

How Effective are Exosomes in Overcoming Blood-Labyrinth Barrier in Sensorineural Hearing Loss? A Comprehensive Review of the Literature

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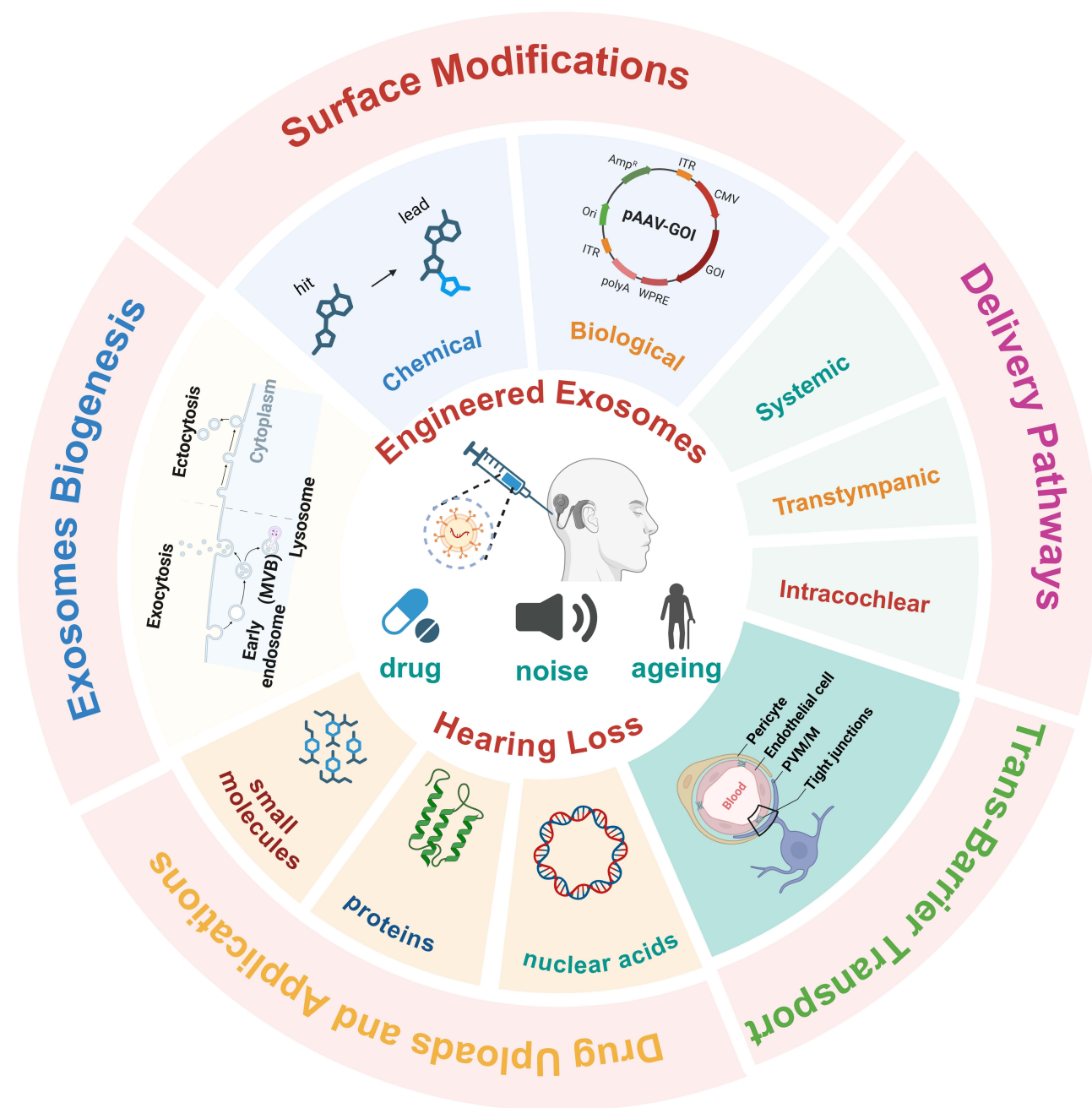
Abstract: Sensorineural hearing loss (SNHL) is a prevalent global health issue, and its pharmacological treatment is severely hindered by the blood-labyrinth barrier (BLB). Exosomes, natural extracellular vesicles (30–150 nm), have emerged as a highly promising nanoplatform to overcome this delivery challenge. Their innate biocompatibility, low immunogenicity, and ability to cross biological barriers make them ideal for targeted drug delivery. This review examines the inner ear barrier systems and elucidates the mechanisms, such as receptor-mediated transcytosis, by which exosomes can traverse the BLB. It further discusses engineering strategies to optimize drug loading, enhance targeting, and improve therapeutic efficacy for SNHL. The application of engineered exosomes in delivering diverse cargoes—including nucleic acids, proteins, and small-molecule drugs—is comprehensively reviewed, highlighting their potential in preclinical models to preserve auditory function. Despite this promise, significant challenges remain in standardization, scalable production, loading efficiency, long-term safety, and clinical translation. Future research should focus on refining engineering techniques, elucidating in vivo pharmacokinetics, and advancing preclinical studies to facilitate the clinical adoption of exosome-based therapies, ultimately offering a novel and precise paradigm for SNHL treatment.

Keywords: sensorineural hearing loss, engineered exosomes, drug delivery, blood-labyrinth barrier, clinical translation

Introduction

Sensorineural hearing loss (SNHL) is a form of hearing impairment caused by damage to the inner ear structures—including hair cells, spiral ganglion neurons, and elements of the central auditory pathway. It represents a growing public health challenge on a global scale. Recent epidemiological data estimate that over 1.5 billion people worldwide are affected by some degree of hearing loss, with SNHL constituting the predominant type. Projections indicate that this number may exceed 2.5 billion by 2050.^{1,2} Key contributing factors encompass both exogenous insults, such as ototoxic medication and noise exposure, and endogenous causes, including age-related hearing loss (presbycusis) and genetic mutations.^{3,4} Beyond impairing communication ability, SNHL is associated with broader psychosocial and cognitive sequelae, such as social isolation, accelerated cognitive decline, and significantly reduced quality of life. Current standard interventions, including hearing aids and cochlear implants, provide palliative support and improve auditory function to varying degrees; however, they do not restore native sensory structures and are of limited utility in cases of profound or genetic hearing impairment.⁵ Consequently, the development of pharmacotherapeutic strategies aimed at preserving or regenerating inner ear cell populations has become an urgent research priority.

Graphical Abstract



A major obstacle in the pharmacological treatment of SNHL is the challenge of effective drug delivery. The inner ear is characterized by a highly regulated microenvironment, maintained by the blood-labyrinth barrier (BLB). Similar in structure and function to the blood-brain barrier (BBB), the BLB comprises tightly joined endothelial cells, pericytes, and perivascular melanocyte-like macrophages. This system restricts the passage of over 98% of systemically administered drugs into the cochlea.^{6–8} While intratympanic injection offers a partial means of bypassing the BLB, its clinical utility is constrained by the need for repeated invasive procedures, increased infection risk, and limited tissue penetration. Thus,

developing innovative strategies to achieve targeted and efficient drug delivery across the BLB remains a pivotal challenge in auditory medicine.

