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Regenerative Biotechnology of the Auditory System: Recent Advances in Cell Therapy, Tissue Engineering, Gene Therapy, and Genome Editing Toward Personalized Medicine

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ABSTRACT

Sensorineural hearing loss ranks among the most common auditory disorders, arising mainly from injury to the cochlear sensory hair cells and their associated afferent neurons. Because the mammalian cochlea possesses only a minimal capacity for self-repair, achieving a definitive cure remains a persistent clinical obstacle. Recent advances in biotechnology, particularly in the fields of stem cell biology, tissue engineering, gene therapy, and genome editing, have opened new avenues for auditory system regeneration. This article surveys how hair cells differentiate at the molecular level, assesses the regenerative capabilities of different stem cell populations for repairing the inner ear, and reviews applications of newer tools such as RNA interference, CRISPR/Cas9-mediated editing, viral and non-viral gene-delivery systems, inner-ear organoid models, and bioengineered scaffolds. Preclinical studies indicate that integrating stem cell–based therapies with advanced biotechnological approaches can enhance the structural and functional regeneration of the inner ear. Despite these promising findings, further research is required to improve the efficacy, safety, and clinical translation of these technologies before they can be widely implemented in therapeutic practice.

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INTRODUCTION

Cell-based therapy has emerged as a promising strategy for treating numerous diseases, and developing novel therapeutic interventions for hearing loss is of particular importance. The application of stem cells for the treatment of deafness and hearing impairment has become one of the most active areas of biomedical research (1, 2). The differentiation of embryonic and adult stem cells into auditory hair cells, followed by their transplantation into the organ of Corti, represents a critical objective of regenerative medicine for hearing restoration (3). These approaches rely on the intrinsic capacity of stem cells to engraft, proliferate, differentiate, and survive within the target tissue, serving as replacement or adjunctive therapies for damaged cells. Most congenital and acquired hearing loss results from destruction of cochlear hair cells and/or auditory neurons (4). In mammals, this damage is essentially irreversible, since hair cells cannot be replaced through cell division or differentiation of other inner ear epithelial cells (5); yet no definitive cure exists, leaving only partial rehabilitative compensation available. In recent years, stem cell–based therapy has been proposed to replace damaged or lost hair cells in mammals. Initial studies showed that embryonic, adult inner ear, and neural stem cells can be induced to differentiate into hair cells, strengthening the prospect of treating hearing loss through regenerative medicine (4). Cell therapy and tissue engineering have therefore attracted considerable attention as approaches to

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restore both structural and functional integrity of the auditory system, though challenges remain in cell-source selection, control of differentiation, efficient delivery/engraftment, and achieving durable outcomes. Therefore, this review aims to critically examine current evidence on cell therapy and tissue engineering in auditory system regeneration, evaluate the potential and limitations of these approaches, and discuss future perspectives for developing effective therapies for hearing loss and deafness.

Anatomy and Underlying Developmental Mechanisms of the Inner Ear

The inner ear is organized into two distinct functional units: a hearing-related component and a balance-related component. The latter, which incorporates the semicircular canals, governs the maintenance of equilibrium (Figure 1).

The auditory portion of the inner ear centers on the cochlea, a spiral structure built from four main compartments. The scala vestibuli lies next to the semicircular canals and holds perilymph, divided from the cochlear duct by Reissner's membrane. Parallel to it, the scala tympani sits adjacent to the tympanic membrane, likewise perilymph-filled, and is partitioned from the cochlear duct by the basilar membrane. At the cochlear apex, these two chambers merge at a point known as the helicotrema. Between them runs the scala media (cochlear duct), an endolymph-containing space enclosed by Reissner's, the reticular lamina, and the basilar membrane; it houses the organ of Corti, the true auditory sensory structure (Figure 1). Mechanical displacement of the endolymph caused by incoming sound waves bends the stereocilia atop the hair cells, gating open ion channels permeable to K^+ and Ca^{2+}; the resulting membrane depolarization drives glutamate release at the presynaptic terminal, generating the electrical impulse relayed to the brain. **Modiolus:** the cone-shaped bony core at the center of the cochlea. **Cochlear cupula (apex):** the tip of the cochlea, where the bony canal completes ~2.5 turns around the modiolus (6, 7).

Each stage of inner ear development is regulated by the coordinated activation of defined gene sets. The precise expression of the *Lfng*, *Six1*, *Eya1*, *Ngn1*, *Sox2*, and *Delta1* genes is essential for the development of the otic cup. *Ngn1* and *Delta1* play pivotal functions in the differentiation of the sensory–neural domain. Specifically, when the Notch ligand Delta1 is expressed, it suppresses a subset of prosensory epithelial cells from committing to a neuroblast fate. In contrast, the expression of *Ngn1* (neurogenin 1), which encodes a basic helix–loop–helix (bHLH) transcription factor, in adjacent sensory epithelial cells promotes their differentiation into supporting cells, auditory hair cells, and several other specialized cell types (8).

Genetic and Molecular Pathways Governing Hair Cell Fate Specification

Atoh1 (also referred to as Math1) stands as the earliest and most critical gene linked to the emergence of hair cells. This bHLH transcription factor is expressed, during embryonic life, exclusively within cells that have been directed towards becoming hair cells (9).

