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REVIEW

Potential therapeutic effect of stem cells on sensorineural hearing loss

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Abstract Sensorineural hearing loss (SNHL) remains a global health challenge with limited regenerative therapeutic options. This review delineates advancements in stem cell-based therapies, emphasizing their potential to restore auditory function through cellular regeneration and molecular modulation. Stem cells, including mesenchymal (MSCs), induced pluripotent (iPSCs), and embryonic stem cells (ESCs), exhibit multilineage differentiation and paracrine signaling capabilities, enabling hair cell (HC) regeneration, spiral ganglion neuron (SGN) repair, and inflammation modulation. Cochlear organoid models derived from stem cells have advanced mechanistic studies, though challenges persist in replicating cochlear-specific HC phenotypes. Exosomes, as nanoscale bioactive vesicles, demonstrate enhanced biocompatibility and barrier penetration, effectively mitigating oxidative stress, apoptosis, and aminoglycoside ototoxicity while promoting HC survival. Gene-editing technologies, notably CRISPR-Cas9 and adeno -associated virus (AAV) gene delivery systems, synergize with stem cell platforms to correct pathogenic mutations and engineer therapeutic cells for targeted inner ear repair. Preclinical studies highlight MSC transplantation and exosome administration in improving auditory thresholds and neuronal morphology, yet clinical translation faces hurdles including delivery precision, immune responses, and scalability. Current limitations in replicating cochlear cytoarchitecture and standardizing differentiation protocols necessitate further exploration of combinatorial strategies, such as integrating stem cell therapy with cochlear implants or medicament delivery systems. Future research needs prioritize optimizing cell lineage specification, enhancing exosome targeting, and validating long-term safety to realize the transformative potential of regenerative medicine in SNHL treatment.

Keywords Stem cell, Hearing loss, Hair cells, Exosomes, Regenerative medicine, Cell differentiation

INTRODUCTION

Otological disorders constitute a substantial global health challenge, exerting significant impacts on individual well-being and public health infrastructures (Nieman and Oh 2020). Contemporary epidemiological studies indicate that over 466 million individuals globally suffer from disabling hearing impairments, with projections suggesting this number could reach nearly 1 billion by 2050 (Qin *et al.* 2024). As the most common sensory deficit among humans, these conditions include sensorineural hearing loss (SNHL), acute or chronic inflammation of the ear, and nerve defects of the ear that span genetic predispositions and environmental factors (Pan *et al.* 2024). The clinical implications of auditory dysfunction encompass more than mere deficits in sound perception. Notable consequences include compromised linguistic communication, diminished occupational performance, and social

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withdrawal, often exacerbated by comorbid psychiatric conditions such as chronic anxiety disorders and major depressive episodes (Luo *et al.* 2022). Pediatric populations are of particular concern, as early-onset hearing impairment can disrupt crucial developmental milestones related to language acquisition and socioemotional integration.

The inner ear of a human contains upwards of 70,000 sensory hair cells (HCs), with 13,150,000 found in the cochlea and 60,000 in the peripheral vestibular end organs. Age-related degeneration manifests through progressive loss of outer hair cells (OHCs) and inner hair cells (IHCs), with comparative histopathological studies demonstrating superior HC preservation in fetal specimens versus significant IHC depletion in septuagenarian cohorts (Ekdale 2016). Aging, drug toxicity, chronic basic diseases, genetic problems, and environmental noise may lead to the continuous reduction of hearing-related cells (Wu *et al*. 2021; Zhang *et al*. 2020). This cellular attrition accelerated by genetic mutations, metabolic comorbidities, and chronic noise exposure, precedes neural degeneration characterized by afferent synapse depletion and subsequent spiral ganglion neuron (SGN) apoptosis (Muthu *et al.* 2019; Yang *et al.* 2024). Contemporary therapeutic strategies, while demonstrating incremental progress in cochlear implantation safety and pharmaceutical interventions, remain fundamentally limited in achieving functional auditory restoration. The intricate cytoarchitecture of the organ of Corti and the immune-privileged status of the inner ear present unique challenges for regenerative medicine approaches.