In recent years, exosomes—endogenous extracellular vesicles with diameters between 30 and 150 nm—have gained attention as a promising nanoplatform for overcoming the BLB as bio-inspired nano-vehicles for drug delivery applications.^{9–11} Compared with synthetic nanoparticle carriers, exosomes demonstrate superior biocompatibility profiles, minimized immunogenicity, and enhanced biological barrier penetrability.¹² Notably, their intrinsic capacity to traverse the BBB renders them particularly advantageous for treating neurological pathologies, including glioblastoma.¹³ Despite their promise, key translational barriers remain, including the lack of standardized manufacturing protocols, potential immunogenicity of allogeneic exosomes, and challenges in achieving cell-specific targeting within the intricate cochlear microenvironment.¹¹ These hurdles will be critically examined in subsequent sections to provide a balanced perspective on the path toward clinical application.

As a comprehensive narrative review, this article systematically consolidates recent advances in exosome-based delivery for SNHL, with a distinct focus on BLB traversal—a bottleneck often underexplored in prior reviews. We further integrate the latest engineering approaches, cargo-loading technologies, and preclinical evidence, while critically addressing translational hurdles such as manufacturing standardization, targeting specificity, and long-term safety. To ensure comprehensive coverage, we conducted a literature search across PubMed, Web of Science, and Google Scholar (2015–2024) using keywords including “exosomes,” “blood-labyrinth barrier,” “sensorineural hearing loss,” and “drug delivery,” prioritizing experimental studies and translational assessments.

What Do We Understand About BLB-Mediated Impediment to Drug Delivery?

Drug delivery to the inner ear is hindered by multiple physiological barriers. Although these barriers are essential for maintaining the homeostasis of the inner ear microenvironment, they substantially impede drug absorption and distribution.¹⁴ The primary barriers include: Blood-Perilymph Barrier: primarily comprises the spiral ligament vessels, stria vascularis, and the round window membrane. These anatomical structures function to restrict the passive diffusion of substances from the systemic circulation into the perilymph, primarily through the presence of intercellular tight junctions. A complex network of tight junction proteins, including claudins, occludins, and ZO-1, is present between the endothelial cells of the spiral ligament vessels, contributing to the formation of a selectively permeable barrier that regulates both molecular size and charge-based transport.¹⁵ Blood-Endolymph Barrier: The blood-endolymph barrier is predominantly situated within the stria vascularis and is formed by tight junctions located between marginal cells.^{16,17} The stria vascularis serves as a critical site for the generation of the endolymphatic potential, with its marginal cells expressing a diverse array of ion channels and transporters, including Na⁺/K⁺-ATPase and KCNQ1/KCNE1 potassium channels.¹⁸ These molecular components collectively contribute to the maintenance of the high potassium ion concentration characteristic of endolymph.

The physiological functions of the BLB can be categorized into three major aspects: the maintenance of ion homeostasis through selective permeability and active transport mechanisms, the elimination of toxins and pathogens via physical barriers and efflux pump systems, and the establishment of immune privilege through the secretion of immunosuppressive factors and the maintenance of minimal lymphocyte infiltration.^{19,20} Although these functions are essential for protecting the delicate sensory cells of the inner ear, they simultaneously pose significant challenges to the effective delivery of therapeutic agents.^{19,21} Pathological states induce dynamic modifications in barrier properties. Inflammatory conditions or acoustic trauma can disrupt BLB integrity through cytokine-mediated mechanisms (eg, IL-6-induced disassembly of tight junction complexes), although this pathological window of increased permeability remains transient and clinically unmanageable.^{22–24} Conversely, presbycusis is frequently associated with stria vascularis degeneration, leading to diminished endolymphatic potential and exacerbating the intrinsic challenges of cochlear drug delivery.²⁵ The primary mechanisms by which the BLB impedes drug delivery can be categorized into two major types: physical barriers, characterized by tight junctions that restrict paracellular transport²⁶ and transporter barriers,¹⁹ involving efflux pumps such as P-glycoprotein that actively expel xenobiotics (Figure 1). Additionally, pharmacokinetic limitations such as low lipid solubility, high molecular weight (>500 Da), and molecular charge further hinder trans-BLB drug permeability.⁸ Accumulating evidence indicates that less than 5% of systemically administered therapeutic agents