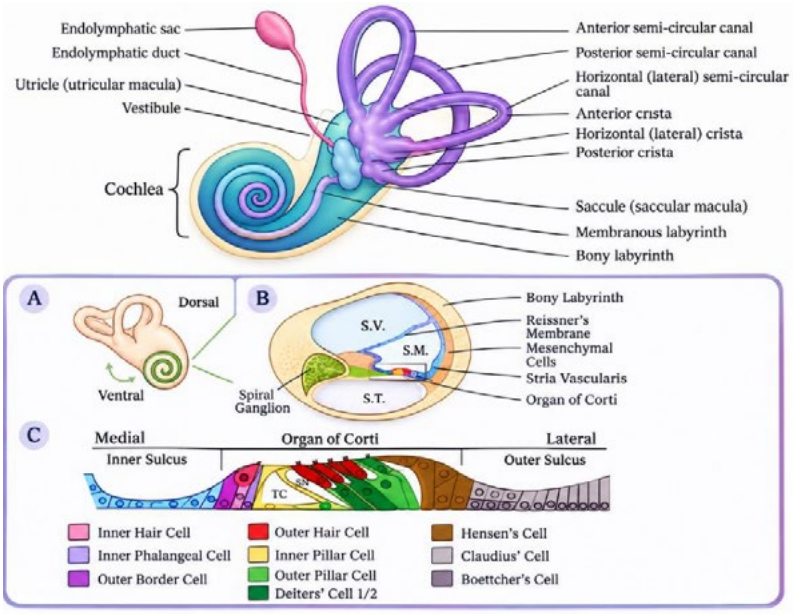


Fig 1. Structural organization of the inner ear, cochlea, and organ of Corti. (A) General layout of the inner ear and the position of the cochlea. (B) Cross-sectional view depicting three fluid-filled compartments — the scala vestibuli, scala media, and scala tympani — separated by Reissner›s, basilar, and tectorial membranes, with the organ of Corti resting atop the basilar membrane and receiving innervation from spiral ganglion neurons. (C) Magnified depiction of the organ of Corti, delineating inner and outer hair cells alongside pillar cells, Deiters› cells, and Hensen›s cells.

Multiple regulators acting in parallel govern both how much Atoh1 is expressed and where. As depicted in Figure 2, Sox2 present across the entire sensory domain is required to switch on Atoh1; yet prolonged Sox2 expression works against Atoh1-mediated hair cell differentiation, whereas lowering Sox2 levels leads to a greater number of hair cells forming (8, 10). A separate regulatory layer comes from the Id (Inhibitors of Differentiation) proteins Id1, Id2, and Id3 which are abundant in the cochlear duct during early development but decline sharply once hair cell differentiation begins, consistent with a role as Atoh1 antagonists: forcing Id3 expression blocks hair cell formation, pointing to the Id family as candidate targets for future therapeutic intervention (11). The most extensively studied pathway regulating *Atoh1* is Notch signaling, in which membrane-bound receptors and ligands restrict signal transduction to directly contacting cells, allowing multipotent progenitors to diverge into distinct lineages (12). expressed in epithelial cells, while its ligands Delta-like 1 (Dll1) and Jagged2 are restricted to hair-cell-committed cells (13, 14), and the inhibitory bHLH factors Hes and Hey1 are expressed exclusively in supporting cells (15, 16). Genetic deletion of individual Notch pathway components increases hair cell number, with the magnitude depending on the specific gene disrupted (17).

Key Molecular Markers for Understanding the Differentiation of Inner Ear Stem Cells into Auditory Hair Cells

The path by which inner ear stem cells become hair cells unfolds across three sequential phases prosensory specification, lineage commitment toward hair cells, and final maturation. Prior to E12, the future sensory epithelium is broadly marked by Notch1, Jagged1, and Sox2 expression (17, 18). Once E12 is reached, climbing levels of the cell-cycle inhibitors $p27^{Kip1}$, $p19^{Ink4d}$, and Rb push prosensory cells out of the cell cycle, such that by E14 every $Sox2^{+}$ cell has also become $p27^{Kip1+}$. After this point of mitotic arrest, a fraction of these cells switches on *Atoh1* the pivotal determinant of hair cell identity with the Notch ligands *Jagged2* and *Delta1* coming online shortly afterward; these ligands, in turn, trigger Notch signaling in neighboring cells and induce *Hes1*/*Hes5*, steering those neighbors toward becoming supporting cells instead (19). By E16–E17, *Notch1*, *Jagged1*, p27, and *Hes5* have become confined to the supporting-cell population, with Sox2 levels now considerably higher in supporting cells than in hair cells; come P0, hair cells no longer retain any Sox2, whereas supporting cells continue to express it. Over the interval from birth through P7, the hair-cell-associated markers *Atoh1*, *Jagged2*, and *Delta1* gradually fade out (accompanied by a parallel decline in *Notch1*/*Hes5* within supporting cells), while Sox2, p27, and *Jagged1* remain detectable in supporting cells right through to full maturation (18).

