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Cell Therapy in Hearing Loss Treatment: A Review of Recent Advances

Behnaz Ahrabi[1,2], Hojjat-Allah Abbaszadeh[1,2*], Shahrokh Khoshsirat[1], Ali Asghar Peyvandi[1], Maryam Sadat Khoramgah[1], Somayeh Niknazar[1], Shahram Darabi[3], Foozhan Tahmasebinia[1], Hassan Peyvandi[1*]

1. Hearing Disorders Research Center, Loghman Hakim Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Department of Biology and Anatomical Sciences, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
3. Cellular and Molecular Research Center, Qazvin University of Medical Sciences, Qazvin, Iran.

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Corresponding Authors:
Dr. Hojjat-Allah Abbaszadeh
Email:
dr.abbaszadeh@sbmu.ac.ir
Dr. Hassan Peyvandi
Email:
hassan.peyvandi@gmail.com

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Abstract

Background: The mammal's inner ear is responsible for hearing and balance. To perform these tasks, it requires the vestibular and cochlear system. Sensor neural hearing loss (SNHL) is the most common type of hearing loss resulting in degeneration of internal sensory hair cell, where cochlear nerve in cochlear stem cell and gene-based strategies provide the opportunity for replacement for these cells.

Aim: In this review, we evaluated the efficiency of stem cell therapy in inner ear.

Methods: In this study we examined different articles in different databases such as Google Scholar, PubMed, and Elsevier.

Results: The stem cells have offered desired results in the delivery of gene and tissue engineering programs. Evidence suggests that stem cells are considered as a promising tool in medical applications thanks to their high plasticity and trophic characteristics.

Conclusion: In this review, Stem cell transplantation is widely used in clinical practice, and the source is highly desirable, since the patient's bone marrow cells can be potentially transplanted without any safety problems.

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Introduction

The mammals' inner ear is responsible for hearing and balance, which occur through the vestibular and cochlear system. Auditory disturbances and the exposure to excessive noise, ototoxicity, aging and genetic mutations are associated with the damage or loss of various cell types in the inner ear. The common types of cells that are destroyed in these lesions include sensory hair cells, auditory and violet neurons, sterile vasculature, and fibrocytes in the spiral ligaments (1-7). In the mammals' inner ear, if there is no replacement of internal progenitor cells, the permanent loss of sensory and neuronal cells is very limited, but in contrast, non-sensory cells such as fibrocytes in the spiral ligaments can be found after the damage caused by drug or noise (8, 9). Ischemia in the inner ear is associated with hearing impairment including sudden hearing loss, neurological sensitivity, presbycusis, hearing loss, tinnitus, and Meniere disease. In addition, the trauma also causes damage to the hair cells in the ear and to the labyrinth barrier blood in the Stria vascularis (10). Autoimmune inner ear disease (AIED) is an advanced, bilateral, and asymptomatic disease, in which the levels

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of INFY produced by T cells are very high compared to normal people.(11). In this regard, Meniere disease is an autoimmune disease. It has been shown in immunohistological that beta-tubulin proteins accumulate in tremendous amounts in the inner ear tissue, such as hair cells, supportive cells, and spiral ganglion. In response to the accumulation of this protein, spatial distribution is altered in the ear, leading to the degeneration of the spiral ganglion. Some oral beta-tubulin treatments result in a reduction in INFY in response to beta-tubulin antigen, which is considered as a method for the treatment of EAHL (11).

Sensorineural hearing loss (SNHL) is the most common type of hearing loss resulting in degeneration of internal sensory hair cells where cochlear nerves in the cochlear Stem cell and gene-based strategies provide the opportunity for replacement for these cells (12). The hair cells are produced only in the embryonic period and no hair cells are born after birth. The peripheral hearing process in the inner ear cochlear depends on two types of cells. 1: Spinal Ganglion neuron and hair cells (13). The acoustic waves cause mechanical stimulation in the hair cell, which leads to the release of neurotransmitters. Lack of hair cells will lead to deafness permanent (13). Hearing loss (SNHL) is a permanent sensory disorder that affects more than 270 million people worldwide (14). The prevalence of this disease in infants is 2 in 1,000; in children from 3 to 17 years of age, 5 in 1,000; in people aged 65-74, it is 33%, and in people over 85, it affects 50% of the population (14). After hearing-related age, noise-induced hearing loss (NIHL) is the second most common hearing which that can lead to preventable SNHL (15). In Europe, 7% of workers are affected by hearing impairments and the consumption costs in this disease make up 10% of other occupational diseases.

