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Exosomes as Targeted Drug Delivery Systems: Strategies and Mechanisms for Mitigating Cisplatin-Induced Hair Cell Damage

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Abstract: Cisplatin is a highly effective chemotherapeutic agent widely used for various solid tumors; however, its clinical utility is severely compromised by cisplatin-induced ototoxicity (CIO), which leads to permanent sensorineural hearing loss. The primary pathological hallmark of CIO is the irreversible damage and loss of auditory hair cells, driven by mechanisms including oxidative stress, DNA damage, and inflammatory cascades. Despite numerous candidates for otoprotection, efficient delivery to the inner ear remains a significant challenge due to the blood-labyrinth barrier (BLB) and the risk of systemic side effects. Recently, exosomes—small extracellular vesicles—have emerged as a promising bio-inspired drug delivery system (DDS) for inner ear therapy. Due to their low immunogenicity, high biocompatibility, and innate ability to cross biological barriers, exosomes offer a revolutionary platform for the targeted delivery of therapeutic agents. This review systematically delineates the molecular mechanisms of cisplatin-induced hair cell damage and highlights the recent advances in utilizing exosome-encapsulated drugs, including small molecules, nucleic acids, and proteins for otoprotection. We further discuss innovative strategies for exosome engineering, such as surface modification and active loading techniques, to enhance their targeting precision and therapeutic efficacy within the cochlea. Finally, the challenges of clinical translation and future perspectives of exosome-based nanomedicine in hearing preservation are addressed, providing a theoretical framework for the development of next-generation otoprotective strategies.

Keywords: Exosomes; Cisplatin-induced Ototoxicity; Auditory Hair Cells; Drug Delivery Systems; Otoprotection; Nanomedicine.

1. Introduction

Cisplatin (cis-Diammineplatinum(II) dichloride) remains a cornerstone of systemic chemotherapy for a broad spectrum of solid malignancies, including head and neck, lung, and ovarian cancers[5]. Despite its potent anti-tumor efficacy, the clinical utility of cisplatin is significantly constrained by its debilitating side effects, most notably CIO[6]. CIO typically manifests as a progressive, bilateral, and irreversible sensorineural hearing loss (SNHL), often accompanied by high-pitched tinnitus. Epidemiological studies indicate that up to 60–90% of pediatric patients and a substantial proportion of adults treated with cisplatin suffer from permanent hearing impairment[7]. This sensory deficit not only severely compromises the quality of life and social communication of cancer survivors but, in children, also impairs speech development and cognitive acquisition, creating a long-term socio-economic burden.

The primary pathological target of cisplatin in the inner ear is the organ of Corti, specifically the sensory hair cells[8]. Unlike avian species, mammalian auditory hair cells possess negligible regenerative capacity; once lost to apoptosis or necrosis, their functional deficit is permanent[9]. The molecular orchestration of CIO is multifactorial, involving the excessive accumulation of ROS, depletion of antioxidant defense systems, DNA damage, and the activation of pro-apoptotic signaling cascades. Over the past decades, numerous otoprotective agents, such as antioxidants and anti-inflammatory compounds, have shown promise in preclinical models [10]. However, their clinical translation has been hindered by two major hurdles: the presence of the BLB, which restricts the entry of systemic drugs into the cochlea, and the rapid clearance or systemic toxicity of these agents when administered at high doses. Although transtympanic injection offers a localized alternative, it remains invasive and often fails to achieve sustained therapeutic concentrations within the hair cells[11].

In recent years, the intersection of nanotechnology and regenerative medicine has birthed a paradigm shift in drug delivery: the use of exosomes[12]. Exosomes are a subset of endosome-derived extracellular vesicles (EVs), typically 30–150 nm in diameter, secreted by almost all cell types. Distinct from synthetic nanoparticles like liposomes, exosomes are considered "nature's delivery system." They exhibit innate low immunogenicity, exceptional biocompatibility, and the unique ability to traverse complex biological barriers, including the BLB. Furthermore, the lipid bilayer of exosomes protects delicate molecular cargoes—such as small-molecule drugs, microRNAs, and proteins—from enzymatic degradation in the systemic circulation[13]. By engineering the surface of exosomes with specific ligands, researchers can now achieve "precision targeting" of auditory hair cells, thereby maximizing therapeutic efficacy while minimizing off-target effects[14].