Converting inner ear stem cells into functional auditory hair cells unfolds through a multistep sequence, one that hinges on the tightly coordinated interplay of numerous transcription factors and signaling cascades (Figure 3). It is this same regulatory circuitry that underpins present-day cell-based and tissue-engineering approaches aimed at hair cell regeneration in sensorineural hearing loss, and reproducing these developmental steps both in vitro and in a living organism continues to stand as a

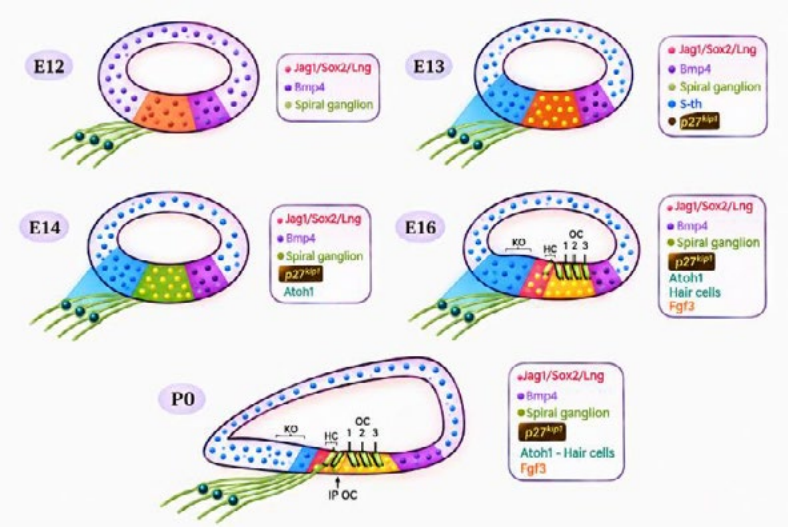


Fig2. Role of Sox2 in regulating Atoh1 expression during inner ear development. At E12, the prosensory domain expresses Jag1, Sox2, and Lng; BMP4 then refine the sensory domain boundaries while p27kip1 drives cell cycle exit. Atoh1 expression begins at E14, initiating hair cell differentiation. Fgfr3 subsequently marks pillar and Deiters› cells, and by birth (P0) the organ of Corti reaches its mature architecture one row of inner and three rows of outer hair cells with supporting cells.

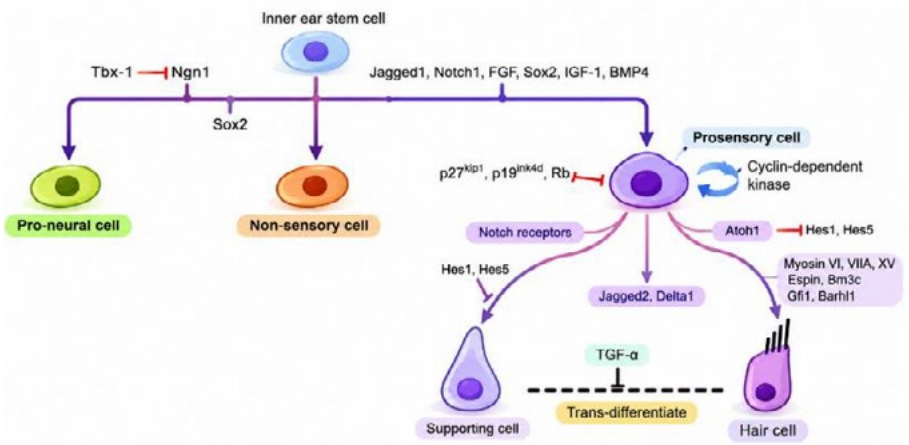


Fig3. Signaling pathways governing inner ear stem cell fate decisions. Stem cells of the inner ear give rise to three lineages — pro-neural, non-sensory, and prosensory — with commitment to the prosensory lineage driven by Notch/Jagged signaling together with Sox2, Atoh1, FGF/BMP4/IGF-1, and the cell-cycle regulators p27Kip1 and p19Ink4d. From this prosensory pool, both hair cells and supporting cells subsequently emerge: Notch signaling, acting through Hes1/Hes5, keeps the two populations in balance, while Atoh1 pushes cells toward the hair cell fate and switches on hair-cell-specific genes such as Myosin VI/VIIA/XV, Espin, Brn3c, Gfi1, and Barhl1.

core objective for the field (4, 18).