CHARACTERISTICS OF STEM CELLS

Stem cells are hierarchically classified into two developmentally defined populations based on differentiation potential: lineage-committed effector cells that maintain tissue homeostasis through specialized function, and stem cells, scientifically termed as undifferentiated pluripotent progenitors, capable of self-renewal and differentiating into various lineages. The former experiences terminal cell cycle arrest, which is accompanied by the epigenetic stabilization of tissue-specific transcriptional profiles. In contrast, the latter exhibits regenerative therapeutic properties, such as properties that reduce inflammation, modulate immunity, provide antioxidant benefits, prevent fibrosis, combat microbes, and have antitumor effects, attributable to their intrinsic biological characteristics. These pluripotent cells, sourced from mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), embryonic stem cells (ESCs), and other lineages, exhibit multidifferentiation potential across germ layer boundaries (Araki *et al.* 2020). Paracrine signaling through bioactive molecules, such as growth factors, chemokines, and cytokines, is primarily how their therapeutic mechanisms work. Substantial evidence confirms that stem cell-derived secretomes possess significant immunoregulatory capabilities (Chai *et al.* 2023).

PROSPECT OF STEM CELLS IN COCHLEAR ORGANOIDS

We discuss the progress made in generating *in vitro* derivatives of inner ear hair cells, neurons, and organoids from stem cells. Research has shown that these iPSCs are used in preliminary treatment trials to understand the mechanisms of inner ear disorders. Studies have revealed that these iPSCs are applied in preliminary treatment trials to understand the mechanisms behind inner ear conditions and to restore inner ear function (Mei *et al*. 2020; Zheng and Holt 2021). Products derived from ESCs and iPSCs have the capability to induce the formation of otic epithelial progenitor cells (OEPs), hair cells, sensory neurons, and three-dimensional organ structures. These developments hold significant scientific and therapeutic potential, particularly in the generation of otic neural progenitor (ONP) cells and ear neural progenitor cells (Koontz *et al*. 2023; Tang *et al*. 2020). The active participation of supporting cells in the sensory epithelia in ion metabolism is essential for the operation of hair cells that have enhanced regeneration (Chen *et al*. 2021). In mouse 3D inner ear organoids, activation of FGF in stem cells leads to increased expression of CX26 in 1 week (Sanchez and Verselis 2014). The aggregation of isolated small vesicles with mouse cochlear feeder cells in 2D conditions led to hemichannel formation, which was disrupted in CX26-deficient cell lines (Fukunaga *et al*. 2016).

However, the induction of iPSCs or MSCs into inner ear organs demonstrated various methods for inducing stem cells into special inner ear tissues. Among the commonly used induction methods, iPSC is a commonly used induction (Yamanaka 2020). These types of cells can currently be stably induced to form specific tissue clusters (Ohnuki and Takahashi 2015). For example, the addition of extracellular matrices, in the 3D inner ear organoid systems facilitated the formation of fluid-filled vesicles containing hair cells and supporting cells (Koehler *et al*. 2017; van der Valk *et al*. 2023). However, through the rotary cell culture system, iPSCs give rise to vestibular tissue-like organoids that form hair cell-like

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cells on their surface (Steinhart *et al*. 2023). Currently, the precise mechanisms by which extracellular matrices affect cell differentiation and survival remain inadequately understood. Regrettably, hair cell-like cells derived from iPSCs exhibit molecular markers and electrophysiological characteristics akin to vestibular hair cells rather than cochlear hair cells (Moeinvaziri *et al*. 2022; Moore *et al*. 2023). Identifying new small molecules or culture conditions to create cochlear hair cells from PSCs remains necessary.

