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Gene Therapy in Hearing Loss Treatment: A Review

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Abstract

Background Hearing loss, which is highly heterogeneous, is the most common sensorineural disorder in humans. More than 50% of the causes of deafness are attributed to genetic factors. Numerous studies have shown the persistent negative impact of deafness on communication and quality of life. Therefore, action to optimize performance and maintain or improve hearing ability seems necessary. In so doing, interventions are performed after assessing hearing loss. The most important intervention is gene therapy; For several genetic diseases, gene therapy is a potential treatment that is being investigated. Gene therapy will restore the ability to hear by overcoming functional defects caused by genetic mutations. Furthermore, gene therapy might potentially be used to trigger the regeneration of hair cells by transferring genes required in the cochlea for hair cell differentiation.
Aim: We review recent research about hereditary hearing loss and technologies in animal.
Methods: In this study, we review current reports in clarifying genomics of hereditary hearing loss and technologies between 2014 and 2020 in PubMed, Scopus, and Google Scholar to create a gene therapy that may soon become a treatment choice. We also discuss recent research applied to animal models of hearing loss by gene therapy.
Conclusion: Gene therapy allows for the treatment of sensorineural hearing loss by restoring and/or preserving the inner ear cells functioning. Hopeful results from recent research have contributed to cochlear gene therapies being created for end-use in patients.

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Introduction

Loss of hearing is one of the most common disorders in humans with a prevalence of 1 in 1000 births (1). The World Health Organization (WHO) reports that over 5% of the world's population suffers from hearing loss, and 34 million of these are children. It is estimated that more than 900 million people will increase by 2050 (2). Hearing loss implies the inability to hear in one or both ears as well as a person with normal hearing or a hearing threshold level of some more than 25 dB. In addition, hearing loss may be categorized as conductive, Sensorineural, or combined hearing loss. Conductive hearing loss is when there is an issue with the propagation of sound waves to the cochlea along with the outer ear, the ossicles of the middle ear, and the tympanic membrane. Sensorineural hearing loss (SNHL) occurs when there is an issue in the cochlea converting sound stimuli into the electrical signals of sensory hair cells (HCs) or when it transmits information to the brain about the afferent nerves (3). Unfortunately, none of these neurosensory cells can regenerate. Therefore,

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there is no replacement for these cells if are damaged due to injury or the normal aging process, as a consequence, the loss of these cells causes permanent sensory impairment in hearing (4-6). Numerous studies have shown the persistent negative impact of deafness on communication and quality of life. Deafness is a risk factor for dementia recently, too. It is also related to reduce functional ability and increased mortality (7-9).

Hearing loss is very heterogeneous as a result of mutations in several genes, mutations in each of these genes are sufficient for the disease to occur. It can also be said in the development of these disorders, genetic variants play a key role (10, 11). In addition, environmental causes such as cephalosporin use, noise exposure, middle ear infection, and aging should be considered (12). The development of new and effective methods in the treatment of deafness is extremely important. In recent years, gene therapy technology has advanced which makes it a potential way to treat certain inner ear disorders (13). This review article focuses on the recent advancement in gene therapy development to prevent or restore hearing loss. We looked at hearing loss-related genes and how genes can be used to retrieve or preserve hearing and how to transmit them to our target cells.

Methods

Here, we review current reports in clarifying genomics of hereditary hearing loss and technologies between 2014 and 2020 in PubMed, Scopus, and Google scholar to create a gene therapy that may soon become a treatment choice. We also discuss recent research applied to animal models of hearing loss by gene therapy.

Genetic loss of hearing

Syndromic versus non-syndromic loss of hearing

Hearing loss can clinically be related to many other disorders (syndromic) or be just a sign (non-syndromic). Syndromic hearing loss is associated with external ear incontinence and other organs incontinence. Non-syndromic hearing loss does not show any change in the visible shape, but if you can have inner or middle ear problems.

Genes of hearing loss

Between about 50 to 60 percent of children born with hearing loss, genes are responsible for hearing loss. The total of 121 genes for non-syndromic hearing loss have been reported to date, with 76 autosomal recessive, 49 autosomal dominant, and 5 X-related genes. Currently, an autosomal recessive mutation in the STRC is the primary cause of mild to severe hearing loss. However, approximately 30% of inherited hearing loss is correlated with a syndrome. Syndromic hearing silver is genetically less heterogeneous than non-syndromic. There are currently 11 syndromes associated with hearing loss with 32 autosomal recessive, 16 autosomal dominant, 4 autosomal dominant or recessive, and 2 X-linked recessive inheritance patterns (14).