Prospects for the Application of Stem Cells in the Treatment of Deafness

Work in recent years has made it clear that success in cell-engineering and regenerative-medicine therapeutics hinges largely on how well the molecular circuitry controlling self-renewal, differentiation, and plasticity in stem cells can be regulated. It follows that pinpointing and manipulating these regulatory pathways holds real potential for boosting the effectiveness of stem-cell-based approaches to regenerating specialized tissue (20). Broadly, stem cells are undifferentiated cells capable of self-renewal; they are grouped by origin into embryonic and adult types, and by their differentiation range into toti-, pluri-, multi-, or unipotent categories. Applications span much of regenerative medicine, extending from neural tissue to bone, cartilage, and the cornea. Embryonic stem cells (ESCs) in particular originate from the blastocyst's inner cell mass, growing as tightly packed, Sox2-positive colonies that divide indefinitely and retain the ability to give rise to all three germ layers (2, 3, 21), and have been investigated for infertility, neurological, cardiovascular, and metabolic disease (22). Worldwide, congenital deafness impacts hundreds of millions of individuals, most commonly stemming from injury to the cochlea's hair cells and the neurons connected to them (23); Since these specialized mechanosensory cells are responsible for translating sound into neural impulses and possess only a narrow window for spontaneous repair, the resulting damage tends to be permanent (24). No cure currently exists, leaving hearing aids and cochlear implants as the sole clinical options — devices that come with drawbacks, not least their reliance on external hardware, which has spurred interest in regenerative alternatives instead. Foundational work mapping the genes driving auditory system development and regeneration across rodents, birds, and amphibians (25-28), together with the extensive use of rodent models for their genetic and physiological similarity to humans (29), established a key distinction: unlike fish, amphibians, and birds, mammalian hair cells cannot regenerate once lost, since they cannot be replaced through cell division or endogenous regeneration. This fundamental difference has made cell-based therapy, alongside other stem cell sources such as inner ear epithelial and cochlear supporting cells, one of the leading strategies for inner ear repair (4, 30, 31). The first study testing this approach stem cell transplantation into ototoxin-deafened mice found accelerated hearing recovery (27), prompting numerous follow-up studies (28, 32, 33). Building on this, later research established several complementary findings: ESC-derived progenitor cells were capable of turning into hair-cell-like cells and taking up residence within injured inner ear epithelium (34), while ESC-derived neural progenitors, once transplanted into the cochlear nerve trunk, extended outgrowths oriented specifically toward the organ of Corti (35). Elsewhere, neural stem cells placed in co-culture with hair cells were driven towards an auditory identity (36), and inner ear stem cells proved able to give rise to sensory neurons that were functionally active (37). Human embryonic auditory stem cells, for their part, could be expanded in culture and directed to differentiate into both neurons and hair cells, yielding useful models for studying ototoxicity and for drug-screening applications (38). Differentiation conditions were further shown to influence the mechanosensitivity of hair-cell-like clusters derived from ESCs and induced pluripotent stem cells (iPSCs) (25), while mouse ESCs cultured in stromal-conditioned medium (39), or engineered to overexpress *Atoh1* in co-culture with spiral ganglion neurons, likewise acquired

mechanosensory, hair-cell-like properties (26). Non-sensory supporting cells show similar promise: in co-culture systems, cells located closest to sensory hair cells display the greatest capacity for hair-cell regeneration (28, 32). Among the stem cell types investigated, adult mesenchymal stem cells (MSCs) have emerged as one of the most promising candidates in preclinical research; the following sections review the principal cell sources and their applications in auditory system regeneration.

Application of Adult (Mesenchymal) Stem Cells

Mesenchymal stem/stromal cells (MSCs) are mesoderm-derived progenitors characterized by fibroblast-like morphology, plastic adherence, self-renewal, and differentiation into osteogenic, adipogenic, and chondrogenic lineages; their immunomodulatory and regenerative properties have made them one of the most widely used cell types in regenerative medicine (40). Three principal cell sources have been examined as candidates for inner ear regeneration, namely those derived from bone marrow (BM-MSCs), adipose tissue (AD-MSCs), and umbilical cord tissue (UC-MSCs), and the evidence supporting each differs considerably. Of the three, BM-MSCs carry the most substantial experimental backing when it comes to restoring auditory function and driving regeneration of both hair cells and spiral ganglion neurons a strength attributable to their ability to migrate toward sites of injury, release neurotrophic factors, and reshape cochlear architecture. AD-MSCs are more accessible and proliferate more readily, making them attractive for clinical translation, but evidence for their direct differentiation into auditory cell types remains limited. UC-MSCs combine high proliferative potential with low immunogenicity and anti-inflammatory activity, though preclinical evidence in inner ear regeneration is still sparse. Overall, BM-MSCs currently represent the most promising candidate for auditory cell therapy (41). Numerous studies have investigated different strategies to enhance the survival, regenerative potential, and differentiation capacity of mesenchymal stem/stromal cells (MSCs) under both in vivo and in vitro conditions. In a study conducted by Lin et al. in 2012, adipose-derived mesenchymal stem cells isolated from the subcutaneous adipose tissue of mice (of mesodermal origin) were co-cultured with spiral ganglion neurons isolated from the organ of Corti of the mouse cochlea (of ectodermal origin) to induce the differentiation of MSCs into auditory hair cells under in vitro conditions. The authors concluded that spiral ganglion neurons secrete factors that are required for the differentiation of mesenchymal stem cells into auditory hair cell-like cells. RT-PCR served to profile the expression of the relevant molecular markers, whereas immunocytochemistry was employed to examine cellular morphology and structural characteristics (42). By contrast, when human BM-MSC-derived neural progenitor-like cells were co-cultured with chick utricular stromal cells under retinoic acid, EGF, and Sonic Hedgehog signaling, neuronal markers increased but hair-cell markers (Myosin VI and VIIa) remained absent indicating that these these culture conditions were insufficient to induce the complete differentiation of mesenchymal stem cells into functional auditory hair cells (43). Numerous studies have employed UC-MSCs for differentiation into various cell types under in vitro culture conditions. For example, in a research conducted by Yoo et al. in 2010, human UC-MSCs were co-cultured with hair follicle-derived cells to induce their differentiation into dermal papilla cells, which possess the potential to promote hair formation, as a potential therapeutic approach for alopecia (44), but no study to date has reported their differentiation into auditory hair cells.