The spatiotemporal differences in gene expression may be the reason for the variability and effectiveness of known hair cell generation (Nist-Lund *et al*. 2022; Steinhart *et al*. 2023). Therefore, adjusting the culture environment may alter the differentiation direction of such stem cells, as demonstrated by using TGF-β (Ueda *et al*. 2022). The inner ear progenitor cells can proliferate and spontaneously shape into spheres with a cochlear organoids-integrated conductive hydrogel biohybrid system, which also showed great application potential in organoid cultivation and deafness drug evaluation (Hu *et al*. 2024b). Different concentrations of Matrigel altered the developmental duration of inner ear organs, resulting in more stable and viable hair-like cells (Hocevar *et al*. 2021; Zhang *et al*. 2022). What's more, if Fibroblast growth factor receptor-3 (FGF3) related substances are used to induce cell differentiation, extracellular mechanism cultures of deaf or healthy samples can also obtain ear tissue of different qualities in a relatively short period of time (Jacques *et al*. 2012). As our understanding of inner ear hair cell development or culture conditions deepens, more future improvements of these protocols will be obtained.

THERAPEUTIC POSSIBILITIES OF STEM CELLS IN ADDRESSING HEARING LOSS

Currently, the objectives of stem cell therapy for SNHL include the prevention of further auditory deterioration, the preservation of existing auditory function, the augmentation of hair cell populations through targeted differentiation, and the potential restoration of normal auditory physiological function in patients (Bergman *et al.* 2021; de Figueiredo Colla *et al.* 2023). MSCs constitute a class of differentiated stem cells that are present in various tissues, such as bone marrow, adipose tissue, placenta, and umbilical cord blood. With the ability to self-renew, these cells are frequently utilized in cell therapy (Mani *et al.* 2008; Takebe *et al.* 2013). The application of MSC therapy resulted in better morphology and increased numbers of spiral neurons *in vivo*, with a normal arrangement throughout the cochlea (Mellott *et al.* 2016; Sato *et al.* 2009). These animal models showed hair cell regeneration in both the middle and bottom sections of the cochlea (Gunewardene *et al*. 2022). During a clinical trial focused on pediatric acquired SNHL, more than four children treated with MSC intravenous infusion of autologous umbilical cord blood experienced shortened V wave latency and reduced auditory brainstem response (ABR) in the auditory nerve (Roverud *et al*. 2021), which may indicate a certain degree of repair of hair cells, Corti apparatus, and spiral ganglia.

In addition, there are different methods for surgical transplantation for MSCs, among which tympanic membrane transplantation and intravenous injection are the most commonly used (Liu *et al*. 2024). The tympanic membrane's greatest advantage is its larger operating area compared to other cochlear structures, facilitating a cochleostomy near or directly through the round window, causing less iatrogenic injury. Moreover, with the assistance of the perfusion system, the peripheral lymphatic circulation can distribute the transplanted cells to different regions of the cochlea. Transplanting cells into the fragile cochlea is a great challenge (Qiu and Qiu 2019; Xue *et al*. 2010). The primary objective of stem cell injection is to facilitate the delivery of cells to the site of injury (Xia *et al*. 2023). Firstly, it depends on the status and location of cochlear damage (HCs or SGNs). Another challenge is how to make the transplanted cells reach all the damaged parts of the cochlea, while minimizing the additional damage caused by the transplantation (Eshraghi 2006; Garrada *et al*. 2021). These cells could potentially evolve into hair cells, support cells, spiral neurons, and other kinds of cells. An alternative way to effectively avoid iatrogenic injury to the cochlea is by infusing MSCs intravenously, allowing them to circulate through the bloodstream to the cochlea (Schulze *et al*. 2018; Warnecke *et al*. 2021). However, these cells are exclusively localized within the spiral ganglion region of the cochlea. This distribution may be attributed to the presence of perforated capillaries at the cochlear axis, spiral ganglion, and osseous spiral lamina, in contrast to the continuous capillaries found in the stria vascularis. Notably, there is a scarcity of labeled stem cells in the organ of Corti (Toyoda *et al*. 2015).