The manifestation of deafness varies in autosomal dominant and recessive patterns. The onset of deafness is affected in the dominant autosome, and this will have trending images. While autosomal recessive, deafness was more severe than speech. In deafness with an autosomal recessive inherited pattern, the mutations have a dramatic loss of function, resulting in gene products being created or not present at all. The goal of gene therapy should be to replace the dysfunctional gene with functional gene copies. However, in autosomal dominant deafness, the type of mutation was specifically the functional gain or negative mutation, in which there were abnormal products or they continued to interfere with normal gene products. In such cases, the aim of gene therapy should be to eliminate the mutated form of the gene to regain normal gene function (15).

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Gene therapy in the inner ear

As a model for gene therapy, the inner ear has many specific advantages. First, the cochlea is well adapted to in vivo gene therapy anatomically. Relative cochlear chamber isolation reduces the gene's undesirable effects on the other structure. The inner ear is filled with fluid and allows all functional cells to access a transfection reaction. Furthermore, the concentration and dosage of complexes injected into the cochlea can be achieved easily by simply injecting them. Second, numerous physiological measurement techniques have been developed to evaluate the activity of specific cells and to determine the function and protection of gene therapy. Third, mutations have been reported in this organ in more than 100 genes that cause deafness, enabling structural and physiological study of the effect of these genetic mutations on various cells in the inner ear (16). Eventually, there are many options for treating deafness with gene therapy in the cochlea.

Introduction of vectors for gene therapy in cochlea

The cochlea, surrounded by the bone, is divided into three chambers full of fluid called the scala. Tympanic scala and vestibular scala have high level of sodium and low potassium perilymph. At the end of the scalae base is the round window. Middle scala comprises low sodium and high potassium endolymph. In this chamber, there is an organ of Corti. The cochlear bone and the round window (RW) are two typical access points used for the perfusion or injection of vectors into the perilymph. For entry to the scala tympani, a cochleostomy may be carried out. Both of these techniques have been shown to successfully deliver medications without hindering the cochlear function of rodent. In gene transfer effectiveness, the cochleostomy is preferable, whereas the RW is less invasive (17).

Delivery methods in gene therapy

Non-viral

Liposomes are the conventional non-viral vectors used in inner ear investigation. They are simple to produce, can be complicated with any size of DNA, and the risk of mutation is very low. Evidence has not shown the effects of clinically effective transmission. An effective vector may result in a broader study of vectors and promotors, and the integration of nuclear localization sequences and targeting ligands. Other techniques, like electroporation (18) and the gun gene (19), provided substantial results in vitro but were not designed for successful use in vivo.

Adenovirus

Most research on inner ear gene therapy has been done with adenovirus (Ad) vectors that can be produced in large concentrations and can carry large DNA fragments (8 kb) (20). In vivo they are effective in infecting several kinds of inner ear cells, including SGCs (21, 22). It is essential to know a significant amount of variation in specific expression between the studies. This difference may be due to changes in adenovirus concentrations, vector production, and detection of transgenic proteins. Ideally, the mechanisms of Ad transfection should be identified by studying the function of Ad receptors in the inner ear. Latest studies have utilized ad vectors in animals to avoid deafness. The delivery of Ad-GDNF protects SGCs from the autogenous toxicity of gentamicin (23). The explanation for the protective role is unclear, but it can be related to the producing proteins. Growth factor cytokine (TGF) -B1/GDNF gene therapy improves this defense, but which is correlated with fibrosis (24). The delivery of Ad-GDNF also protects IHCs after severe blood flow cessation (25). Antioxidant gene therapy in mice has also proved beneficial (26). Models of Neurotrophin and antioxidant gene therapy promise to cure deafness (17). In several inner ear studies, cytotoxicity was found, likely as a result of the immune response. Two forms of immunosuppressants were initially produced to

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counter these immune responses: T lymphocyte-suppressing inhibitors and anti-inflammatory steroids. The Ad immune response can be inhibited by both types of suppressors and development of the second transgenic Ad delivery can be allowed (27).

Adeno-associated virus

Adeno-associated viral vectors (AAVs) generate much lower immune responses than Ad vectors. AAV has been shown to mediate up to 6 months, at a low level (28). The AAV vector can hold 3.5-4.0 kb (kb) DNA (29). AAV carriers are less toxic than Ad carriers (30), such as Ad vectors, there are differences in different profiles. AAV typically infects a variety of cochlear tissues, or stria vascularis and SGCs (21, 30). In particular reducing the immune response makes exploring AAVs more appealing.

Herpes simplex virus

The virus of herpes simplex is neurotrophic. HSV vectors primarily transfect SGC in the cochlea (31). NT-3 stimulates neuronal survival. One group found that an HSV / NT-3 vector injected into the vestibular scale could boost the survival of SGC 2 days after the administration of low-level cisplatin. HSV has been shown to reach a dormant process in some neuronal cell type, which provides the possibility of stable transfection (32). The pathogenic nature of the virus and its development difficulties are a downside. Besides, HSV has affected many people. HSV investigation is in the development stage for inner ear purposes but has the potential to facilitate the survival of neuronal cells.