Among infants and children with SNHL, 23 to 50 percent of SNHLs result from a genetic mutation (mutated canxin 26, Wardnerberg syndrome, arsenic syndrome, mitochondrial disorders, etc.). Other infants and children are affected by SNHL due to insufficiency, infection (in the uterus or after delivery), and exposure to noise or narcotics (14). In the mammals' inner ear, if there is no substitution for the endogenous progenitor cells, the permanent loss of sensory and neuronal cells is very limited, but in contrast, non-sensory cells such as fibrocytes in the spiral ligament can damage themselves after the injury caused by drugs or noise (8, 9). It is estimated that the number of patients with neuronal hearing loss will double by 2030. The main current therapeutic option for SNHL patients is cochlear implantation. While these interventions are effective in many cases, some patients still struggle with physiological and psychosocial deafness. The cochlear implant transmits mechanical signals to electrical signals and delivers electric pulses to the auditory nerves to replace the function of the hair cells. However, these do not reproduce the sensory cells of the inner ear epithelium.

The success of the cochlear nerve depends on the auditory nerves that send electrical signals to the auditory brain. Note that cochlear implantation for patients with auditory nerve disorders is limited (16). The function of a cochlear implant depends on the presence of the remaining spiral ganglion neurons, although the exact correlation between the number of ganglia and the result is not known. These observations indicate that the improvement of the spiral ganglion neuron can potentially enhance hearing in a number of people (17).

Among other types of deafness, hearing neuropathy can be noted with the disease being associated with major damage to SGNs and relative intactness of hair cells (18). The auditory nerve damage in the ears of adult mammals is irreversible, leading to SNHL. The degenerative potential of the auditory

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nerve has been tested in the mouse model of auditory nephropathy. Following the degeneration of the auditory nerve, glial cells are activated and the nucleus chromatin density decreases. The expression of histone deacetylase is altered while the expression of the neurogenesis gene is enhanced. The auditory nerve neurospheres are caused by neuronal damage or hypoxia conditions. The neurosphere formation assay shows that the neurons have progenitor cells. Glial cells in the auditory nerve exhibit different forms of progenitor cells that are very important in the auditory nerve repair (19).

Corti's physical structure may be a barrier to stem cells where targeting stem cells in the sensory epithelium is an important challenge. Further, the fact that many of the trophic factors cause the stem cells to absorb the affected area is not supported in some studies. The activity of stem cells within the inner ear is an ideal source of epithelial-sensory regeneration of the ear. Although some studies have shown that the number of stem cells in mature Cochlear may have been somewhat low so far, many studies have been conducted on the use of stem-cell types in the inner ear with different results (17).

In order to better understand the failure of epithelial regeneration and repair, a few therapeutic approaches to injury have been introduced. One of these methods is the transplantation of stem cells into the inner ear, where the transplanted cell is distinguished according to internal signals to the cells specific to that tissue. In the suspension culture of hearing epithelial cells, spherical cells have exhibited self-renewal features and genetic markers such as sox2, nestin, and nerve-developing inner ear (20). The ultimate way to treat hearing loss is through applying genetically modified stem cells as a vector containing factors to enhance the regeneration of specific structures in the inner ear (17).

Hair cells:

The function of the hair cells depends on maintaining the electrochemical gradient between the endolymphatic and perilymphatic spaces. The boundary between these spaces is a tight junction between the luminal surface of the hair cells and the supporting cells. When a hair cell is destroyed, lamina reticula is disrupted causing defects. To prevent such a defect, the surrounding supporting cells expand their luminal surface by creating a fingertip, and closes the affected penetration like a dam. It seems likely that this scar can limit stem cell transplantation from access to the Corti organ which includes endolymph.