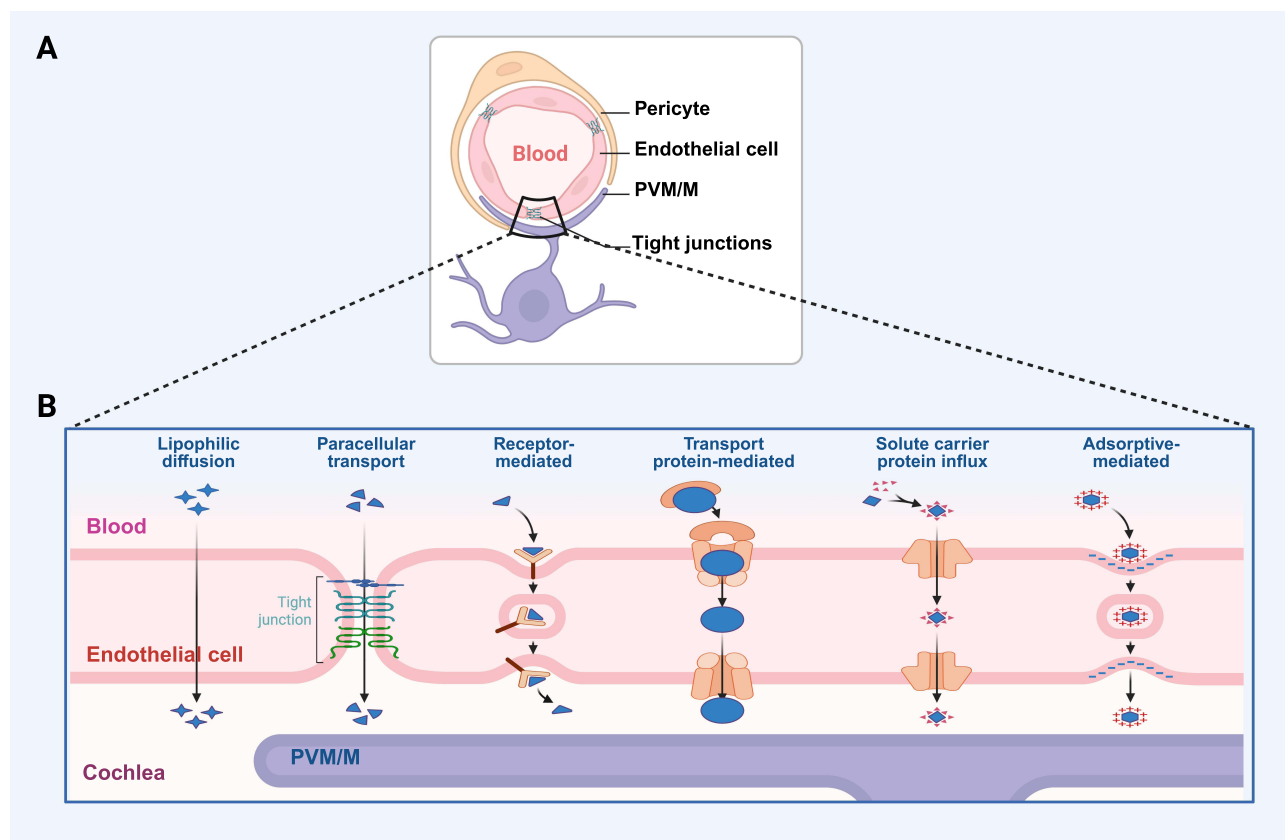


Figure 1 Mechanisms of substance transport across the BLB. **(A)** Schematic location of the BLB separating systemic circulation from the cochlear fluids. **(B)** Illustration of the primary transcellular and paracellular transport pathways for molecules crossing the BLB. These include: Lipophilic diffusion, Paracellular transport via tight junctions, Receptor-mediated transcytosis, Transport protein-mediated efflux, Solute carrier (SLC) protein-mediated influx, and adsorptive-mediated transcytosis. The barrier is formed by endothelial cells connected by tight junctions and is reinforced by pericytes and PVM/M. (Created with BioRender.com) Abbreviations: PVM/M, perivascular macrophage-like melanocytes.

successfully reach their target sites within the inner ear, thereby significantly compromising the efficacy of pharmacological interventions for SNHL.^{8,27}

Strategies for Overcoming Trans-Barrier Transport Limitations of the BLB

The inner ear maintains its homeostatic microenvironment and functional integrity through multiple specialized barrier systems. These anatomical structures mediate selective substance exchange between the cochlea and external milieu.⁸ Theoretically, these physiological pathways may be exploited for therapeutic agent delivery.²⁸ However, the absorption kinetics and metabolic fate of pharmacological compounds are substantially influenced by the selective permeability characteristics of these barriers, which exhibit differential permeability based on molecular properties, including mass, charge distribution, and hydrophobicity.¹⁹ Current clinical approaches for inner ear drug delivery encompass three principal routes: systemic pharmacological delivery, transtympanic therapeutic delivery, and direct intracochlear administration (Figure 2).

Systemic Pharmacological Delivery

Systemic administration constitutes a pharmacologically conventional delivery approach, encompassing oral ingestion, intravenous injection/infusion, and intramuscular injection. This modality is fundamentally constrained by the selective permeability of the BLB, which shares considerable structural and functional homology with the BBB.¹⁹ Consequently, only low molecular weight cationic compounds demonstrate sufficient BLB penetrance. Notwithstanding these limitations, systemic delivery remains clinically prevalent for managing SNHL and autoimmune labyrinthine pathologies, particularly corticosteroid regimens for sudden SNHL^{29,30} and autoimmune inner ear disease.³¹ However, this approach

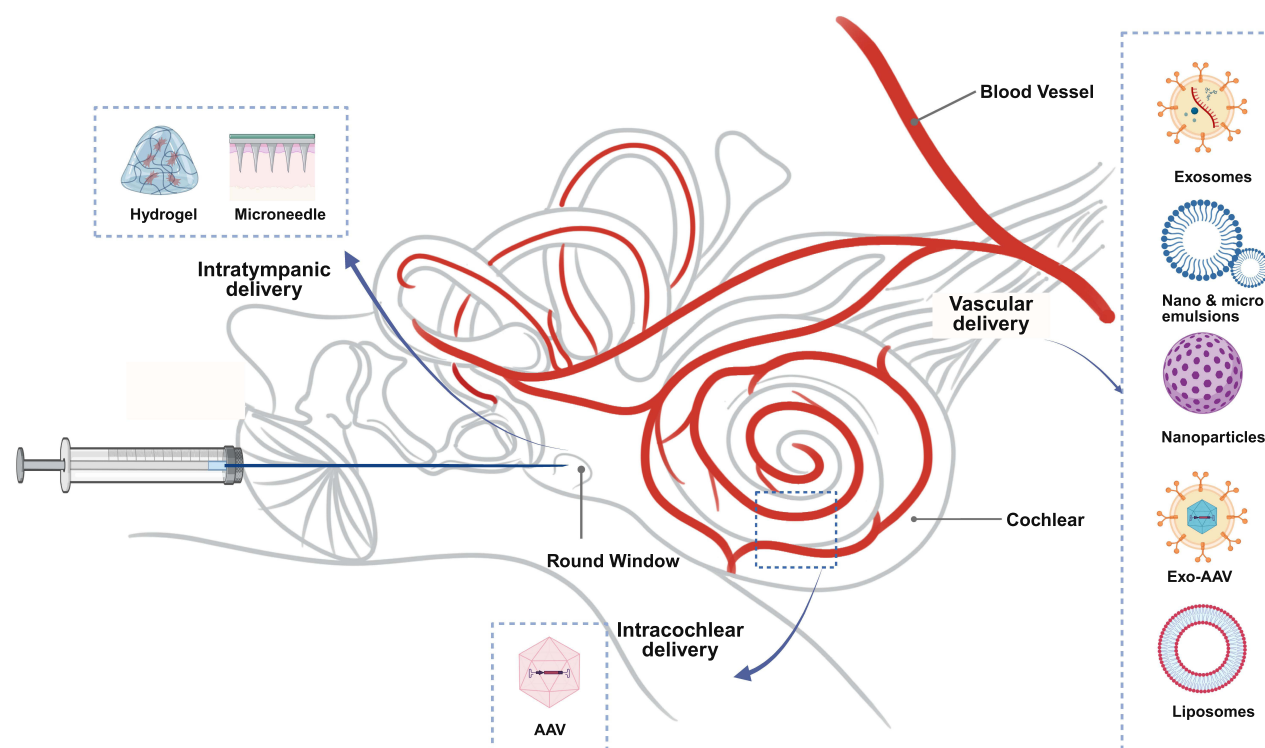


Figure 2 Principal routes for inner ear drug delivery. Trans-oval window invasive delivery: This pathway involves intratympanic administration via the external auditory canal, crossing the tympanic membrane with the aid of hydrogels or microneedles to access the vestibular system through the oval window. Intracochlear invasive delivery: Direct invasive access into the cochlea is achieved through structures such as the scala vestibuli, scala tympani, or scala media. This method often employs viral vectors (eg, AAV) or lipid-based nanoparticles for localized therapeutic delivery. Non-invasive vascular delivery: Systemic administration via the vasculature, such as through the anterior vestibular artery or common cochlear artery, allows for non-invasive targeting of the cochlea and vestibular system. This route utilizes advanced carriers including exosomes, nano/micro emulsions, nanoparticles, and liposomes (Adapted from Nyberg S, et al. *Sci Transl Med*. 2019. Created with BioRender.com).

presents substantial pharmacological challenges, including poor target specificity, suboptimal and heterogeneous local drug concentrations, and considerable systemic adverse effect profiles.