Animal studies and preclinical trials have demonstrated that the intravenous administration of umbilical cord blood-derived MSCs in the treatment of SNHL exhibits a significant therapeutic effect. This approach may contribute to the repair of inner ear structures and the partial restoration of auditory function, suggesting its potential as a viable cell source for stem cell therapy (Choi *et al*. 2012; Steinberg *et al*. 2012). There

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continues to be an insufficiency of research data, especially from large-scale randomized double-blind placebo-controlled trials, to further establish its effectiveness and persistence. How to ensure that MSCs entering the body through different transplantation pathways are recruited and migrated to ideal locations, such as Corti. Among these new findings, it is believed that intravenous infusion of stem cells is difficult to enter the Corti apparatus through the blood labyrinthine barrier of the stria vascularis, and various surgical transplantation techniques also struggle to move stem cells to the Corti apparatus, potentially harming the cochlea (Takagi *et al*. 2014). Therefore, how to overcome these difficulties is the next step of the experiment that needs to be focused on.

EXOSOMES DERIVED FROM STEM CELLS ALLEVIATE HEARING LOSS BY PROTECTING HCS

Exosomes are nanovesicles with a diameter of 30–150 nm secreted by cells, they are rich in bioactive molecules such as proteins, lipids, mRNA and miRNA, and can regulate the functions of recipient cells by transmitting these substances. In comparison to the direct application of stem cells, exosomes exhibit enhanced capabilities to traverse biological barriers, demonstrate chemotactic properties towards inflamed tissues and tumors, and offer superior safety and stability. Additionally, they reduce the risk of immune rejection linked to allogeneic transplantation (Welsh *et al.* 2024). In the management of otological disorders, exosomes derived from stem cells demonstrate numerous significant regulations of cell activities. Investigations have revealed that these exosomes can augment regenerative functions and modulate tissue inflammation by overseeing oxidative stress responses, mitigating inflammation, aiding the regeneration of some stable cells (Hu *et al.* 2024a), and secreting specific inflammatory substances (Hu *et al.* 2023). Furthermore, the diminutive size of exosomes allows them to effectively traverse the intricate architecture of the inner ear, presenting a potential non-invasive therapeutic option for various other conditions (Kalluri and LeBleu 2020).

Based on current clinical treatment guidelines, the typical pharmacological approach to treating hearing loss mainly involves the use of hormonal and neurotrophic therapies. Moreover, the eligibility for cochlear implant surgery is restricted to a relatively small subset of individuals, and certain patients with hearing loss may also have no response to hormonal therapy (Kollmeier 2018; The Lancet 2016). The mammalian cochlea contains a robust antioxidant protection system that attaches importance to managing reactive oxygen species (ROS) produced during normal metabolic processes (Ramkumar *et al.* 2021). Nevertheless, following injury, the efficacy of ROS clearance within the inner ear tissue is markedly diminished, leading to an increased release of pro-inflammatory substances in the cochlea (Fetoni *et al.* 2019). The impairment of hair cells can obstruct the functions of regular cells, further aggravating cell apoptosis and leading to hearing loss. Compared with traditional inner ear drug delivery methods, exosomes derived from stem cells possess a favorable ability to regulate ROS. They contribute to cell survival by influencing autophagy, reducing mitochondrial oxidative stress, and decreasing the apoptosis rate in hair cells, which are also capable of ameliorating the toxic effects of aminoglycoside drugs in specific regions of the cochlea (Liu *et al.* 2024). Conversely, ototoxicity resulting from commonly used chemotherapeutic agents, such as cisplatin, generally results in more pronounced hearing loss at middle and low frequencies in patients (Kros and Steyger 2019). Recent studies have demonstrated that exosomes originating from stem cells may protect the cochlear from undergoing apoptosis. Furthermore, certain small nucleic acid molecules, specific miRNAs, encapsulated within these vesicles, have been proven to aid in sustaining the normal functions of cochlear cells (Hade *et al.* 2021). For example, specific miRNAs present in MSC exosomes, including miR-132, miR-16-5p, and miR-182-5p, have the capacity to engage in redox reactions (Heo and Kim 2022; Lai *et al.* 2020; Li *et al.* 2024). This action successfully reduces ROS levels in tissues, thus decreasing cellular inflammation. Furthermore, small extracellular vesicles originating from MSC-Exo have the potential to function as nanoscale delivery vehicles for brain-derived neurotrophic factor (BDNF). This approach effectively safeguards hair cells against oxidative stress-induced apoptosis in both *in vivo* and *in vitro* settings, and markedly mitigates the degeneration of cochlear nerve terminals (Min *et al.* 2023). Exosome products originating from bone marrow-derived hematopoietic stem cells and certain embryonic stem cells have been observed to specifically accumulate in the cochlear base and scala vestibuli (Tsai *et al.* 2021). This observation suggests that exosomes exhibit specific tropism and could be further investigated as targeted delivery vehicles for cellular products to specific regions within the inner ear. Research has demonstrated that exosomes derived from stem cells inherently possess significant biological activities, as illustrated in Fig. 1. As secretory products of cells, exosomes facilitate intercellular communication and hold promise as therapeutic agents for the amelioration of SNHL. There