Application of Embryonic Stem Cells (ESC)

Evidence for ESC-based hair cell generation comes from two complementary approaches. Co-culturing inner ear-derived auditory stem cells with Math1/nGFP mouse ESCs directed sequential differentiation first into Nestin^{+} progenitor cells, then into hair cell-like cells confirmed by Myosin VIIa, Espin, *Math1*, and *Atoh1* expression alongside loss of the supporting-cell marker pan-cytokeratin (34). Building on this, a comparative co-culture study found that intact ESC-derived embryoid bodies generated significantly more neuron-like cells when paired with auditory hair cells than with auditory neurons, indicating that hair cells provide a more effective inductive microenvironment than neurons for directing stem cell differentiation (36).

Strategies for Reprogramming Stem Cells Through Genetic Manipulation and Modulation of Key Gene Expression

Among the applied fields within biotechnology, stem cell research occupies a particularly prominent place, given the fresh possibilities it offers for cell-based therapy and the replacement of damaged tissue. A turning point came in 1998, when the first human embryonic stem cells were successfully isolated; combined with their striking versatility in generating diverse cell and tissue types spanning neurons, hepatocytes, and insulin-secreting cells this discovery ushered in a new phase for tissue engineering and drew biological science and clinical practice closer together. Even so, considerable obstacles continue to stand between stem cells' therapeutic promise and their actual clinical use. Our grasp of the molecular processes steering stem cell differentiation has advanced substantially thanks to progress across developmental biology, tissue and scaffold engineering, genetic engineering,

and nanoscale cell manipulation (3, 45). Gene transfer or modulation of gene expression, achieved by delivering gene expression cassettes into target cells, can influence not only the behavior of the transplanted cells and their interactions with neighboring host cells, but also their responsiveness to environmental changes such as hypoxia, hormonal fluctuations, and pharmacological exposure. A variety of delivery methods have been developed for this purpose: viral vectors for stable, long-term gene expression, and non-viral approaches DNA plasmids together with physical and chemical transfection techniques including liposomes, microinjection, microporation, nucleofection, electroporation, and magnetofection. Compared with viral approaches, non-viral delivery systems tend to trigger a weaker immune response and carry a lower chance of insertional mutagenesis, although this comes at the cost of reduced transfection efficiency and expression that is only short-lived. On the viral side, four vector types retroviruses, lentiviruses, adenoviruses, and adeno-associated viruses (AAVs) dominate current practice for gene delivery, whether the setting is in vivo or in vitro. Retroviral and lentiviral vectors achieve stable gene transfer through genomic integration, but this remains technically challenging in mesenchymal and hematopoietic stem cells because of their relatively low transduction efficiency; moreover, the random integration of viral genomes into the host genome can disrupt endogenous or pluripotency-associated genes, raising the risk of insertional mutagenesis and tumorigenesis. Lentiviral vectors are most commonly used for genetically modifying hematopoietic stem cells for example, to deliver the β-globin gene in mouse models of β-thalassemia (46-48) and lentiviral HSP70 overexpression has similarly been used to improve MSC survival under ischemic stress (49), yet the limited tissue penetration of these vectors in vivo makes them poorly suited to transfecting inner ear sensory epithelium. Adenoviral and Sendai virus vectors, by contrast, achieve high, non-integrating transduction efficiency across diverse inner ear cell types and are considered comparatively safe despite a risk of immune activation at high doses, making them the preferred vehicle for auditory gene delivery (50). A great deal of research has focused on how stem cells transform into the specialized cell types that make up different tissues and organs. As one illustration, Talens-Visconti and colleagues (2006) set out to compare transduction efficiency between bone marrow- and adipose-derived mesenchymal stem cells, delivering the transcription factors C/EBPα and C/EBPβ both known to control expression of numerous hepatocyte-specific genes — via adenoviral vectors, with the goal of pushing these cells toward a hepatocyte-like identity (51). As noted earlier, *Atoh1* ranks as the earliest and most consequential gene tied to hair cell formation: this bHLH transcription factor is expressed, during embryonic development, only within cells already committed to becoming hair cells, and a substantial body of work has pinpointed its upregulation as the pivotal molecular trigger for hair cell differentiation. Oshima and colleagues explored this by examining how stem cells were distributed across the auditory and vestibular regions of the inner ear in Math1/nGFP transgenic mice. What they found was evidence of separate stem cell populations, each with its own regenerative capacity, within the inner ear a distinction they argued carries real implications for designing stem cell-based therapeutic strategies aimed at auditory system regeneration (52). A large number of studies have also examined the potential of adenoviral vectors to promote stem cell differentiation under in vivo conditions. Kawamoto et al. used adenoviral vectors carrying the *LacZ* reporter gene to deliver the *Math1* gene into the endolymphatic compartment of the cochlea in adult guinea pigs and to monitor transgene expression. Four days after viral inoculation, the animals were sacrificed, and cochlear tissues were analyzed to evaluate the expression of hair cell differentiation markers (53). Similarly, Izumikawa et al. investigated the effect of adenovirus-mediated *Atoh1* overexpression on the differentiation of auditory hair cells in deaf guinea pigs under in vivo conditions. Their findings confirmed the essential role of *Atoh1* in hair cell differentiation and further demonstrated the high efficiency of adenoviral vectors in mediating gene transfer to cochlear cells (54). Accordingly, Chen et al. employed the simultaneous expression of Pax2 and Math1 in supporting cells isolated from the cochleae of neomycin-treated mice to generate hair cells. Their results confirmed the high efficiency of adenoviral vectors for delivering therapeutic genes into supporting cells and further demonstrated their potential for promoting hair cell regeneration (55). In these studies, only cellular differentiation was evaluated using techniques such as the analysis of marker gene expression, and no investigations were conducted to assess the electrophysiological responsiveness of the differentiated hair cells to external stimuli. In addition to the aforementioned studies, numerous investigations have examined the differentiation of MSCs, ESCs, and iPSCs into auditory hair cells under *in vitro* conditions. Owing to their long lifespan, high homing capacity, and ability to evade immune rejection, mesenchymal stem cells are considered promising candidates for regenerative therapies and cellular differentiation.