Transtympanic Therapeutic Delivery

Transtympanic administration involves the direct instillation of pharmacologic agents into the tympanic cavity, primarily facilitating inner ear drug absorption through the round window membrane (RWM). The oval window substantially contributes to drug permeation during transtympanic procedures. In a seminal study by King et al,³² selective oval window gentamicin administration in patients with Ménière's disease demonstrated superior vestibulotoxicity sparing effects, substantially preserving vestibular end-organ integrity and cochlear hair cell populations while maintaining low auditory brainstem response (ABR) thresholds. However, post-RWM penetration, peri lymphatic drug distribution exhibits a pronounced basal-to-apical concentration gradient. Furthermore, the negligible longitudinal flow dynamics of the perilymph restrict drug dispersion to passive diffusion mechanisms, substantially compromising distribution efficiency.

Direct Intracochlear Administration

Intralabyrinthine injection techniques (including intracochlear and intra-labyrinthine approaches) enable precise therapeutic targeting through controlled dosage delivery. However, these methods require invasive surgical intervention and risk disrupting the critical endolymph-perilymph ionic segregation, potentially compromising mechanoelectrical transduction mechanisms.^{33,34} Consequently, intracochlear administration protocols must meticulously preserve cochlear microenvironmental homeostasis to ensure both therapeutic efficacy and procedural safety.

Table 1 Delivery Pathways and Systems for Inner Ear Drug Delivery

Type of Delivery Systems	Syndrome	Therapeutic Agents	Delivery Routes	Outcomes
AAV	Genetic etiologies	OTOF cDNA	RWM-mediated delivery	20–30 dB improvement in low-frequency thresholds ⁴⁰
siRNA	Drug induced hearing loss	NOX3 siRNA	Intracochlear delivery	Intracochlear delivery of NOX3-sirnas induces a robust temporal NOX3 downregulation ⁴¹
Exo-AAV	Genetic etiologies	scAAV-CBA-HA-Lhfp15	RWM injection	Exo-AAV1 efficiently transduces ihcs and transduces ohcs ⁴²
Thermoresponsive hydrogel	Noise-induced hearing loss	BDNF	Intra-tympanic	Complete hearing restoration achieved by the 14th day ⁴³
Electrospun patches	Tympanic membrane perforations	Ciprofloxacin	Tympanic membrane patch	A sustained release of CIP and antibacterial responses for 7 days ⁴⁴
Solid lipid nanoparticles	Noise-induced hearing loss	Edaravone	Intratympanic or intravenous	Sustained release of edaravone over a 6-day period ⁴⁵
Amphiphilic drug–drug conjugate	CDDP-induced hearing loss	Dexamethasone and salivianolic acid B	Intratympanic injection	The conjugates almost completely restored hearing at all tested frequencies ⁴⁶

Abbreviations: BDNF, brain-derived neurotrophic factor; RWM, round window membrane; CDDP, cis-dichlorodiammineplatinum; CIP, ciprofloxacin; AAV, adeno-associated virus; OHC, outer hair cell; IHC, inner hair cell.

While nanocarrier systems show considerable promise for improved cochlear drug distribution, several challenges remain, including potential inner ear toxicity of biomaterials and incomplete pharmacokinetic characterization (Table 1).^{35–37} Extracellular vesicle (EV)-based delivery platforms are emerging as particularly attractive alternatives, combining low immunogenicity with high cargo-loading capacity and innate biological barrier penetration capabilities.^{38,39} These attributes position EV-mediated delivery as a potentially transformative strategy for overcoming the formidable challenge of targeted auditory system drug delivery.

How Advanced are Exosomes as Drug Delivery Vesicles?

Exosomes represent a distinct subtype of extracellular vesicles, typically ranging in size from 30 to 150 nanometers in diameter. These vesicles are secreted into the extracellular environment following the fusion of intracellular multivesicular bodies (MVBs) with the plasma membrane. In recent years, exosomes have garnered substantial scientific interest owing to their unique biological properties and their capacity to serve as effective vehicles for intercellular communication and molecular delivery.

Exosome Biogenesis

The biogenesis of exosomes constitutes a tightly regulated cellular process, predominantly mediated through two major mechanisms: the endosomal sorting complex required for transport (ESCRT)-dependent and ESCRT-independent pathways.^{12,47} Within the ESCRT-dependent pathway, the sequential action of ESCRT-0, -I, -II, and -III complexes facilitate the recognition and sequestration of cytoplasmic cargo, ultimately leading to the formation of intraluminal vesicles (ILVs) within multivesicular bodies (MVBs). In contrast, the ESCRT-independent pathway is primarily governed by tetraspanin proteins (eg, CD63 and CD81) and specialized lipid microdomains, such as ceramide-enriched regions generated by sphingomyelinase activity. Upon maturation of MVBs, these structures may undergo one of two fates: fusion with lysosomes for cargo degradation or fusion with the plasma membrane, thereby releasing ILVs—commonly referred to as exosomes—into the extracellular environment. The secretion of exosomes is subject to complex regulatory mechanisms involving multiple cellular factors, including the physiological stress status of the cell, intracellular calcium concentrations, and the activity of Rab GTPase family members, particularly Rab27a and Rab27b.⁴⁸ Accumulating evidence indicates that cellular exposure to stress conditions, such as oxidative stress and inflammatory stimuli, leads to an increased rate of exosome release.^{49–51} This phenomenon is hypothesized to function as a stress-responsive

intercellular signaling mechanism, facilitating communication between stressed and neighboring cells. As pivotal mediators of intercellular communication, exosomes orchestrate both paracrine and endocrine signaling cascades across physiological and pathological contexts.⁵² Their molecular cargo, encompassing proteins, nucleic acids (RNA/DNA), and lipid species, enables sophisticated intercellular crosstalk capable of modulating recipient cell phenotypes.⁵³

Biological Functions and Intercellular Communication

Exosomes, as critical mediators of intercellular communication, perform their biological functions through the following mechanisms:

Immune Modulation

Exosomes derived from antigen-presenting cells carry MHC-peptide complexes that can activate T cells and regulate immune responses.⁵⁴ Exosomes originating from dendritic cells may either enhance or suppress immune reactions, depending on the physiological status of the parent cells.⁵⁵

Regulation of Cellular Metabolism

Adipocyte-derived exosomes contain miRNAs, such as miR-34a, which can influence the insulin sensitivity of hepatocytes and contribute to systemic metabolic homeostasis.⁵⁶

Promotion of Tumor Progression and Metastasis

Tumor cell-derived exosomes facilitate tumor growth and dissemination by transferring oncogenic miRNAs and proteins to establish a “pre-metastatic niche”.^{57,58}