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is a current absence of definitive studies that compare the therapeutic effectiveness of traditional hormonal drugs and stem cell-derived exosomes in SNHL treatment. This gap in knowledge presents a potential avenue for future research in the field of exosome studies.

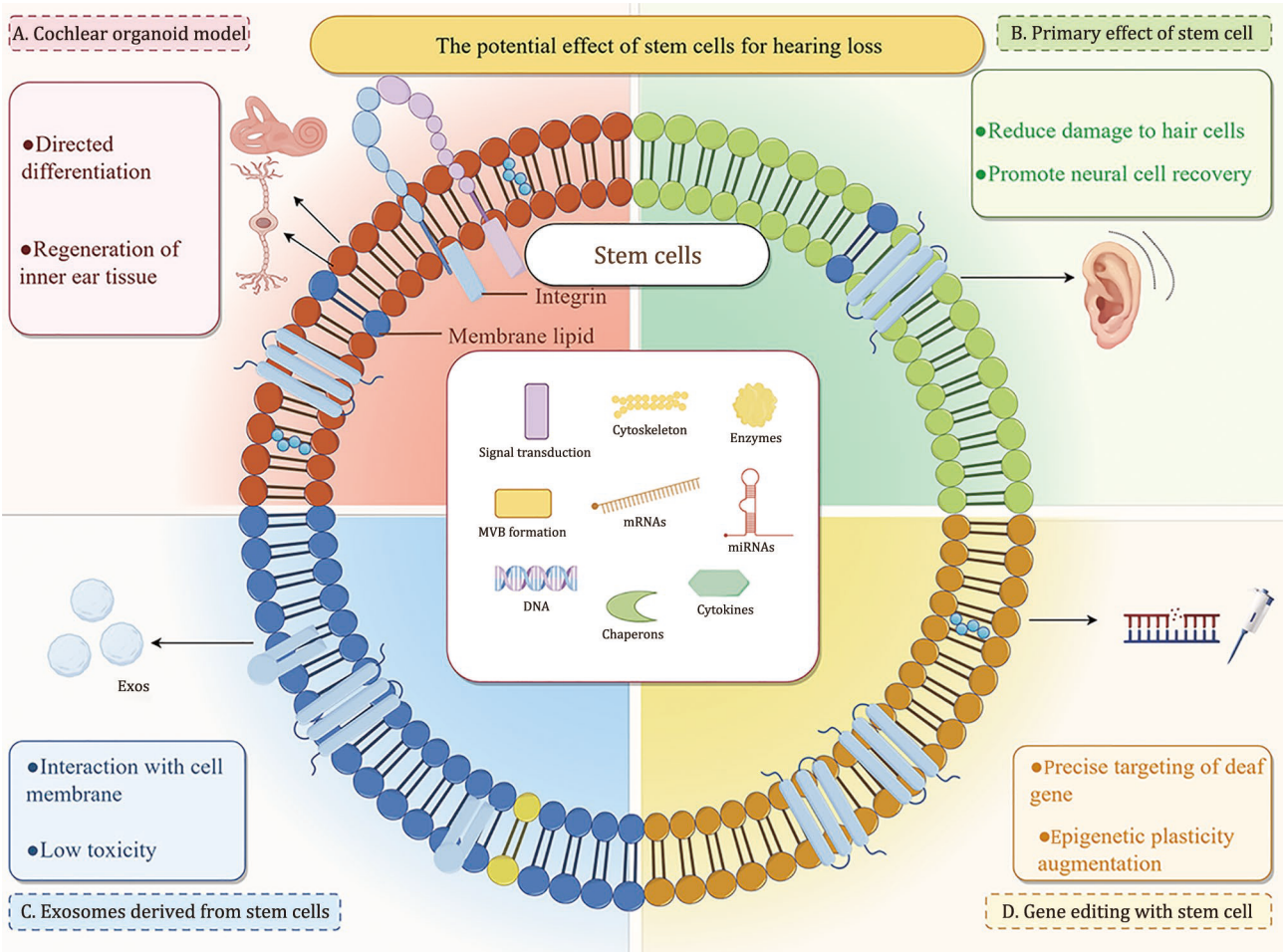

Fig. 1 Illustration of stem cell-driven oto-regenerative prospect in hearing loss therapy. This figure was generated using FigDraw online platform (www.figdraw.com)

When the permanent cells within the cochlea sustain damage, their regeneration is exceedingly challenging (Mammano and Bortolozzi 2018). The field of regenerative medicine has seen a proliferation of scientific studies aimed at investigating the potential roles of stem cell-derived exosomes in facilitating cellular regeneration and mitigating cellular senescence (Jin *et al.* 2023; Zhong *et al.* 2023). Current research on exosomes also focuses on delaying this cell death by reversing programmed death through specific genes and reducing cochlear inflammation. The potential of stem cell-derived exosomes to regenerate damaged tissues and enhance inner ear function has been observed. Their growth factors and nucleic acids can promote supporting cells to become hair cells, enhance neuronal repair, and restore auditory signal transmission (Yamamoto-Fukuda *et al.* 2023; Yang *et al.* 2021). MSC-derived exosomes have been demonstrated to alter the shape of rat SGNs and promote neurite growth. This is the first indication that human umbilical cord MSC-Exos could potentially restore hearing after noise trauma, prevent hair cell degeneration in noise-exposed mice, and protect primary rat auditory nerves *in vitro* (Warnecke *et al.* 2020). Currently, scientists have employed specific viral vectors to deliver the crucial element Atoh1 and associated coordinating

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factors to encourage the conversion of cochlear supporting cells into hair cells, aiming to boost cochlear cell proliferation (Iyer *et al.* 2022). Exosomes from stem cells can also carry nucleic acid fragments, and certain stem cell populations can overexpress proliferative genes. This raises the possibility of using these exosomes to deliver gene fragments that stimulate cochlear supporting cells, potentially reprogramming them into hair cells. This novel method could aid cochlear hair cell regeneration. Current research on stem cell-derived exosomes in hearing loss is promising, as it may enhance cochlear cell regeneration, delay hair cell death, and increase hearing ability by targeting the proliferation, differentiation, and inflammation of cells within the inner ear.

GENE EDITING MAY AID STEM CELLS IN THE TREATMENT OF HEARING IMPAIRMENT

More than 100 genes have been identified as causing human non-syndromic HL, with more than 40 associated with autosomal dominant HL (DFNA), 76 with autosomal recessive HL (DFNB), and five with X-linked HL (DFNX) (Bommakanti *et al*. 2019). Therefore, the use of stem cell regeneration characteristics combined with gene editing technology or adeno-associated virus (AAV)-mediated therapeutic gene delivery is expected to treat some patients with hearing impairment with gene defects (Sun *et al*. 2025).

The Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) system constitutes a groundbreaking gene therapy approach that permits the treatment of a diverse array of diseases via DNA splicing technology, thereby enabling precise genomic targeting in any human cell type (Barrangou and Marraffini 2014). The introduction of the CRISPR-associated nuclease 9 (CRISPR/Cas9) genome editing system has significantly transformed the use of gene-edited stem cells in the treatment of hereditary hearing loss. For example, researchers have effectively corrected PCDH15 frameshift mutations in a mouse model of DFNB23 deafness utilizing CRISPR-Cas9, thereby restoring mechanotransduction in cochlear hair cells and auditory function (Liu *et al.* 2022). This methodology utilizes induced iPSCs and MSCs as optimal platforms, based on their ability of regeneration and differentiation. By rectifying pathogenic mutations in stem cells, the edited cells are differentiated into functional hair cells or SGNs, thereby facilitating the replacement of irreversibly damaged auditory components.

Interestingly, some iPSCs extracted from patients with Charcot-Marie-tooth disease transiently recovered their ability to differentiate and proliferate into hearing cells after gene editing, but did not form a statistical difference with the healthy control group (Calame *et al.* 2023; Morena *et al.* 2019). Furthermore, hearing loss resulting from autosomal recessive mutations can potentially be addressed through therapeutic gene repair or replacement. In contrast, hearing loss caused by dominant missense mutations, such as those in the COCH or TMC1 genes, is frequently observed in auditory impairment disorders (György *et al.* 2019). ESC was first isolated with four factors (KLF4, OCT4, SOX2 and cMYC) that showed some similarities with iPSCs (Kinoshita *et al*. 2021; Takahashi *et al*. 2007). The DFNA36 deafness of the mouse model showed discrimination with Cas9 enzyme, which had a point mutation in the TMC1 gene that encodes a pore-forming component of the mechanosensory pathways in the hair cells of the inner ear (Anzalone *et al*. 2019). Because regenerative medicine attempts to combine the findings of development and stem cell biology, human stem cell lines subjected to gene editing have been able to specifically differentiate into specific inner ear organoids or specific hearing hair cells desired in research (Berthiaume *et al*. 2011). Stem cell makes it possible to simulate the gene therapy of hearing loss *in vitro*. The WNT, FGF, BMP, and SHH signaling pathways required for induction by neuronal progenitor cells expressing perineural genes have been shown in gene editing, and are able to have properties-level hearing levels that can improve the electrophysiology of hearing in some animals after the corresponding stem cells regulating (Terzic *et al*. 2015).

Stem cells modified with adeno-associated virus (AAV) vectors showed great possibility as efficient carriers for delivering therapeutic genes to the inner ear. AAV-mediated deaf gene delivery via stem cells has restored synaptic transmission in inner hair cells of DFNB9 patients, achieving hearing thresholds of 45 dB post-treatment (Qi *et al.* 2024; Qi *et al.* 2025b). In China, MSCs transfected with GJB2 or SLC26A4 common deafness-causing mutations have shown potential in regenerating gap junctions in cochlear supporting cells (Lv *et al.* 2024). Beyond gene delivery, edited stem cells secrete neurotrophic factors like BDNF or NGF enhancing neuronal survival and synaptic repair. It revealed that BDNF-secreting stem cells mitigate cisplatin-induced ototoxicity and improve auditory brainstem response thresholds in murine models (Min *et al.* 2023).