Non-viral delivery has also been tested directly against this viral evidence. Plasmid-mediated delivery of *Math1*/GFP into MSC-derived progenitors successfully induced Myosin VIIA expression, confirming feasibility, but transfection efficiency reached only ~2% illustrating the efficiency trade-off

of non-viral methods relative to adenoviral approaches (33). Because of their capacity to give rise to all three embryonic germ layers, ESCs and iPSCs likewise stand out as potent starting material for differentiation studies. Work carried out in 2006-2007 revealed that embryonic stem cells could be pushed towards becoming neural progenitors and, further along, auditory sensory neurons. A later study, published in 2010, went a step further by devising a multistep protocol that steered embryonic stem cells down the ectodermal path and ultimately towards auditory cell generation; this work examined how Wnt and TGF-β signaling shaped iPSC differentiation using iPSCs reprogrammed from mouse fibroblasts alongside embryonic stem cells sourced from Math1/nGFP transgenic mouse blastocysts across a range of different culture substrates (25). Then, in 2012, Ouji and colleagues took a different route, using a doxycycline (DOX)-controlled Tet-on inducible system to drive embryonic stem cells towards a hair-cell-like fate; although the approach worked, differentiation efficiency remained low (39). A parallel strategy exploits RNA interference miRNAs, siRNAs, and shRNAs which post-transcriptionally silence target genes by forming double-stranded complexes with their mRNA, either blocking translation or triggering degradation, offering a specific (if imperfect, given seed-region-driven off-target effects) tool for probing gene function without permanent genomic modification (56, 57). This approach has been used to direct MSC differentiation toward bone, cartilage, liver, and neural lineages (57-59). For example, Weimin Qiu (2014) demonstrated that transfection of human mesenchymal stem cells with a miR-141-3p mimic using the lipid-based transfection reagent Lipofectamine RNAiMAX significantly increased miR-141-3p expression. This upregulation directly targeted the *CDC25A* gene, resulting in G1 cell cycle arrest, reduced alkaline phosphatase activity, and inhibition of the osteogenic differentiation of these cells. Taken together, these results underscore just how central a role microRNAs play in governing both the proliferation and differentiation of stem cells, while also pointing to their promise as tools within cellular engineering and regenerative medicine (60). The same interference tools have directly tested the Notch–*Atoh1* axis introduced earlier. Genetic deletion of Notch pathway components increases hair cell number to a degree that depends on the specific gene disrupted: *Hes1*$^{+}$□$^{-}$;*Hes5*$^{-}$□$^{-}$ and *Hes1*$^{-}$□$^{-}$;*Hes5*$^{+}$□$^{-}$ mutant mice show a marked rise in both hair cell number and *Math1* expression (19, 61, 62). Furthermore, siRNA-mediated silencing of Math1 in ESCs reduced Brn3c expression and hair cell number, and reporter assays confirmed that Math1 directly activates Brn3c transcription (63). Turning to the Notch pathway itself, Jung and colleagues (2013) examined its contribution to hair cell regeneration by knocking down Hes5 with a targeted siRNA in mice whose utricles had been damaged using an aminoglycoside. What emerged was that suppressing Hes5 pushed Atoh1 expression upwards, and this in turn drove supporting cells to convert into newly formed hair cells. Taken together, this work made the case that using RNA interference (RNAi) to selectively knock down downstream elements of the Notch pathway offers a viable route towards encouraging hair cell regeneration within the inner ear (64).