Maintenance and Regeneration of the Nervous System

Neural cell-derived exosomes participate in key processes including synaptic plasticity, neuronal survival, and myelination.^{59,60} Research indicates that astrocyte-derived exosomes can enhance neuronal viability and functional integrity through the delivery of protective miRNAs and neurotrophic factors.^{61,62}

These intrinsic biological functions position exosomes as promising endogenous vehicles for drug delivery, particularly in applications requiring precise modulation of cellular activities, such as the protection and regeneration of inner ear sensory cells (Table 2).⁶³

Innate Capacity of Exosomes to Traverse the Blood-Labyrinth Barrier

Exosomes possess the intrinsic capability to traverse the BLB, positioning them as a promising endogenous delivery platform for the treatment of SNHL. This translocation mechanism is complex and highly coordinated, primarily involving the following molecular pathways:

Receptor-Ligand-Mediated Transcytosis

Exosomes express specific surface proteins, including tetraspanins, integrins, and members of the immunoglobulin superfamily,⁶⁴ which can interact with corresponding receptors on BLB endothelial cells, such as ICAM-1 and PECAM-1.⁶⁵ This interaction initiates receptor-mediated transcytosis, a multistep process comprising: binding (specific recognition between exosomal ligands and cell surface receptors), internalization (formation of clathrin-coated vesicles), intracellular transport (vesicle trafficking across the cytoplasm), and exocytosis (release at the basolateral membrane).^{10,66} Research indicates that the integrin profile on exosomal surfaces determines their organ-specific tropism.⁶⁷ For instance, integrins $\alpha 6 \beta 4$ and $\alpha 6 \beta 1$ are associated with lung targeting, whereas $\alpha v \beta 5$ correlates with hepatic tropism.⁶⁸ Genetic or biochemical engineering of integrin expression on exosomes may enhance their targeting specificity to inner ear tissues.

Membrane Fusion and Cargo Delivery

Exosomes possess a lipid bilayer that is enriched in cholesterol, sphingomyelin, and ceramide. These components facilitate direct fusion with the target cell membrane, thereby releasing intraluminal cargo into the cytoplasm. The

Table 2 Comparative Analysis of Nanocarrier Properties: Exosomes, Liposomes, and Polymer Nanoparticles

Characteristics	Exosomes	Liposomes	Polymer Nanoparticles
Biocompatibility	High and inherently favorable. As endogenous nanovesicles naturally secreted by cells, exosomes possess a lipid bilayer structurally similar to the plasma membrane, enabling efficient cellular uptake and exhibiting minimal cytotoxicity.	High and tunable. Composed primarily of phospholipids and cholesterol—key constituents of biological membranes—liposomes demonstrate excellent biocompatibility. However, certain synthetic lipid components may introduce potential toxicological concerns.	Variable and material-dependent. Naturally derived polymers (eg, PLGA, chitosan) exhibit good biocompatibility and are biodegradable; in contrast, some synthetic polymers may produce toxic metabolites or pose risks of long-term accumulation.
Targeting Ability	Intrinsic targeting capability. Surface-associated proteins confer natural tropism toward specific cell types or tissues. Engineerable for enhanced specificity. Targeting ligands can be introduced via genetic modification or post-isolation surface functionalization.	No intrinsic targeting. Primarily rely on passive targeting mechanisms. Highly engineerable. Active targeting is readily achieved through conjugation of antibodies, peptides, or aptamers to the liposomal surface, supported by well-established protocols.	No intrinsic targeting. Depend mainly on passive targeting. Engineerable. Active targeting can be implemented by covalent attachment of targeting moieties to the polymer matrix, although the chemical complexity may increase process challenges.
Immunogenicity	Low under autologous conditions, but context-dependent. As self-derived particles, exosomes typically elicit minimal immune responses. However, allogeneic or xenogeneic exosomes may provoke immunogenic reactions.	Generally low, but formulation-dependent. Conventional formulations exhibit limited immunogenicity. Cationic liposomes can activate immune responses. PEGylation reduces recognition by the mononuclear phagocyte system.	Variable, depending on polymer composition. Certain synthetic polymers may induce complement activation or inflammatory responses. PEGylation is commonly employed to mitigate immunogenicity, though it carries a risk of ABC effect with repeated dosing.
Production Scalability	Isolation and purification: Techniques such as ultracentrifugation and size-exclusion chromatography are labor-intensive, low-yield, costly, and often result in variable purity and heterogeneity. Large-scale manufacturing: Limited by stringent cell culture requirements, low exosome yield, and significant inter-batch variability, posing major hurdles for clinical translation.	Well-established and highly scalable. Manufacturing process: Utilizes mature methods (eg, thin-film hydration, extrusion) that support robust, reproducible, and GMP-compliant industrial production. Reproducibility: High batch-to-batch consistency enables reliable quality control. Several liposomal formulations have received regulatory approval and are commercially available.	Good scalability with established methodologies. Manufacturing process: Multiple scalable synthesis techniques (eg, nanoprecipitation, emulsion-solvent evaporation) are available for large-scale production. Reproducibility: Consistent batch-to-batch quality has been demonstrated, with several polymer-based nanotherapeutics approved for clinical use.

Abbreviation: GMP, Good Manufacturing Practice.

process of membrane fusion is mediated by SNARE proteins, including vesicle-associated membrane protein and syntaxin, as well as annexin family proteins.^{69,70} The efficiency of this process is modulated by factors such as lipid composition and membrane fluidity.⁷¹ This direct delivery mechanism is especially well-suited for the transport of hydrophobic drugs and nucleic acid-based therapeutics, enabling them to bypass lysosomal degradation and thereby enhancing their bioavailability.⁷² Research has demonstrated that exosome-delivered mRNA can be efficiently translated into functional proteins within target cells, while siRNA can effectively induce gene silencing.^{73,74} These findings offer promising new strategies for developing gene therapies targeting SNHL.

Immune Privilege Characteristics

As endogenous nanocarriers, exosomes exhibit low immunogenicity and excellent biocompatibility. They display key surface proteins including CD47,⁷⁵ known as the “do not eat me” signal, as well as CD55 and CD59—complement inhibitory factors that collectively prevent rapid clearance by the mononuclear phagocyte system (MPS) and thereby extend their circulation time in vivo.^{76–78} Moreover, exosomes are capable of actively modulating immune responses

through the expression of immunoregulatory molecules such as Fas ligand (FasL),⁷⁹ transforming growth factor-beta (TGF- β),⁸⁰ and interleukin-10 (IL-10).⁸¹ This immunomodulatory function is of particular relevance in the inner ear, a recognized immune-privileged organ. Research has demonstrated that exosomes derived from neural progenitor cells can effectively mitigate inflammatory responses within the inner ear and protect hair cells from immune-mediated damage.^{82,83}

Experimental Evidence and in vivo Studies

A growing body of research has demonstrated that exosomes are capable of crossing the BLB.⁸⁴ Under pathological conditions, such as noise-induced trauma or inflammatory states, the permeability of the inner ear to exogenous substances is markedly increased.¹⁷ This phenomenon may be attributed to increased BLB permeability and the promotion of exosome-endothelial cell interactions mediated by inflammatory cytokines, including tumor necrosis factor-alpha (TNF- α) and interleukin-1 beta (IL-1 β).^{85,86} These properties confer upon exosomes an “adaptive targeting” capability, enabling preferential delivery under disease conditions. Notably, exosomes derived from different cellular origins exhibit distinct BLB penetration efficiencies. For instance, mesenchymal stem cell-derived exosomes demonstrate enhanced tropism for the inner ear.¹⁰ These findings provide a solid experimental foundation for the rational selection of exosome sources in targeted therapeutic applications.

