GENE THERAPY
AND IT'S
Implications
IN OPTHALMOLOGY

ESSAY

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Summary

Gene therapy is a powerful and promising tool for replacement or inactivation of abnormal genes in some reported ocular diseases .The ideal gene delivery vector would efficiently and specially transfer the gene to target cells and obtain high level of gene expression .In addition, the vector would not evoke an immune response and would be non toxic to the recipient ***(Zack et al., 1993)***

Improving the transfer efficiency and prolonging the duration of transgene expression will be accomplished through a better understanding of the mechanisms by which vectors gain access to cells, what factors influence their access, and what factors can tribute to the loss of transgene expression ***(Feuerbach et al., 1996)***

Vector used to deliver the specific gene to the target cells include viral and non viral vectors reaching the target cells by in vivo, ex vivo or in situ approaches ***(Da Cruze et al., 1997)***

Hereditary retinal dystrophy is a target for gene therapy by controlling apoptosis achieved by using gene which antagonize apoptosis e.g. Hereditary retinal dystrophy is a target for gene therapy by controlling apoptosis achieved by using gene which antagonize apoptosis e.g.by using growth factors as ciliary neurotrophic factor (CNT F) using direct intravitreal injection or indirectly using recombinant adenovirus (rAV) or recombinant adenoassociated viral(rAAV) vectors ***(Chen et al., 1996)***

In 1996,Bennett and his associates use (rAV) vector to deliver B. photodiesterase (B.PDE) gene to the photoreceptor cells by subretinal

injection in retinal degeneration (rd) mice and observe an increase in the number of payers of cells indicating success of the experiment (Bennett et al., 1996)

In 1999,Nobutsugu and his associates together with Hurwitz and his associates used herpes simplex virus thumidine himase (Hsv-TK) gene delivered by retroviral vector to suppress tumorgenesis in prepared retinoblastoma (rb) cell cultures and observe inhibition of the humor cells. Also, experimental mice were used by intraperitoneal injection of Rb cells followed by intraocular injection of significant prolongation of progression .Free survival in comparison to the untreated ones ***(Nobutsugu et al., 1999)***

In age related macular degeneration Intravitreal injection of AAV vector mainly results in the transduction of the ganglion cells, whereas subretinal administration results in the transduction of the RPE and the photoreceptors. Bovine immunodeficiency lentivirus vector similarly has been used for subretinal gene delivery in mice. With the advent of antineovascular pharmacotherapy, the visual prognosis of patients with wet AMD has improved. However, the current standard-of-care therapies require monthly intravitreal injections by a retina specialist due to their short half-life in the vitreous. Besides the logistic difficulties ,the patient's discomfort, cataract formation, endophthalmitis, vitreous hemorrhage and retinal detachment. ***(Pechan et al., 2008).***

To study the mechanism by which the genetic abnormalities lead to primary open angle glaucoma (POAG), Masanori and his associates in 1998 used non viral vector,The hemagglutinationing virus of Japan liposomes to transfer lacz DNA and flourscin iso –thiocyanate (FITC) labeled phosphor thioate oligonucleotides genes into the anterior chamber of rats and monlceys and found great result in controlling the resistance to aqueous humor out flow thus controlling POAG ***(Masanori et al., 1998)***

Finally, gene therapy is progressing rapidly because of the better understanding of genetic disease. Methods suggest that it is feasible to insert genes where they are missing or defective and suppress gene whene they produce abnormal proteins. They are forming the basis of a completely new type of treatment that may be used to a group of wide spread ocular disease that currently have no cure ***(Bennett et al., 1996)***

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List of Abbreviations

A	Adenin
AAV	Adenoassociated virus
AC	Anterior chamber
ACV	Acyclovirus
ADRP	Autosomal dominant retinitis pigmentosa
Adv-TK	Adenoviral-Thymidine kinase
AMD	Age related macular degeneration
Anti-TGF-B1	Anti transforming growth factor beta 1
AV	Adenovirus
Bc1	B-cell lymphoma
BDNF	Brain derived neurotrophic factor
BFGF	Basic fibroblast growth factor
B-gal	B-galactosidase
B-PpDE	B-phosphodisterase
C	Cytosin
CaPo4	Calcium phosphate
CAT	Chloramphenicol acetyle transferase
CB	Ciliary body
CECs	Chorohdal endothelial cells
Ced	Ccell death
CGMP	Cyclic gaunisidin monophosphate
CM	Centimorgan
CM	Ciliary muscle
CNTF	Ciliary neurotrophic factor
CNV	Choroidal neovascularization
CNVM	Choroidal neovascular membrane

CO	Cornea
DNA	Deoxyribonucleic acid
DsDNA	Double strand DNA
ELISA	Enzyme linked immunosorbent assay
EPs	Electric pulses
ERGs	Electroretinograge
FITC	Floroscein isothiocynate
G	Gounine
GCV	Gancyclovir
GTPase	Gaunasine triphosphatase
HAMA	Human antimouse antibody
HSV1	Herpes simplex virus 1
HSV-TK	Herpes simplex virus thimidine kinase
HUVECs	Human umbilical vein endothelial cells
I	Iris
ICE	Interleuken converting enzyme
IOP	Intraocular pressure
IPE	Iris pigment epithelium
Kb	Kilobase
KbP	Kilobase pair
MAbs	Monoclonal antibodies
MMPS	Matrix metalloproleinase
MRNA	Massenger ribonucleic acid
MW	Molecular weight
NGF	Nerve growth factor
NT4/5	Neurotrophin 4/5
PDE	Phosphidiesterase
PFU	Plaque forming unit