Emerging Technologies for Auditory System Regeneration

One of the most significant recent advances in auditory tissue engineering and cell-based therapy has been the development of three-dimensional inner ear organoids derived from ESCs and iPSCs. These three-dimensional culture systems are capable of recapitulating many of the developmental and functional characteristics of the sensory epithelium of the inner ear and can generate auditory hair cells and auditory neurons with morphological and molecular properties closely resembling those of native tissue. In addition to providing an appropriate model for investigating inner ear development and hereditary hearing disorders, these organoids have emerged as promising platforms for evaluating gene therapy, cell-based therapy, and drug screening strategies in regenerative medicine. Nevertheless, enhancing the functional maturation of differentiated cells, establishing the spatial organization characteristic of the human cochlea, and improving synaptic connectivity with auditory neurons remain among the major challenges facing this technology (65, 66). A systematic review published in 2025 evaluated both preclinical and clinical studies investigating cell-based therapies for sensorineural hearing loss. The review demonstrated that mesenchymal stem cells, embryonic stem cells, and inner ear-derived stem cells were able to produce partial improvements in hearing thresholds in animal models through the secretion of neurotrophic factors, modulation of inflammatory responses, protection of spiral ganglion neurons, and stimulation of auditory hair cell regeneration. Despite these encouraging findings, the authors emphasized that heterogeneity in cell delivery methods, differences in cell sources, limited survival of transplanted cells, and the lack of large-scale clinical trials remain the principal barriers to the clinical translation of these therapeutic approaches (67). In recent years, CRISPR/Cas-based genome editing has emerged as one of the most promising biotechnological tools for the treatment of hereditary hearing loss and the enhancement of inner ear regenerative strategies. By introducing precise and targeted genomic modifications, this technology enables the correction of pathogenic mutations, inactivation

of dominant disease-causing alleles, and reactivation of molecular pathways involved in auditory hair cell differentiation. Preclinical studies have demonstrated that CRISPR/Cas9, base editing, and prime editing platforms can successfully correct mutations in genes such as *TMC1*, *MYO6*, *KCNQ4*, and *Stereocilin* in animal models, resulting in measurable improvements in auditory function. Furthermore, the integration of CRISPR technology with iPSCs has enabled the generation of genetically corrected auditory hair cells, which may serve as valuable resources for cell-based therapy, disease modeling, and drug discovery. Despite these remarkable advances, several important challenges remain, including the targeted delivery of genome-editing systems to inner ear cells, reduction of off-target effects, improvement of editing efficiency in postnatal cells, and the establishment of long-term safety. Nevertheless, the convergence of CRISPR-based genome editing with tissue engineering, biological nanocarriers, and advanced gene delivery systems has created a promising outlook for the development of personalized regenerative therapies for patients with sensorineural hearing loss (68-71). Recent advances in base editing technology have opened new avenues for the treatment of hereditary hearing loss. In a study published in Nature Biomedical Engineering in 2024, an adenine base editor (ABE) was employed to correct a pathogenic mutation in the *OTOF* gene in a mouse model of congenital deafness. The genome-editing system was delivered to the inner ear via adeno-associated virus (AAV) vectors through the round window membrane, enabling precise correction of the genetic mutation without inducing DNA double-strand breaks. As a result, Otoferlin protein expression was restored in approximately 88% of inner hair cells, synaptic transmission was significantly improved, and hearing function was maintained at near-normal levels for more than 18 months, with no significant off-target effects observed. These findings suggest that next-generation base-editing technologies may provide a safer and more efficient alternative to conventional CRISPR/Cas9 genome editing for the treatment of hereditary inner ear disorders (72). One of the most promising emerging technologies in inner ear tissue engineering is the application of three-dimensional (3D) bioprinting and bioactive scaffolds to create a microenvironment that closely mimics the extracellular matrix (ECM) and thereby directs stem cell behavior. This strategy relies on bioinks made from hydrogels and biomaterials either natural or synthetic, including gelatin methacryloyl (GelMA), alginate, collagen, fibrin, hyaluronic acid, and polyethylene glycol (PEG) to keep cells viable while encouraging stem cells to proliferate, migrate, and take on the identity of auditory hair cells and spiral ganglion neurons. Beyond this, such scaffolds can be designed to load and gradually release growth factors among them brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), fibroblast growth factor-2 (FGF2), and insulin-like growth factor-1 (IGF-1) together with regulatory molecules from pathways like Atoh1 and Notch, all of which work to boost tissue regeneration right at the injury site. Evidence from recent work shows that pairing bioactive scaffolds with either MSCs or iPSCs does more than just help transplanted cells survive; it also improves how they organize spatially and encourages them to form structures resembling sensory epithelium. That said, some obstacles persist: accurately rebuilding the complex architecture of the organ of Corti, replicating the precise arrangement of inner and outer hair cells, and forming working synaptic links with auditory neurons remain among the toughest barriers to bringing this technology into clinical use. Still, despite these hurdles, recent progress in smart bioinks, multimaterial bioprinting, and stimuli-responsive bioactive scaffolds has opened up encouraging prospects for regenerative treatment of sensorineural hearing loss (72, 73). In addition, recent evidence has showed that long non-coding RNAs (lncRNAs) role as key regulators of gene expression networks by interacting with microRNAs (miRNAs) and messenger RNAs (mRNAs) to modulate diverse cellular signaling pathways (74, 75). Accordingly, targeting these regulatory molecules has appeared as a encouraging approach in genetic engineering and regenerative medicine, particularly for directing stem cell differentiation and promoting the regeneration of damaged tissues.

