REVIEW ARTICLE

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Auditory Repair Mechanisms by Using Mesenchymal Stem Cell and Pluripotent Stem Cell Induction: A Promising Novel Target: Review Article

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Abstract

Background: Sensorineural hearing loss is a prevalent condition that affects many and results from damage to cochlear hair cells and spiral ganglion neurons. Current treatments offer partial auditory restoration but fail to address the underlying cellular damage. Cell-based therapies have emerged as a potential strategy for regenerating damaged auditory structures.

Aim: This review examines the recent progress and ongoing challenges in the application of cell therapy for hearing loss.

Methods: A comprehensive review of the literature was conducted searching through PubMed, Scopus, and Google Scholar with a focus on publications between 2000 and 2023. Studies were included if they addressed the use of stem cell-based therapies in hearing loss, involving both preclinical models and human trials. Data were collected on the used cell types, mechanisms of action, outcomes, and barriers to clinical application.

Results: ESCs, iPSCs, MSCs, and NPCs have been explored for hearing loss therapy. ESCs and iPSCs demonstrated the ability to differentiate into auditory hair cells and SGNs, showing potential for direct auditory repair. While preclinical studies in animal models showed partial restoration of auditory function, challenges such as limited cell survival, maturation, and integration persist. Initial clinical trials using MSCs have demonstrated safety, with mild improvements in hearing function, though significant functional recovery is not yet definitive.

Conclusion: Cell therapy offers a novel approach for treating SNHL, but further research is necessary to optimize cell survival, delivery, and integration. Future clinical trials and advancements in stem cell technology will be critical to translating these findings into viable treatments.

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Introduction

Hearing loss is a prevalent condition affecting over 466 million people globally, with an estimated rise to nearly 900 million by 2050, according to the World Health Organization (1). It can significantly impair communication, social interaction, and overall quality of life (2). The most common type, sensorineural hearing loss (SNHL), results from damage to the inner ear structures, particularly the loss of cochlear hair cells and spiral ganglion neurons (SGNs), which are essential for the transmission of sound to the brain (3,4). While hearing aids and cochlear implants provide some relief, they do

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not restore normal hearing and have limitations, especially in severe cases (5). Cell-based therapy has emerged as a promising approach to treating hearing loss, particularly SNHL, by potentialky regenerating damaged tissues in the inner ear (6,7). The stem cells ability to differentiate into key auditory structures, such as hair cells and neurons, offers hope for restoring hearing function (8). In recent years, significant advancements in stem cell technology, including the use of embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs), have opened new doors for treating hearing disorders (9,10). In this review we aim to summarize the current status of research on cell therapy for hearing loss, explore the various types of stem cells under investigation, the mechanisms by which they can repair auditory damage, and the challenges that remain in translating these therapies from experimental models to clinical practice.

Methods

This review was conducted to evaluate the current available research on cell therapy for hearing loss, with a particular focus on studies involving stem cell-based interventions. A comprehensive literature search was performed using several scientific databases, including PubMed, Scopus, and Google Scholar focusing on studies published between 2000 and 2023. The search terms included "cell therapy," "stem cells," "hearing loss," "sensorineural hearing loss," "hair cell regeneration," and "auditory neuron regeneration."

Inclusion Criteria: Studies were included if they (1) focused on cell therapy as a treatment for hearing loss, (2) involved animal models or human clinical trials, and (3) were published in peer-reviewed journals after the year 2000. Both preclinical and clinical studies were included.

Exclusion Criteria: Articles were excluded if they (1) did not focus on cell-based therapy, (2) discussed non-research-based therapeutic approaches (e.g., hearing aids, cochlear implants), or (3) were reviews or meta-analyses that did not present original findings.

Data Extraction and Synthesis: Data were extracted from the selected articles, focusing on the types of cells used, mechanisms of hearing restoration, outcomes, and limitations. The findings were then synthesized to identify trends in the current literature, gaps in research, and potential future directions for cell-based therapies in hearing loss.