Engineering Exosomes for Optimized Drug Delivery

Drug Loading

Exosome drug loading primarily employs two distinct strategies: pre-loading and post-loading. Pre-loading approach involves pretreating donor cells prior to exosome isolation. It can be accomplished through genetic engineering techniques to induce overexpression of specific therapeutic molecules—such as neurotrophic factors and protective microRNAs in the donor cells.^{87,88} Alternatively, donor cells can be pretreated with small molecule drugs to promote the natural encapsulation of target cargo into the secreted exosomes.⁸⁹ While this method is relatively straightforward in terms of operational procedures, it is generally associated with low loading efficiency and limited specificity. Post-loading: Following exosome purification, therapeutic agents are incorporated into the exosomal lumen through in vitro incubation with drug molecules, facilitated by physical or chemical approaches. Various physical techniques facilitate cargo loading, eg sonication-assisted membrane permeabilization, electroporation-mediated nucleic acid encapsulation, freeze-thaw cycle incorporation, extrusion-based payload integration, and dialysis-assisted low-potential loading.^{90,91} These engineering strategies collectively enhance exosome functionality while preserving their native biological advantages, positioning engineered exosomes as transformative tools for precision medicine applications.

Targeting Modification Strategies

Exosomes represent a class of endogenous nanovesicles with exceptional drug delivery capabilities, demonstrating superior performance in encapsulating pharmaceuticals, nucleic acids, and other bioactive molecules while overcoming the limitations of conventional delivery systems (Figure 3).^{12,92–95} Notably, exosomes engineered to express targeting ligands, such as LAMP2B, exhibit enhanced BBB penetrance for central nervous system (CNS) drug delivery. Experimental data indicate that exosome-mediated intracerebral mRNA delivery achieves a significant improvement compared with conventional liposomal systems.⁷⁴ Furthermore, surface-expressed CD47 confers immune evasion properties through “don’t-eat-me” signaling, extending plasma circulation half-life to 12–24 hours compared with 2–4 hours for synthetic liposomes.⁹⁶ As naturally derived nanoscale vesicles, exosomes possess inherent advantages, including minimal immunogenicity, exceptional biocompatibility, and intrinsic biological barrier penetration capacity.^{94,97,98} However, native exosomes exhibit significant constraints in targeting precision, payload capacity, and functional modulation, limiting their therapeutic utility for complex pathologies.¹² Current research efforts therefore focus on engineered modifications to address these limitations and unlock their clinical potential.⁹⁹