Personalized Medicine in Auditory Regeneration

Beyond these molecular and biomaterial-based strategies, the increasing accessibility of genetic diagnosis has positioned personalized medicine as an increasingly central paradigm in the field of auditory regeneration. Hearing loss is genetically and phenotypically highly heterogeneous, with pathogenic variants identified in well over 100 genes underlying non-syndromic forms alone; this diversity means that no single therapeutic strategy is likely to benefit all patients equally. Advances in next-generation sequencing (NGS) have transformed diagnostic capability, enabling comprehensive gene-panel testing that identifies a likely causative variant in a substantial proportion of patients, informs accurate genetic counseling, and directly shapes clinical management and prognosis on a patient-by-patient basis (76). Beyond diagnosis alone, NGS-based approaches have been shown to meaningfully improve precision medicine workflows in hearing loss by refining variant classification and guiding family-specific counseling and surveillance strategies (77). This genotype-first framework has begun to translate directly into genotype-specific

therapy. A clear example is *DB-OTO*, a dual adeno-associated virus gene therapy designed specifically for patients with biallelic pathogenic variants in *OTOF* (encoding otoferlin); in a first-in-human trial, a single intracochlear infusion restored clinically meaningful hearing in the majority of treated children, with several achieving normal hearing thresholds (78). Because this therapy is only applicable to patients with a confirmed *OTOF* genotype, it exemplifies how precise molecular diagnosis and targeted gene replacement together constitute personalized medicine in its most concrete clinical form within the auditory field. These developments converge naturally with the cell- and gene-based strategies discussed throughout this review. Patient-derived induced pluripotent stem cells, in particular, offer a personalized platform: since they carry a patient's own genetic background, they can in principle be used to model an individual's specific form of hearing loss in vitro and to evaluate candidate gene- or cell-based therapies before clinical application, allowing treatment selection to be tailored to genotype rather than applied uniformly. As genetic diagnosis becomes faster and more accessible, integrating this personalized framework with the regenerative approaches reviewed here represents a logical and increasingly attainable next step toward individualized treatment of hearing loss and deafness.

FUTURE PERSPECTIVES

Rapid advances in biotechnology and regenerative medicine have created a encouraging outlook for the development of effective therapies for hearing disorders. In the coming years, the convergence of cell therapy, tissue engineering, genome editing, and nanotechnology is expected to overcome many of the current limitations associated with inner ear regeneration. The development of next-generation bioactive scaffolds and smart hydrogels capable of mimicking the native microenvironment of the organ of Corti, together with controlled-release systems for growth factors, may enhance the survival of transplanted cells, promote their lineage-specific differentiation, and improve their functional integration with host tissue. Furthermore, the use of nanocarriers, exosomes, and hybrid delivery vectors for the transport of genes, regulatory RNAs, and genome-editing systems has opened new avenues for the precise treatment of genetic disorders of the inner ear. At the same time, advances in CRISPR/Cas, Base Editing, and Prime Editing technologies are expected to enable the precise correction of disease-causing mutations with minimal off-target effects. Integrating these technologies with iPSCs and three-dimensional inner ear organoids will make it possible to generate patient-specific hair cells and auditory neurons, thereby paving the way toward personalized therapeutic strategies. In addition, the continued development of three-dimensional culture systems, inner ear organoids, and 3D bioprinting technologies will provide more accurate models for investigating inner ear development, drug screening, and evaluating the safety and efficacy of novel therapeutic approaches. Another emerging trend is the development of targeted delivery systems for the inner ear. The application of guided delivery through the round window membrane, biodegradable microneedles, magnetic nanoparticles, and image-guided delivery systems may enable more precise administration of therapeutic cells and molecules while minimizing damage to the delicate cochlear structures. These advances, together with improvements in the design of biological delivery vectors, are expected to increase the feasibility of minimally invasive, single-stage therapeutic interventions for many patients.

Even with these notable gains, moving these technologies out of the lab and into everyday clinical practice is still contingent on clearing a set of significant hurdles among them, standardizing how therapeutic cells are manufactured, guaranteeing safety over the long run, keeping immune reactions in check, sharpening delivery precision, cutting down off-target effects during genome editing, and tracking functional outcomes well beyond the initial treatment period. That said, mounting preclinical evidence, together with the launch of the earliest clinical trials testing gene therapy and genome editing for auditory disorders, points to a new chapter opening up for inner ear regenerative medicine. Looking ahead to the next ten years, bringing together biotechnology, tissue engineering, biomaterials science, nanotechnology, and precision medicine is likely to pave the way for personalized treatments capable not just of restoring hearing, but of addressing the molecular roots of disease itself and achieving lasting repair of the inner ear's structure and function alike.

Overall, the convergence of emerging biotechnological approaches including cell therapy, tissue engineering, nanotechnology, genome editing, and precision medicine has the potential to transform the treatment paradigm for hearing disorders from supportive interventions to regenerative and disease-modifying therapies, thereby opening a new horizon for the long-term treatment of hearing loss and deafness in the near future.

Conflict of Interest

The authors declared no conflict of interest.

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Author Contributions

Marzieh Alaei: Investigation, methodology, data collection, and writing original draft. Sogol Javaherian-Nia: Investigation, data analysis, and review and editing. Roya Chabi: Conceptualization, supervision, project administration, and writing review and editing. All authors read and approved the final manuscript.

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Availability of Data and Materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

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