Study Selection Process: Articles were independently reviewed by the authors to ensure relevance and quality. Discrepancies were resolved. A final set of studies was selected for inclusion in this review based on the aforementioned criteria.

Results

The literature search identified numerous preclinical and clinical studies investigating the use of cell-based therapies for the treatment of hearing loss. The results of these studies were categorized into the following themes: the types of cells used, the mechanisms by which they promote auditory repair, the outcomes of experimental models, and the current status of clinical trials (Figure 1).

1. Types of Stem Cells Used in Hearing Loss Treatment

The studies reviewed employed a variety of stem cell types, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and neural progenitor cells (NPCs).

- **Embryonic Stem Cells (ESCs)**: ESCs demonstrated the potential to differentiate into cochlear hair cells and SGNs (11). Several studies successfully induced ESCs to form sensory cells in vitro, capable of integration into damaged auditory structures upon animal model transplantation (12–14).
- **Induced Pluripotent Stem Cells (iPSCs)**: iPSCs, derived from adult somatic cells, have shown great promise secondary to their pluripotency and ability to differentiate into

Journal of Otorhinolaryngology and Facial Plastic Surgery 2024;10(1):1-8.
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hair cells and neurons. Studies reported the generation of auditory cells from iPSCs, suggesting a viable, patient-specific treatment approach for hearing loss (15–18).

• **Mesenchymal Stem Cells (MSCs)**: MSCs, derived from bone marrow or adipose tissue, have been tested extensively in animal models. These cells promote regeneration primarily through paracrine signaling, secreting growth factors that encourage endogenous repair of auditory cells rather than direct differentiation into auditory structures (19–22).

• **Neural Progenitor Cells (NPCs)**: NPCs have been studied for their ability to replace lost or damaged neurons in the auditory pathway. Animal studies have shown promising results in the restoration of auditory nerve function following NPC transplantation (23,24).