POAG	Primary open angle glaucoma
PRV	Proliferation vitreoretinopathy
RAAV	Recombinant adinoassociated virus
RAV	Recombinant adinovirus
RB	Rretinoblastoma
Rb	Rretinal degeneration
RDS	retinal degeneration slow
Rdy	Retinal dystrophy
RHSV	Rrecombenant herpes simplex virus
RNA	Ribonuclic acid
RP	Rretinitis pigmentosa
RPE	Retinal pigment epithelial
RPGR	Retinitis pigmentosa guanosine triphosphatase regulator
SC	Schlemm's canal
SsDNA	Single strand DNA
Ssgal	Single strand galactosidase
SsRNA	Single strand RNA
T	Thymine
TGF-B	Transforming growth factor beta
TMGR	Trabecular meshwork glucocorticoid response
TIMP-2	Tissue inhibitor of metalloproleinase2
TM	Trabecular meshwork
TPA	Tissue plasminogen activator
U-PA	Urokinase plasminogen activator
VEGF	Vascular endothelial plasminogen activator
X-gal	X-galactosidase
UM	Micro milli

List of Figure

List of Table

INTRODUCTION

Gene therapy implies the delivery of gene to somatic tissue for therapeutic purposes. The eye is an attractive target for gene therapy because of its accessibility and its immune privilege. Although history of genetics dates back to more than a century, only the last few decades, encompassing the DNA and genomics era, have witnessed breakthrough research work that have revolutionized various field including medicine. The only possible treatment that was predicted to become available for untreatable genetic disorder was gene therapy. ***(Alcand et al., 2001)***

Genes correspond to regions within DNA, a molecule composed of a chain of four different types of nucleotides−the sequence of these nucleotides is the genetic information organisms inherit.− The sequence of these nucleotides in a gene is translated by cells to produce a chain of amino acids, creating proteins**.** ***(Berg et al., 2002)***

The protein encoded by that gene malfunction. When a protein malfunctions, cells that rely on that protein's function can't behave normally, causing problems for whole tissues or organs. Patients develop a disease due to complete absence of a protein product. Typically, this occurs in autosomal recessive disease in which no protein is made and absence of the protein lead to disease. Medical conditions related to gene mutation are called genetic disorders. Gene controls much for your body's form and function. Throughout your life, your gene turns on and off as needed to control cell activity ***(Lodish et al., 2000)***

Gene therapy replaces a faulty gene or adds a new gene in an attempt to cure disease or make change in your body so it's better able to combat disease. Gene therapy holds promise for treating a wide rang of diseases including Leber's hereditary optic neuropathy, Retinitis pigmentosa, Macular degeneration, Retinoblastoma and Glaucoma. In early 2007 Leber's congenital amaurosis is an inherited blinding disease caused by mutations in the RPE65 GENE. The results of the Moorfields/UCL they researched the safety of the subretinal delivery of recombinant adeno associated virus (AAV) carrying RPE65 gene, and found it yielded positive results, with patients having modist increase in vision and perhaps more importantly, no apparent side effects. ***(Maguire et al., 2008)***

Scientists first took the logical step of trying to introduce genes directly into human cells however; this has proven more difficult than modifying bacteria, primarily because of the problems involved in carrying large sections of DNA and delivering them to the correct site on the comparatively large genome. So a "normal" gene is inserted into the genome to replace an "abnormal" disease-causing gene. A carrier molecule called a vector must be used to deliver the therapeutic gene to the patient's target cells. Currently the most common vector is a virus that has been genetically altered to carry normal human DNA. Virus has evolved a way of encapsulating and delivering their gene to human cells in a pathogenic manner. Wild-type AAV has attracted considerable inserted from gene therapy researchers due to a number of features. Chief amongst these is the viruses' apparent lack of pathogenicity. It can also infect non-dividing cells and has the ability to stably integrate into the host cell genome at a specific site (designated AAVS1) in the human chromosome 19. The feature makes it somewhat more predictable than retroviruses. ***(Surosky et al., 1997)***

Antisense therapy: is not strictly a form of gene therapy, but is a related, genetically-mediated therapy ***(Morcos, 2007).***

- **Types of gene therapy**

Gene therapy may be classified into the following types

1-Germ line gene therapy

2-somatic line gene therapy

Ocular gene therapy research has made rapid progress in the past few years. Although laboratory and animal experiments started were successful many years ago, the application in human being took very long due to several biological and regulatory hurdles. However, the recent successful gene therapy clinical trials are promising and encouraging. There are various methods that may be employed for gene therapy ***(Bainbridge et al., 2008)***

Gene therapy is a promising new field of medical research. In gene therapy, researchers try to supply copies of health gene to cells with variant or missing genes so that the "good" gene will take over. ***(Louis et al., 2009)***

INTRODUCTION OF GENE THERAPY