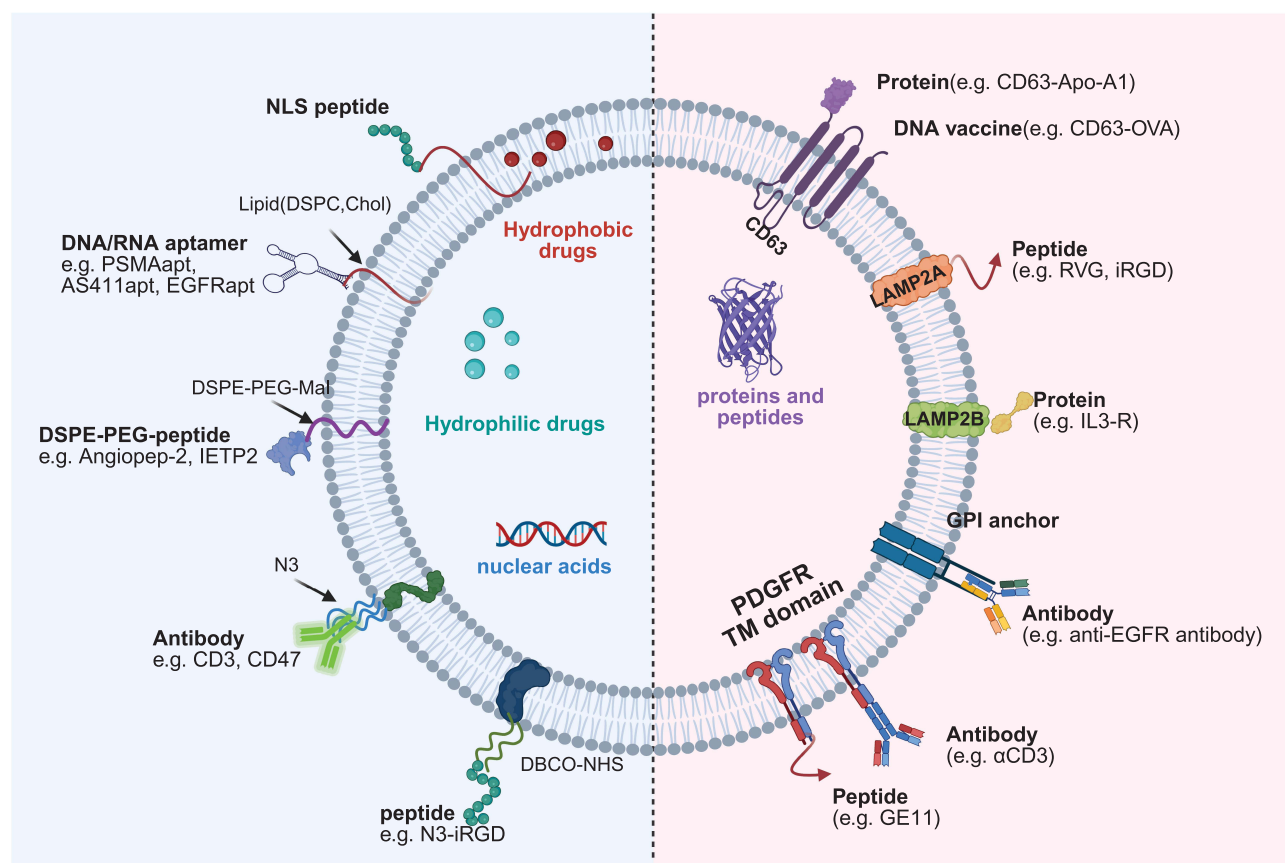


Figure 3 Rational design paradigms and therapeutic implementation of engineered exosomes. Chemical: DSPE-PEG-Peptide/Aptamer/Antibody: A lipid (DSPE) anchors into the exosome membrane, a PEG spacer provides flexibility and reduces immunogenicity, and a terminal group (eg, Mal for coupling) is used to attach targeting moieties like peptides (eg, iRGD), DNA/RNA aptamers, or antibodies (eg, anti-CD3). NLS peptide: Nuclear localization signals for targeting the cell nucleus. Simple lipids (DSPC, Chol): Can be used to modify membrane fluidity and properties. Click Chemistry: A modern bioorthogonal chemistry approach, as shown with DBCO-NHS. One group (eg, DBCO) is first chemically attached to the exosome surface, and then it reacts specifically and efficiently with a complementary group (eg, Azide/N3) on the targeting ligand. Biological: LAMP2B-fusion: The lysosomal-associated membrane protein 2B (LAMP2B) is highly enriched on exosomes. Fusing it to a targeting peptide (eg, RVG for neurons) or protein (eg, IL3-R) ensures display on the exosome surface. Protein Fusions (eg, CD63-Apo-A1, CD63-OVA): Fusing a therapeutic protein or antigen to a common exosome surface protein like CD63. Metabolic Labeling: This method is implied by the GPI anchor strategy. Cells are metabolically engineered to produce proteins with a Glycosylphosphatidylinositol (GPI) anchor, which automatically inserts into the exosome membrane. Common Ligands are PDGFR or TIM domain fused proteins, antibodies (eg, anti-EGFR). (Adapted from Liang Y, et al *Theranostics*. 2021. Created with BioRender.com).

Bioengineering Approaches

Genetic modification of parent cells enables production of exosomes with tailored characteristics. Gao et al developed a CP05 peptide-CD63 binding system, demonstrating that CP05-functionalized exosomes conjugated with muscle-targeting peptides significantly enhanced oligonucleotide delivery and dystrophin restoration in murine muscular dystrophy models.¹⁰⁰ Complementary work by Joao et al established that LAMP2A expression levels can be modulated to optimize protein loading via the chaperone-mediated autophagy pathway, enabling selective packaging of therapeutic targets, such as α -synuclein.¹⁰¹

Chemical Conjugation Techniques

Covalent surface modification strategies have been successfully implemented. Lee et al pioneered a metabolic labeling approach using azido-sugar incorporation followed by biorthogonal click chemistry with ADIBO fluorophores.¹⁰² Similarly, Luo et al achieved targeted delivery through CAQK peptide conjugation via click chemistry, creating a theranostic platform for spinal cord injury treatment.¹⁰³

Therapeutic Applications in Auditory Preservation and Restoration

Exosomes serve as a multifunctional delivery platform capable of carrying diverse therapeutic agents for the treatment of SNHL, exerting protective and restorative effects on auditory function through multiple molecular and cellular mechanisms (Table 3).

Nucleic Acid Delivery

Exosomes can effectively protect nucleic acids from nuclease-mediated degradation and facilitate their targeted delivery to inner ear cells.

miRNA Regulation

Exosomes can deliver protective microRNAs (eg, miR-183 family, miR-96) to modulate cell development and survival.^{110,111} Alternatively, they can carry inhibitory molecules to silence pathogenic miRNAs such as miR-34a, which is implicated in age-related hearing loss.¹¹² Studies have demonstrated that exosomes overexpressing miR-21 mitigate hair cell damage from ischemia-reperfusion injury through inhibition the inflammatory process in the cochlea.⁸²

mRNA Supplementation Therapy

Recent advancements in vector engineering have enabled the development of hybrid exosome-AAV (exo-AAV) delivery platforms to enhance cochlear transduction efficiency.¹¹³ Experimental evidence demonstrates that exo-AAV-GFP administration via round window membrane injection or cochlear explant culture significantly improves transduction rates in murine auditory hair cells.¹¹⁴ The therapeutic potential of this platform was further validated through delivery of the *Lhfp15* gene to *Lhfp15*^{-/-} murine models at postnatal days 1–2 (P1-P2).⁴² Exo-AAV1-mediated gene transfer significantly reduced ABR thresholds at low frequencies, partially restored auditory function, and ameliorated vestibular dysfunction-associated locomotor abnormalities.

Table 3 Exosomes Based Drug Delivery Systems for Inner Ear Pathology

Syndrome	Source of Exosomes	Therapeutic Cargo and Key Critical Parameters	Delivery Routes	Outcomes
Noise-induced hearing loss	Human iPSC-derived MSCs	BDNF; Time Window: Hearing protection assessed in mice after NIHL induction	Intravenous administration	Remarkably ameliorated H ₂ O ₂ -induced oxidative stress, cell apoptosis, and cochlear nerve terminal degeneration ¹⁰⁴
Genetic etiologies	HEK293T transfection	scAAV-CBA-HA- <i>Lhfp15</i> ; Time Window: Hearing preservation measured by ABR 4 weeks post-injection	RWM injection	Exo-AAV1 efficiently transduces IHCs and OHCs ⁴²
CDDP-induced hearing loss	UCMSCs	- Time Window: Evaluation of hearing protection in mice 7 days after cisplatin injection	RWM injection	Improved hearing loss and rescued the loss of cochlear hair cells ¹⁰⁵
Neomycin-induced ototoxicity	MSC	- Time Window: Evaluation of hearing protection in mice 3 weeks after neomycin injection	Round window niche	Increased autophagic activity and decreased the mitochondrial oxidative stress level ¹⁰⁶
Genetic etiologies	HEI-OCI cells	gRNA, Cas9; Time Window: Hearing preservation measured by ABR 6 months post-injection	Posterior Semicircular canal	~ 20dB reduction in hearing threshold ¹⁰⁷
Noise-induced hearing loss	MSC	- Time Window: Hearing protection assessed in mice 2, 4, 6 and 8 weeks after NIHL induction	Intravenous administration	ApoVs mitigates noise-induced hearing loss through the preservation of outer hair cells ¹⁰⁸
CDDP-induced hearing loss	BMSCs	HSP70; Time Window: Evaluation of hearing protection in mice 7 days after cisplatin injection	Trans-tympanically administration	Attenuate the inflammatory response mediated by the NLRP3 inflammasome and reduce hair cell loss ¹⁰⁹

Abbreviations: BDNF, brain-derived neurotrophic factor; MSC, mesenchymal stem cell; NIHL, noise-induced hearing loss; UCMSC, umbilical cord mesenchymal stem cell; CDDP, cis-dichlorodiammineplatinum.

Proteins and Peptide Delivery

Exosomes can efficiently encapsulate and deliver protein- and peptide-based therapeutic agents:

Neurotrophic Factors

Exosomes can deliver neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), which promote the survival of spiral ganglion neurons and support synaptic regeneration. Evidence indicates that exosome-mediated delivery of BDNF achieves over threefold greater neuroprotective efficacy compared to free BDNF, attributable to enhanced stability against degradation and targeted delivery to synaptic regions.¹⁰⁴

Antioxidant Enzymes

Exosomes enable the targeted delivery of antioxidant enzymes—including superoxide dismutase (SOD)¹¹⁵ and catalase (CAT)¹¹⁶—to mitigate oxidative stress. Given that oxidative stress is a shared pathological mechanism in noise-induced, drug-induced, and age-related hearing loss, mitochondrial-targeted delivery via exosomes can significantly enhance the clearance of reactive oxygen species (ROS).