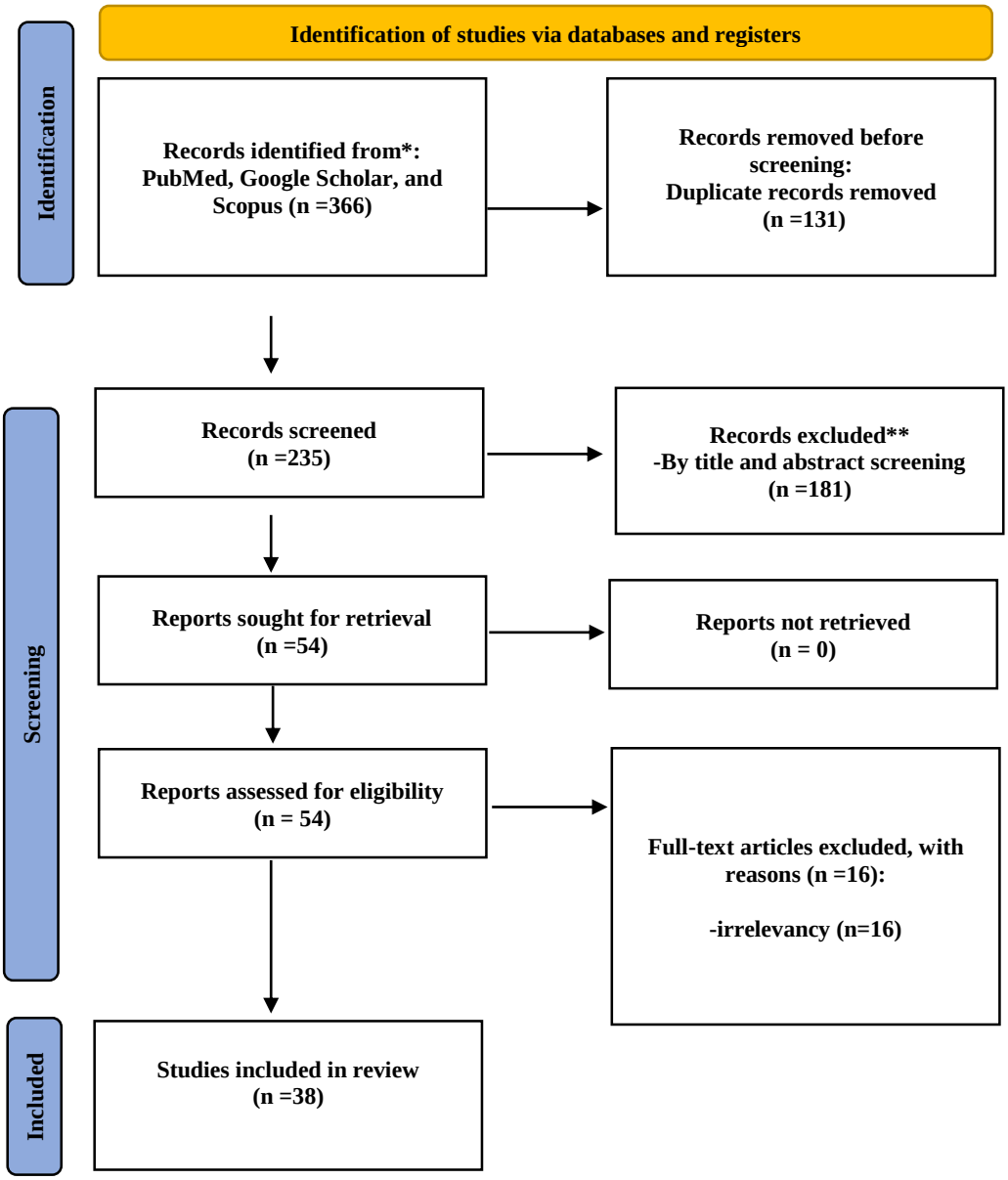

Figure 1. PRISMA flowchart of study selection process

Journal of Otorhinolaryngology and Facial Plastic Surgery 2024;10(1):1-8.
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2. Mechanisms of Auditory Repair

The reviewed studies highlighted two primary mechanisms by which cell-based therapies may restore hearing function: direct differentiation into auditory cells and stimulation of endogenous repair pathways.

- **Direct Differentiation**: ESCs and iPSCs, in particular, demonstrated the ability to differentiate into both cochlear hair cells and SGNs (10). When transplanted into damaged cochleas of animal models, these cells were able to survive, integrate, and partially restore auditory function (25,26).
- **Paracrine Signaling and Endogenous Repair**: MSCs and other stem cells have been shown to release trophic factors that stimulate the repair of residual auditory structures (27). This mechanism is particularly important in cases where surviving auditory cells can be regenerated or preserved through enhanced cellular repair pathways (22,28,29).

3. Outcomes in Animal Models

significant progress in animal models has been made, demonstrating the feasibility of cell-based therapies for hearing restoration (30). Transplantation of ESCs, iPSCs, and MSCs has resulted in varying degrees of hearing recovery, with some studies reporting partial restoration of hearing thresholds and functional integration of transplanted cells into the auditory circuitry (31, 32).

Hair cell regeneration has been observed in several experiments, with evidence of synaptic connections between newly formed cells and the auditory nerve. However, challenges remain. The survival rate of transplanted cells was inconsistent across studies, and in many cases, the extent of functional recovery did not correlate with the number of surviving cells (33). Additionally, the long-term survival and integration of cells into the complex cochlear architecture remain areas of investigation (34).

4. Clinical Trials and Translational Progress

Few clinical trials have been conducted to date, as most researches remain in the preclinical phase. However, early-phase clinical trials have begun to explore the safety and feasibility of stem cell therapies for hearing loss (35). For example, mesenchymal stem cells have been tested in small pilot studies, showing potential for improving hearing thresholds in some patients (21,36). No major adverse effects were reported, indicating the relative safety of these approaches (37). Despite these early successes, no stem cell therapy has reached clinical trials yet (38). Ongoing research focuses on optimizing cell delivery methods, improving cell survival and differentiation, and ensuring that regenerated cells can form functional connections with the auditory system.