Endolymph contains a high concentration of K+, which can be toxic to cells that are implanted in this chamber. The base levels of the supporting cells are on the basilar membrane, composed of various collagen forms. This membrane also seems to be a significant barrier to access of stem cell to Scala Tympani (17). In addition to the challenges mentioned above, it is also important to note that hair cells are not homogeneous in cochlear length and width. The longitudinal slope in cellular morphology corresponds to changes in the frequency regulation, while the internal and external hair follicle cells are located in the special position along the channel axis (internal to external). Finally, in order to improve the function, new hair cells should recognize synaptic functionalities with spiral ganglion neurons (17).

Spinal ganglion neurons

The spiral ganglion neurons have a unique bipolar morphology, and each neuron reconstructed requires not only the proper link with hair cells, but also proper communication with the auditory brain stem. They grow in neurotrophins, such as BDNF and NT3, with these factors being released from stem cells that lead to increased growth. As the inner ear is filled with three parts of the fluid, the

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secreted factors of the transplanted cells can potentially be spread across a specific chamber. Genetically engineered stem cells that release specific metabolic components can be used with endogenous stem cell transplantation to enhance regeneration in the inner ear. Another application of stem cells is in regeneration of spiral ganglion neurons. In humans, loss of spiral ganglion neurons is generally associated with hearing loss (21). There are reports of patients involving use of stem cells for regeneration of spiral ganglion cells (22).

Types of cells used in treating the inner ear

1) Human Pluripotent Stem Cell-derived Progenitor

A study in 2018 showed that the first successful transplantation of exogenous cells was performed in prenatal rat otocysts. In this study, the otic progenitor cell from human IPS was successfully reported. The cells of the IPS were differentiated into the otic progenitor cells and then the progenitor of the otocyst cells as donation cells was used in mice (18).

A study by Barboza and colleagues in 2016 was performed to assay the auditory function in guinea pigs. Deafness was induced by neomycin. In this study, the inner ear progenitor cells were used. After transplantation, a number of these cells were observed at all points of the basal Scala in the damaged cochlea, which revealed the marker of myosin 7a hair cells, where some of them were found in the basilar coclide membrane. This study also showed the survival of cells in the corti's organ after cochleostomy (20).

In a study, multipotent cells were differentiated into committed progenitor cells initially in inner ear. Then, the committed progenitor cells were cultured on chicken utricle stromal cells and differentiated into hair-like cells. These cells have stereo cilia bundles (20).

2) Bone marrow mesenchymal stem cells

Bone marrow transplantation is widely used in clinical practice, and the source is highly desirable, since the patient's bone marrow cells can be potentially transplanted without any safety problems. Depending on the feasibility of many additional steps, such as surgical procedures for cellular transplantation to the damaged cochlea, it may be a treatment for hearing loss. Bone marrow mesenchymal stem cells also differentiate into different classes, including neurons, but the question is whether they can be differentiated into sensory cell lines (10). Bone marrow stem cells are a source of blood cells, but in addition to hematopoietic stem cells, there are mesenchymal stem cells that can be differentiated into the types of cells in the three layers of the fetus. In in-vivo studies, tracing stem cells transplanted into a specific tissue has been observed and found to differentiate into the same type of cell in the tissue (23, 24). Many of these cells have been used for transplantation and are a source of new cells for treatment (25). For regeneration of internal ear cells, the source for sensory cells and neurons is a valuable tool for clinical practice because neurons and hair cells can ultimately be used to treat patients with deafness. A recent study has shown that hair cells and neurons can differentiate from stem cells in the inner ear. Other studies have found that endogenous epithelial cells can be transformed into hair cells through the Math1 transcription factor, while intraocular stem cells themselves cannot produce hair cells (9, 26). Injection of the entire bone marrow to repair a mouse resulted in the absorption of these cells in areas occupied by the internal mesenchymal cells and fibrocytes, but did not produce hair cells (27).