This review aims to provide a comprehensive synthesis of the current landscape regarding exosome-mediated drug delivery for the mitigation of CIO. We first delineate the core molecular mechanisms underlying cisplatin-induced hair cell damage[15]. Subsequently, we evaluate the unique advantages of exosomes as therapeutic vehicles and detail the

innovative strategies for drug loading and surface modification. By reviewing recent preclinical breakthroughs, we highlight how exosome-encapsulated therapeutics provide superior protection against hair cell loss compared to conventional formulations. Finally, we discuss the technical challenges and regulatory milestones required to transition these bio-inspired nanoplatforms from the laboratory bench to the patient's bedside[16].

2. Molecular Mechanisms of Cisplatin-Induced Ototoxicity

2.1. Cellular Uptake and DNA Damage

Cisplatin enters hair cells through specific transporters, primarily Copper Transporter 1 and Organic Cation Transporter 2, which are highly expressed in the cochlea. Once inside the low-chloride environment of the cytoplasm, cisplatin undergoes aquation, forming highly reactive positively charged species. These molecules bind to nuclear and mitochondrial DNA, forming DNA-platinum adducts. This genomic insult triggers the DNA damage response, activating p53 and shifting the cellular rheostat toward pro-apoptotic signaling[18].

2.2. Oxidative Stress: The Role of ROS and NOX3

A hallmark of CIO is the surge in Reactive Oxygen Species . Unlike other tissues, the cochlea expresses a specific isoform of NADPH oxidase, NOX3, which is a major source of cisplatin-induced superoxide production[19]. Cisplatin exposure leads to the overactivation of NOX3 and the simultaneous depletion of endogenous antioxidant enzymes. This redox imbalance causes lipid peroxidation, protein carbonylation, and high levels of oxidative stress, which serves as a central trigger for downstream toxic pathways.

2.3. Activation of the JNK Signaling Pathway

The JNK pathway, a member of the MAPK family, is a critical mediator of stress-induced hair cell death. ROS-induced oxidative stress activates the JNK signaling cascade. Phosphorylated JNK translocates to the nucleus to activate pro-apoptotic transcription factors and acts directly on the mitochondria[20]. The JNK pathway serves as a "bridge" connecting the initial oxidative insult to the final apoptotic machinery.

2.4. Mitochondrial Dysfunction and Apoptosis

The mitochondria are both the source and the victim of CIO. Cisplatin-induced stress leads to the activation of pro-apoptotic members of the Bcl-2 family, such as Bax and Bak, which translocate to the outer mitochondrial membrane. This causes the loss of mitochondrial membrane potential and the release of Cytochrome c into the cytosol. Cytochrome c binds to Apaf-1 to form the apoptosome, which sequentially activates Caspase-9 and Caspase-3, the "executioner" of apoptosis[21]. This intrinsic apoptotic pathway results in the irreversible degradation of hair cell structures and permanent hearing loss.

3. Exosomes: A Superior Nano-platform for Inner Ear Drug Delivery

3.1. Intrinsic Biocompatibility and Low Immunogenicity

Exosomes exhibit superior biocompatibility compared to synthetic lipid-based or polymeric nanoparticles. Their membrane composition, rich in cholesterol, sphingomyelin, and specific tetraspanins, mimics the host cell membrane, allowing them to evade clearance by the mononuclear phagocyte system[23]. For inner ear therapy, this low immunogenicity is crucial to prevent secondary inflammatory responses within the delicate cochlear microenvironment, ensuring that the therapeutic intervention does not exacerbate the existing cisplatin-induced damage.