Discussion

Cell-based therapies represent a promising frontier in the treatment of SNHL, offering the potential to restore auditory function by regenerating damaged structures within the inner ear. The results of this review highlight significant progress in the use of various stem cell types, including ESCs, iPSCs, MSCs, and NPCs, to repair or replace lost cochlear hair cells and SGNs. However, while preclinical studies have demonstrated encouraging outcomes, numerous challenges remain before these therapies can be successfully translated into clinical practice. Among the stem cells studied, ESCs and iPSCs hold the most promise due to their pluripotency and ability to differentiate into cochlear hair cells and SGNs (11, 39). iPSCs, in particular, offer a major advantage because they can be derived autologously from a patient's somatic cells, reducing the risk of immune rejection (40). However, several key issues remain unresolved. The process of directing stem cells to differentiate specifically into auditory cells is not fully optimized. While many studies have demonstrated that ESCs and iPSCs can generate hair cells and SGNs in vitro, the efficiency and consistency of this differentiation vary widely (10). Even when stem cells successfully differentiate into hair cells or neurons, their ability to fully mature and integrate into the

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damaged cochlea remains a significant hurdle. Further research is needed to develop more precise protocols that yield higher numbers of functional auditory cells (41). Delivering stem cells to the inner ear poses significant technical challenges. The cochlea is a highly specialized and compartmentalized structure, making it difficult to target cell transplants effectively (42). Intracochlear injections, the most commonly used method in animal studies, have shown some success in delivering stem cells to the appropriate regions, but this approach carries the risk of additional trauma to the cochlear structures (43).

Many stem cells do not survive long-term within the cochlea, and those that do often fail to proliferate or form functional networks with existing cells (44,45). One of the most promising findings from this review is the ability of stem cells, particularly MSCs, to promote endogenous repair through paracrine signaling. Rather than differentiating into auditory cells themselves, MSCs secrete a variety of trophic factors that stimulate the repair of damaged cochlear tissues (22). This paracrine effect has been observed in several studies, where MSCs contributed to improved auditory function without directly replacing lost cells (19–22).

The use of MSCs may represent a less invasive approach compared to other cell types, as it does not require the same degree of cellular integration (46). While preclinical models have provided valuable insights, translational research for human applications has proven difficult. Clinical trials involving stem cell therapy for hearing loss are still in their infancy, with only a handful of small-scale studies completed to date. These trials, primarily focused on MSCs, have reported minimal adverse effects and some improvement in hearing thresholds. However, no trials have yet demonstrated significant or sustained auditory recovery. As with any new therapeutic approach, safety remains a paramount concern.

Future Directions

The future of cell-based therapies for hearing loss is promising, but several areas require further investigation:

- **Improving Differentiation and Functional Integration**: Continued research is needed to refine protocols for differentiating stem cells into functional auditory cells. Techniques such as gene editing (e.g., CRISPR-Cas9) and bioengineering approaches may enhance the maturation and integration of transplanted cells (47,48).
- **Developing Non-Invasive Delivery Methods**: Advancements in delivery technologies, such as nanoparticle carriers or minimally invasive surgical techniques, could improve the precision and safety of stem cell transplantation into the cochlea (49,50).
- **Combining Cell Therapy with Other Modalities**: Future strategies may involve combining cell therapy with other interventions, such as gene therapy, pharmacological agents, or cochlear implants, to maximize auditory restoration. Additionally, the identification of biomarkers could enable more personalized approaches, tailoring treatments to the specific needs of individual patients (6,51,52).

Conclusion

In conclusion, while substantial progress has been made in preclinical research on stem cell-based therapies for hearing loss, significant challenges remain in terms of cell survival, differentiation, and functional integration. Future research efforts should focus on overcoming these barriers, as well as implementing clinical translation for these therapies. With continued advancements, cell therapy holds the potential to revolutionize the treatment of sensorineural hearing loss, offering a means for restoring auditory function to millions of affected individuals.

Journal of Otorhinolaryngology and Facial Plastic Surgery 2024;10(1):1-8.
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Conflicts of Interest

The authors declare no conflicts of interest.

Ethics

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