Through combining stimulation of growth factor and expression of the transcription factor (Math1), which is required for the formation of hair cell in inner ear, it has been shown that MSCs derived from bone marrow

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can be differentiated into hair cells which expressed myosin VIIa genes, espin, jagged 2, Brn3c, p27Kip, representing a feature of the hair cells (28). Bone marrow mesenchymal stem cells isolated from guinea pigs, using recombinant lentivirus expressing IL4, can relieve the sensory nervous hearing loss caused by autoimmune disease. Bone marrow mesenchymal stem cells were implanted in Scala Tympani and Scala vestibule and reduced inflammatory injury by production of IL-4 (29). The source of mesenchymal cells and fibrocytes cells in the inner ear may be from bone marrow cells, and in particular from hematopoietic cells. In this study, bone marrow stem cells or colonies derived from hematopoietic stem cells were transmitted from transgenic mice expressing EGFP to adult mice (27). In a human pilot study, mesenchymal stem cells derived from bone marrow and their differentiation into hair cell and ganglionic cells were observed, but no significant improvement was observed in hearing.

In the treatment of ischemia induced in the inner ear, different therapeutic methods have been used. One of these is use of vasoactive agents to improve the cochlear perfusion. For a damaged blood-labyrinth barrier, the iNOS was used with bone marrow stem cells. In this study, the first week following the injury, bone marrow stem cells GFP+were filtered into Blood-labyrinth barrier which accumulated more in two weeks post injury. iNOS improves the filtering of bone marrow stem cells. The cxcr4 and SDFa1 factors are essential for iNOS, and inhibition in the iNOS/SDFa1 signaling pathway reduced damaged vessel regeneration.

In a study, human bone marrow mesenchymal stem cells also differentiated into neurons which were transplanted to Scala tympani in a Guinea pig. Following the neuronal differentiation, a high level of neuronal markers and ion channel markers was expressed which is necessary for neuronal function. The number of the spiral ganglion cells also increased. These cells were found in pre lymphatic space, the corti's organ, along the Cochlear neural fiber, spinal ganglion.

The use of mesenchymal stem cells derived from bone marrow and its differentiation into the neuron in auditory neuropathy revealed that the number of spinal ganglion cells also increased. The results of this study suggested that there is a possibility of replacing degenerated spiral ganglion cells with transplantation of stem cell in Scala Tympani.

3) Stem cells derived from umbilical Cord

The human embryonic mesenchymal stem cells are believed to be multipotent stem cells and have shown desired results in the delivery of gene and tissue engineering programs. UCMSCs are isolated from the Wharton's jelly of umbilical cord and have some common properties with bone marrow mesenchymal stem cells (BMSCs) .(30). Umbilical cord is a rich source of cells. This can be due to the high frequency of umbilical cord and low immune rejection and non-tumor properties as a suitable source for cellular transplantation in medicine. These cells differentiate into several types of cells and have a potential potency in the gene delivery. Mesenchymal cells derived from Wharton jelly can also differentiate into different types of cells in three embryonic layers.

In vitro, the differentiation of these cells has been observed into osteocyte cells, hepatocytes, chondrocytes, adipocytes and neural cells, pancreatic cell (19-22). The Atoh1 gene is expressed in the internal hair cell of the ear and nerve cells in the hindbrain, spinal cord and germinal layer of the cerebellum (23). The Atoh1 gene in the mesenchymal cells produced by umbilical cord causes the cells to differentiate into cells similar to those of the hair cells in the inner ear. Also, mesenchymal cells derived from human umbilical cord in the subarachnoid space have been injected into congenital Albian pigs, resulting in the appearance of

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these cells in three days and four weeks post injection. Further, the cells in this study were evaluated at 2 hours, 3 days and 1, 2, 3, 4 weeks after the transplantation in the cochlea. These cells also migrated from the subarachnoid space to the inner ear, the central nervous system and environmental organs. Indeed, mesenchymal cells were able to migrate from the CSF to the inner ear, as the presence of these cells in the cochlea may be due to changes in ABR waveforms (24). The use of umbilical cord blood cells in children aged 6 months to 6 years in the clinical trial phase 1 showed no side effects. No toxicity related to injection has been recorded. Improvement in the cochlear nerve and ABR reduction was also observed (25).