Anti-Apoptotic Proteins

The mechanism underlying cisplatin-induced ototoxicity is closely associated with the induction of hair cell apoptosis via the Bcl-2/Bax signaling pathway.¹¹⁷ Exosomes are capable of delivering anti-apoptotic proteins, such as Bcl-2 and XIAP, to target cells,¹¹⁸ thereby potentially suppressing drug-induced hair cell injury and auditory neuron apoptosis.

Small-Molecule Drug Delivery

Exosomes can enhance the delivery efficiency and therapeutic efficacy of small molecule drugs in the inner ear:

Steroids

Dexamethasone, a representative corticosteroid, exerts anti-inflammatory and anti-edematous effects in the inner ear.¹¹⁹ Exosome encapsulation improves its aqueous solubility and target specificity while reducing systemic exposure and associated side effects.¹²⁰

Neuroprotective Agents

Rosmarinic acid exhibits potent antioxidant and anti-inflammatory properties but suffers from low oral bioavailability and rapid metabolism.¹²¹ Exosomal encapsulation enhances its stability and facilitates intracellular delivery. Notably, tFNA-RA@G-Ang2 nanocomplexes have been shown to effectively cross the BLB, leading to marked improvements in synaptic preservation and auditory functional recovery following noise-induced injury.¹²²

Ferroptosis Inhibitors

Ferrostatin-1 is a specific inhibitor of iron-dependent lipid peroxidation and ferroptotic cell death.¹²³ Exosome-based delivery enhances its intracellular bioavailability and retention. Accumulating evidence indicates that ferroptosis contributes to ototoxicity induced by cisplatin, neomycin, and noise exposure.^{124–126} Therefore, pharmacological inhibition of this pathway effectively protects both hair cells and spiral ganglion neurons.

Preclinical Evidence

Multiple studies have demonstrated the therapeutic potential of exosomes in SNHL models. In noise-induced hearing loss models, intravenous administration of mesenchymal stem cell-derived exosomes significantly reduces ABR thresholds by 20–30 dB, while attenuating hair cell loss and synaptic damage.¹⁰⁴ This protective effect is mediated through antioxidant mechanisms (activation of the Nrf2/HO-1 pathway), anti-inflammatory actions (suppression of NF-κB activation), and neurotrophic support (upregulation of BDNF expression). In drug-induced ototoxicity models—such as those involving cisplatin or aminoglycosides—Intraperitoneally administered exosomes derived from umbilical cord mesenchymal stem cells (UCMSCs) effectively mitigate damage to hair cells and spiral ganglion neurons, leading to improved auditory function.¹⁰⁵ In age-related hearing loss models, exosomes-mediated delivery of Apelin promotes M2 macrophage polarization, thereby delaying hair cell senescence and functional deterioration, enhancing hair cell regeneration, and

facilitating the recovery of auditory function, resulting in improved hearing performance in aged animals.¹²⁷ Collectively, these findings provide robust proof-of-concept and a strong experimental foundation for the clinical translation of exosome-based therapies for SNHL.

The Future Prospective

Although exosome therapy for SNHL holds significant promise, its translation from laboratory research to clinical application remains challenged by multiple hurdles that require coordinated efforts across disciplines to overcome. Isolation, purification, and standardization: Current exosome isolation techniques—including ultracentrifugation, size-exclusion chromatography, and polymer-based precipitation—suffer from low yield, inadequate purity, and limited reproducibility.^{128,129} Exosomes isolated via different methods exhibit significant variations in particle size distribution, protein cargo, and biological activity, which compromise the consistency and reliability of therapeutic outcomes.¹³⁰ Drug loading efficiency and stability: The encapsulation efficiency of exosomes is generally low, particularly for hydrophilic drugs, and the loading process may compromise membrane integrity and impair intrinsic biological functions.¹³¹ Furthermore, the long-term stability of drug-loaded exosomes—under various storage conditions—and their *in vivo* circulation half-life remain critical factors affecting clinical feasibility. Safety assessment: Although exosomes are endogenous nanovesicles and generally regarded as biocompatible, the safety profile of high-dose systemic administration requires thorough evaluation. Potential concerns include long-term toxicity, immunogenicity (particularly with allogeneic sources), and tumorigenic risks (eg, when derived from tumor cells).^{129,132} Of particular note, exosomes may inadvertently promote oncogenesis or immune suppression through the transfer of oncogenic miRNAs or immunomodulatory molecules. Pharmacokinetics and pharmacodynamics: The biodistribution, metabolic clearance, and pharmacokinetic behavior of exosomes *in vivo* are not yet fully characterized. There is a pressing need to develop sensitive and reliable labeling and tracking technologies to elucidate exosome fate and to investigate the molecular mechanisms underlying their interactions with target cells. Large-scale manufacturing and quality control: The production of clinical-grade exosomes must adhere to Good Manufacturing Practice (GMP) standards, encompassing scalable cell culture, robust purification protocols, and rigorous quality testing.¹²⁸ Currently, the absence of harmonized quality specifications—for attributes such as purity, potency, sterility, and particle concentration—represents a major barrier to regulatory approval and clinical adoption. Challenges in personalized therapy: While autologous exosomes offer minimal immunogenic risk, their use is constrained by high manufacturing costs and prolonged production timelines.¹³³ In contrast, allogeneic exosomes enable off-the-shelf availability but carry potential risks of immune rejection. Balancing the benefits of personalized treatment with the demands of scalable, standardized manufacturing remains a key translational challenge.

This systematic review comprehensively examines the barrier architecture of the inner ear microenvironment and its regulatory mechanisms controlling drug delivery, with particular emphasis on the therapeutic potential of exosomes as nanoscale delivery vehicles. The BLB imposes stringent restrictions on trans-barrier drug transport, whereas exosomes, by virtue of their innate barrier-penetrating capacity, biocompatibility, and engineerability, represent a transformative strategy for targeted therapy of inner ear disorders. Substantial progress has been achieved through elucidation of exosome biogenesis pathways, optimization of drug-loading efficiency and targeting specificity, and empirical validation of their therapeutic efficacy in auditory preservation and functional restoration. Nevertheless, clinical translation remains challenging due to standardization of scalable production protocols, enhancement of *in vivo* delivery efficiency, and comprehensive evaluation of long-term biosafety. Through coordinated interdisciplinary efforts addressing these critical issues, exosome-mediated drug delivery may emerge as a novel therapeutic paradigm in otology, offering precision medicine solutions for patients with SNHL and vestibular dysfunction.

Acknowledgments

This review was supported by grants from the National Natural Science Foundation of China (Grant Nos. 82271178, 82071055, 82471178), the National Science Foundation for Young Scientists of China (Grant Nos. 82401367, 82000986, 82301315), the Anhui Province Scientific Research Preparation Plan Project (Grant Nos. 2022AH050685, 2022AH050655). Clinical and Translational Research Project of Anhui Province (Grant No. 20261216).

Disclosure

The authors declare no conflicts of interest in this work.

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