Current eye research 2013; 38: 569–577.
8. Petrs-Silva H, Dinculescu A, Li Q, et al.: High-efficiency transduction of the mouse retina by tyrosine-mutant AAV serotype vectors. Molecular therapy 2009; 17: 463–471.