4) Embryonic stem cells

Human embryonic stem cells are pluripotent stem cells that differentiate into all types of cells that are present in the human body. One of these cells is hair cells (26). Also in vitro, embryonic stem cells were differentiated into hair cells in stromal cells condition media (ST2-CM) and injected into chick embryos. In addition, EB (embryonic body) cells in stromal culture media expressed hair cell markers, including Brn3c Math1, myosin6, myosin7a, calretinin, and a9AchR, and formed structures similar to stereo cilia (27). Also, embryonic body cells were transfected with math1 and differentiated into hair like cells, and expressed the markers of hair cells, and also produced stereo cilia (28). Note that MIF-induced embryonic stem cells can replace lost or damaged SGNs (spiral ganglion cells).

Neuronal cells and Schwann cells were generated from a population of embryonic stem cells in an ultra-slow flow microfluidics device. In this study, neurons were grown on a population of Schwann cells and their primary myelination was reported. Spinal ganglion cells are mild in the bipolar neurons that receive sensory signals from peripheral sensory receptors in the hair cells and transfer them to the central neurons in the auditory cores in the brain stem (29). Essentially, stem cells must be directed to the cochlea replacing damaged hair cells, where the survival of these cells and their integration with tissue is essential. Following the transfer of cells to Scala Timpani, these cells do not reach the auditory epithelium. The auditory epithelium is extremely effective for transmitting sound, where most of the cells in the transplant in Scala Media are lost due to the high concentrations of K+. Flushing Scales Medium with sodium increases survival before embryonic stem cell transplantation. In this study, in addition to increased survival in embryonic stem cells, differentiation into hair cells was observed (26).

Direct differentiation of embryonic stem cells into bipolar neurons can replace them for degenerated neurons in damaged cochlea. This also facilitates the differentiation of embryonic stem cells into neuron-like cells simultaneously with co-culture of neurons or hair cells that are isolated from postnatal day five rats. This results in an increase in neuronal-like cells and a rise in the number of neurofilaments.

5) Adipose derived stem cells

Evidence suggests that adipose-derived stem cells are considered as a promising means in medical applications due to their high plasticity and trophic characteristics. In this regard, transfusion of fetal stem cells in the acoustic trauma model in guinea pig increases the expression in the chemokine ligand and receptors associated with PDGF, VEGF, and TGFB which are effective in migration of mesenchymal stem cells. Adipose-derived stem cells can migrate to damaged tissue and express trophic factors. Adipose mesenchymal stem cells could also suppress T cells and inducing Treg cells in the model of autoimmune hearing loss in mice. In this study, was observed a reduction in proliferation of TH1/TH2 cells, increased anti-inflammatory cytokines such as IL10 and the production of CD4+CD25+FOXP3+cells (15).

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6) Other cells

Neural stem cell line

The use of neural stem cell line causes a significant increase in satellite cells and spiral ganglion cells of type I. These cells migrate from Scala tympani to Rosenthal's canal channel and the Corti's organs (19).

The Cochlear support cells express Lgr5 +. Lgr5 + is an epithelial marker which responds to stimuli of the wnt signaling pathway and the Gsk3B inhibitor. In this study, Lgr5 + supporting cells were isolated with the aim of replacing damaged cochlear hair cells which were differentiated into hair cells by growth factor and drug (19).

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Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' ORCIDs

Hojjat-Allah Abbaszadeh:
http://orcid.org/0000-0002-7157-1834
Ali Asghar Peyvandi:
http://orcid.org/0000-0001-8229-6594
Hassan Peyvandi:
http://orcid.org/0000-0003-2891-0877

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