Lentivectors

Lentiviral (LV) vectors can affect non-dividing cells, unlike many other retroviral vectors. A wide variety of cells, including neural cells, are transfected by LVs. Such as AAVs, LVs are a relatively low propensity for inflammation. In rodent brains, LV-mediated protein expression has been seen for up to six months (20). Up to 14 days of post-injection expression was observed in the inner ear, without tissue injury (33). After LV/GFP injected into the perilymph, the protein was found in cells that were available directly by fluids. In vitro transfected cells less available such as the spiral ganglia and glial cells. According to these early findings, the possible applications for this vector include the secretion of growth factors and antibiotics into the perilymph. Before a serious consideration of this vector for therapeutic use, the risk of mutagenesis must be investigated carefully in the inner ear. However, the insertion of genes into the chromosome is also helpful in the possible treatment for loss of hereditary hearing. For this purpose, in treating deafness, LV gene therapy holds promise.

Auditory function control following gene therapy

Gene transfer mechanisms should not be toxic and after treatment, cells should be able to revert to normal. There are various methods for testing the physiology of cochlear. First, auditory brainstem response (ABR) to sound feedback is used to document activity non-invasively throughout all areas of the auditory pathway, allowing for long-term monitoring. The CAP method produces, using an electrode mounted on the RW, more response effects than the ABR. Numerous otoacoustic emission (OAE) tests non-invasively determine the cochlear enhancement associated with OHC performance. All of these approaches may be used to assess the return of auditory function following invasive surgery or gene delivery (17).

Discussion

Although the embryonic stage is a very complex period of growth and development; however, this stage is the ideal course for genetic therapy (34). DNFB gene therapy has improved spiral ganglion neurodegeneration associated with GJB gene mutations in a mouse model. Miwa et al. succeeded in growing the

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transmute gene into the inner ear of a developing mouse fetus, which lacks the connexin 30 gene, has persisted since the onset of the deaf phenotype (34).

It should be noted that connexin 30 is one of the most important proteins involved in potassium ion homeostasis in the cochlea of the inner ear and is responsible for creating open intercellular relationships that allow it to give your small molecules. By electroporation, Miva et al. performed the transfer of the Cx 30 gene from wild-type mice into the fetal auditory vesicles, and induced the expression of a strongly critical gene in the developing cochlea; as a result, they prevented postpartum deafness (35, 36).

Akil et al. reported the transfer of the VGLUT3 gene by AAV from wild-type mice to the cochlea of mice lacking the gene and observed a significant improvement in their auditory function (36). It is noteworthy that a deficiency in the VGLUT 3 gene causes severe deafness due to the loss of glutamate secretion in the afferent synapses in the inner hair cells of the cochlea (37).

Recently, according to a Yu et al. report, mice that conditionally lacked the GJB 2 gene were incurable in the neonatal gene therapy by vector gene transfer based on the AAV1 vector. In this experiment, the gene transfer time may be normal after full expression of the gene but before the onset of the deaf phenotype (38).

In another study, Choi et al. tested the SLC26A4 gene, which encodes a membrane-passing protein called Pendrin, which passes through chlorine and iodine and is expressed in the inner ear, thyroid, and kidney glands. It is noteworthy that mutations in this gene after GJB gene significantly contribute to the occurrence of non-syndromic deafness with a recessive hereditary pattern (39).

The development of autosomal dominant and recessive non-syndromic deafness is also due to defects in the TMC1 gene. TMC1 is expressed exclusively in the hair cells of the Corti organ and 47 mutations in this gene have been identified so far, of which only 7 cases have been reported in Iranian families (40). Askew et al. recently conducted a study on TMC gene therapy. They inserted the gene into the ear hair cells in mice with mutations in the gene using the AVV vector and eventually observed the return of sensory transmissions, auditory brainstem responses, and rapid sound responses in deaf mice. This study demonstrates the gene therapy of TMC gene as a suitable strategy for hearing restoration in deaf patients caused by mutations in this gene (41).

Conclusion

In general, there are various and useful methods in the treatment of hearing loss, however, for better efficiency of treatment methods and more effective improvement of this type of disorders, access to new and targeted technologies of molecular therapies have evolved and more hope than prompted the recovery of this type of genetic disorder. Gene therapy allows for the treatment of sensorineural hearing loss by restoring and/or preserving the inner ear cells functioning. Hopeful results from recent research have contributed to cochlear gene therapies being created for end-use in patients.

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Conflicts of Interest

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