AAV is widely regarded as the gold standard vector for gene delivery due to its low immunogenicity, capacity for long-term expression, and modifiable

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capsid structure that allows for targeted interventions (Qi *et al.* 2025a). These attributes make AAV an ideal tool for precise gene delivery within the microenvironment of the inner ear (Sun *et al.* 2024a). By utilizing advanced gene editing technologies, including CRISPR/Cas9, Base Editor, and Prime Editor, AAVs can effectively deliver therapeutic agents to cochlear stem cells or supporting cells, thereby facilitating dual regulation. The approach simultaneously addresses and rectifies pathogenic mutations in high-frequency deafness-related genes, including OTOF, Gjb2 and Gpm6b, thereby restoring the molecular functions of inner ear cells (Sun *et al.* 2024b, 2025). Overexpression of anti-apoptotic genes promotes supporting cell reprogramming in the neonatal mouse cochlea with AAV (Xiao *et al.* 2025; Xu *et al.* 2024). Concurrently, by activating key transcription factors involved in hair cell differentiation, such as Atoh1 and Pou4f3, or by inhibiting the Notch signaling pathway, endogenous stem cells are induced to differentiate into functional hair cells. Simultaneously, the synergistic expression of neurotrophic factors, including BDNF, facilitates the synaptic remodeling of spiral neurons. In comparison to conventional viral vectors, engineered serotypes demonstrate substantial advantages in terms of permeability within the inner ear lymph fluid and the transduction efficiency of hair cells (Zhang *et al.* 2024a). In comparison to conventional viral vectors, engineered serotypes with genes from stem cells demonstrate notable advantages in terms of permeability to inner ear lymph fluid and transduction efficiency in hair cells (Zhang *et al.* 2024b). When utilized in conjunction with local administration at the round window membrane or through nanoparticle embedding techniques, these serotypes can overcome the restrictive barriers of the blood-labyrinth interface (Li *et al.* 2025; Ma *et al.* 2024). This approach enables highly specific transfection of target cells while concurrently minimizing the risk of systemic toxicity. These findings suggest that stem cells applied with a gene editing system are anticipated to specifically differentiate and regenerate within the inner ear, serving as either carriers or therapeutic targets.

CONCLUSION AND FUTURE PROSPECT

Stem cell therapy, as one of the hottest technologies in neurological disorders, has a huge potential in the treatment of hearing loss. Nevertheless, the intricate physiological architecture and internal milieu of the cochlea, coupled with the complexity of the neurogenesis mechanism, result in a therapeutic effect *in vivo* that is not readily apparent. In addition, these stem cells have a strong ability to regenerate and differentiate, which may increase the risk of inducing other diseases, such as tumor formation, tissue metaplasia, or abnormal activation of organs. Even as knowledge about potential therapeutic interventions for hearing loss has been accumulating, there are no explicitly genetic and/or stem cell-based regenerative therapies in the clinic to address the growing burden of hearing loss. Most studies face difficulties in treatment pathways, lack of sufficient molecular level validation, and lack of standardized *in vitro* modeling. So far, iPSCs have not been able to replicate the diversity and complexity of inner ear cells, producing HCs that are intrinsically more vestibular than cells. We still need to constantly try to normalize the differentiation of stem cells into hearing cells, not only a single kind of cell population, but also the cell tissue distribution community of the whole inner ear system. Similarly, the combination of stem cell therapy and existing methods (such as cochlear implantation and medical drug delivery system) may improve the therapeutic effect of each other. Cochlear implant electrodes may be able to adsorb on sensory nerves with the specific differentiation of stem cells, or enhance the efficacy of medical drugs into the inner ear.

After going through production and purification with or without modification, In the realm of clinical practice, stem cell therapy has demonstrated significant potential in treating a range of hearing loss conditions. Although it is currently challenging to achieve factory-scale mass production of relevant stem cell products, their application prospects in a wide range of ear diseases make it worthwhile for researchers to explore individualized or biologically better-compatible edited gene targets or natural cells for treating auditory impairment or serving as an important delivery system. In conclusion, augmenting stem cell production and advancing the scientific research, development, and application of their derivatives are crucial for promoting the clinical translation of regenerative medicine in the treatment of hearing loss.

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Compliance with Ethical Standards

Conflict of interest Zilin Huang, Keshu Liu, and Xiong Chen declare that they have no conflict of interest.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by the any of the authors.

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