3.2. Capability to Traverse the BLB

The BLB represents the primary anatomical hurdle for systemic drug delivery to the cochlea, effectively shielding the organ of Corti from most large molecules and hydrophilic drugs. Exosomes, however, possess an innate ability to cross various biological barriers, including the blood-brain barrier (BBB) and the BLB, via mechanisms such as transcytosis or direct membrane fusion[24]. Their small size (30–150 nm) and flexible lipid bilayer allow them to penetrate deep into the stria vascularis and reach the sensory hair cells—a feat that traditional small-molecule antioxidants often fail to achieve at therapeutic concentrations without high-dose systemic administration.

3.3. Engineering for Precision Targeting of Hair Cells

A defining advantage of exosomes is their capacity for surface modification. By overexpressing specific ligands or "homing peptides" on the exosomal membrane, these vesicles can be "programmed" to recognize specific receptors on auditory hair cells or the spiral ganglion. This targeted delivery approach not only increases the local concentration of the otoprotective drug at the site of injury but also significantly reduces off-target accumulation in the liver or kidneys, thereby minimizing the risk of interfering with cisplatin's systemic anti-tumor efficacy[25].

4. Exosome-Encapsulated Therapeutics for Otoprotection

4.1. Encapsulation of Small Molecule Antioxidants and Inhibitors

Exosomal encapsulation offers a robust solution to the inherent pharmacological limitations of small-molecule antioxidants, such as poor aqueous solubility, rapid systemic clearance, and restricted penetration through the blood-labyrinth barrier. A notable application is the delivery of polyphenols, particularly curcumin, whose clinical utility has long been hindered by exceptionally low bioavailability. Recent investigations utilizing in vitro HEI-OC1 cell models and in vivo zebrafish models have demonstrated that exosome-encapsulated curcumin significantly enhances the drug's stability and biodistribution[27]. Compared to its free form, Exo-cur exhibits a superior capacity to scavenge ROS and suppress the NF-κB-mediated inflammatory cascade, thereby effectively preserving the structural integrity of

auditory hair cells against cisplatin-induced oxidative insult.

Beyond improving solubility, exosomes serve as precision delivery vehicles for potent signaling inhibitors, enabling the targeted modulation of intracellular death pathways in the cochlea. Given that the JNK signaling pathway is a pivotal mediator of cisplatin-induced hair cell apoptosis, the encapsulation of specific JNK inhibitors within exosomes facilitates high-concentration delivery directly to the organ of Corti. This targeted approach effectively attenuates the phosphorylation of c-Jun and thwarts the subsequent activation of the mitochondrial apoptotic machinery. By leveraging the innate homing capabilities and superior cellular internalization of exosomes, this strategy not only maximizes otoprotective efficacy but also minimizes potential off-target effects associated with the systemic administration of potent molecular inhibitors.

4.2. Delivery of Nucleic Acid Cargoes: A Precision Medicine Approach

The delivery of genetic material, particularly microRNAs and siRNAs, represents a sophisticated frontier in exosome research for modulating gene expression within the cochlea. Engineered exosomes enriched with otoprotective miRNAs, such as miR-182-5p and miR-21, have demonstrated a remarkable ability to target pro-apoptotic genes like Foxo3 and Bax, thereby recalibrating the cellular rheostat toward survival.

This therapeutic potential is further complemented by mesenchymal stem cell-derived exosomes, which naturally harbor a potent cocktail of bioactive miRNAs that contribute to their innate regenerative properties. Simultaneously, exosomes have been strategically utilized to deliver siRNAs for the precise silencing of "root-cause" genes in cisplatin-induced ototoxicity, specifically targeting Nox3 and p53 [28]. By suppressing the initial oxidative burst and the subsequent DNA damage response, these exosomal-siRNA complexes significantly attenuate auditory brainstem response threshold shifts in murine models, highlighting the transformative potential of exosome-based gene therapy for robust hearing preservation.

5. Conclusion

In conclusion, exosome-encapsulated drugs represent a transformative approach to mitigating cisplatin-induced hair cell damage. By overcoming the limitations of the blood-labyrinth barrier and offering a platform for precise genetic and pharmacological intervention, these nanovesicles provide a beacon of hope for preserving the hearing of cancer survivors. While technical and regulatory challenges persist, the continued synergy between nanotechnology, auditory neuroscience, and clinical pharmacology will undoubtedly pave the way for a new era of hearing preservation.

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