

Regulation Mechanisms and Research Advances of Cochlear Immune Microenvironment in Sensorineural Hearing Loss

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Abstract

Sensorineural hearing loss (SNHL) is a highly prevalent sensory disorder globally, affecting over 1.5 billion people, with a growing societal burden exacerbated by population aging. Traditional research has focused on direct damage mechanisms to hair cells and spiral ganglion neurons, while current hearing assistive devices cannot achieve biological repair. Recent research paradigms have shifted from a “single-cell injury” perspective to a systemic view of the “neuro-immune-vascular” unit, revealing that the cochlea is not an immune-privileged site but rather a highly dynamic immune microenvironment. This immune microenvironment plays a core, dual-role in maintaining inner ear homeostasis and injury response: moderate inflammation aids repair, whereas uncontrolled inflammation exacerbates secondary damage. This review systematically summarizes the regulatory mechanisms of the cochlear immune microenvironment in the pathogenesis of SNHL, with a focus on the phenotypic plasticity of resident macrophages, infiltration of peripheral immune cells, the immunomodulatory role of glial cells, and key signaling pathways such as Nuclear Factor kappa B (NF- κ B) and the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome. Concurrently, it evaluates advances in research technologies like single-cell transcriptomics and animal models, and discusses potential precision therapeutic strategies targeting the immune microenvironment (e.g., intervening specific pathways, reprogramming immune cells, combining nanodelivery systems), and considers the influence of sex as a biological variable on immune responses, aiming to provide new insights for promoting inner ear repair and advancing personalized medicine.

Keywords

Sensorineural Hearing Loss, Cochlea, Immune Microenvironment, Macrophages, Inflammatory Response, Regulation Mechanisms

1. Introduction

Sensorineural hearing loss (SNHL), one of the most common sensory disorders worldwide, severely impacts communication, quality of life, and imposes a significant socioeconomic burden. The *World Report on Hearing* and the 2019 Global Burden of Disease study indicate over 1.5 billion people experience hearing loss, a number rising with an aging population [1] [2]. SNHL etiology is complex, involving factors like noise exposure, age-related degeneration, ototoxic drugs, and viral infections (e.g., mumps virus, cytomegalovirus), all leading to irreversible damage to the inner ear's sensory structures—hair cells and spiral ganglion neurons—which form the pathological basis of hearing impairment [3] [4]. However, mainstream auditory devices (e.g., hearing aids, cochlear implants) merely amplify sound or provide electrical stimulation, offering functional substitution without biological repair or regeneration of damaged inner ear structures, thus having limited efficacy [5]. Therefore, elucidating the fundamental pathological mechanisms of SNHL, particularly the dynamic regulatory role of the inner ear immune microenvironment during injury and repair, is crucial for identifying novel therapeutic targets and achieving biological restoration.

Conventional research primarily focused on direct damage mechanisms to hair cells and spiral ganglion neurons, such as oxidative stress, calcium overload, and activation of apoptotic pathways [3]. A breakthrough understanding in recent years is that the cochlea is not an immune-exempt zone but an active immune microenvironment comprising sensory epithelium, supporting cells, neurons, the stria vascularis, and resident/recruited immune cells. Following injury, the immediate activation of innate and adaptive immune responses within the cochlea is not only a key driver of secondary pathological changes but also deeply involved in attempted tissue homeostasis restoration, constituting the core of the bidirectional processes of damage and repair [6] [7]. This recognition has shifted the research paradigm from a “single-cell injury” focus to a systemic framework centered on the “neuro-immune-vascular unit” [8]. Within this framework, immune inflammation exhibits a “double-edged sword” effect: timely, appropriate inflammatory responses help clear necrotic debris and initiate repair signals; however, if uncontrolled or chronic, they produce excessive inflammatory mediators and cytotoxic substances, damaging healthy bystander cells and exacerbating hearing impairment [4] [9]. Thus, clarifying the precise regulatory mechanisms maintaining this delicate balance is key to developing novel therapies targeting the immune microenvironment.

The cochlear immune microenvironment is a complex, dynamic system com-

posed of immune cells, immune molecules, signaling pathways, and specialized barrier structures, serving as the core unit regulating inner ear immune homeostasis and pathological responses. Its core components include: first, immune cell populations, notably resident macrophages. These cells are distributed in areas like the spiral ligament, modiolus, and stria vascularis, acting as “sentinels” for tissue surveillance [6]. Second, a soluble immune mediator network, including various pro-/anti-inflammatory cytokines (e.g., Interleukin-1 β (IL-1 β), Tumor Necrosis Factor- α (TNF- α)) and chemokines, mediating recruitment and activation signals between cells. Third, conserved intracellular signal transduction hubs, such as the NF- κ B pathway and the NLRP3 inflammasome, responsible for converting diverse danger signals into orchestrated inflammatory programs [7] [9]. Fourth, the structural Blood-Labyrinth Barrier (BLB), which not only controls substance exchange but also isolates peripheral immune interference, forming the key anatomical basis for the cochlea’s relatively independent immune status [8]. Under physiological conditions, this system maintains a finely balanced state of vigilance, with resident immune cells remaining quiescent through constant environmental sampling. Upon disruption of barrier integrity or tissue homeostasis, the system is promptly triggered, coordinating defense and repair programs across multiple levels, reflecting the high integration of the “neuro-immune-vascular” unit [6] [7].

Based on this paradigm shift from “single-cell injury” to “neuro-immune-vascular” systemic regulation, this review aims to systematically elaborate on the dynamic evolution patterns, core regulatory networks, and pathophysiological significance of the cochlear immune microenvironment in the development of SNHL. First, it will analyze the specific responses of the cochlear immune microenvironment under different core etiologies (e.g., noise exposure, presbycusis, ototoxic drugs, immune-mediated damage), focusing on phenotypic shifts of immune cells (e.g., macrophages), cascade reactions of inflammatory mediator networks, and their decisive impact on auditory cell fate. Second, it will delve into key intracellular signaling pathways (e.g., NF- κ B, NLRP3 inflammasome) and molecular switches mediating these responses. Third, it will evaluate the value of emerging research methods and model systems in this field, particularly using single-cell transcriptomics to resolve cochlear cellular heterogeneity [10], and the application of various SNHL animal models in mechanistic research and preclinical validation [11]. Finally, it will prospect potential novel therapeutic strategies aimed at precisely modulating the cochlear immune microenvironment, such as intervening specific inflammatory pathways or reprogramming immune cell function, to provide theoretical foundations and cutting-edge directions for developing biological therapies that can halt disease progression or promote inner ear repair [4] [9]. This conceptual framework emphasizes that auditory function and pathology cannot be understood by examining neurons, immune cells, or vasculature in isolation. Instead, they operate as an integrated triad: 1) The vascular compartment, centered on the stria vascularis and the BLB, not only supplies nu-

trients and oxygen but also strictly regulates immune cell trafficking and the passage of signaling molecules. BLB disruption is often the initiating event for pathological immune infiltration. 2) The immune compartment, comprising resident and infiltrating cells, responds to danger signals originating from both neural and vascular injury. Its activation state directly dictates the survival of hair cells and neurons, while also releasing mediators that affect vascular permeability and neural excitability. 3) The neural compartment, including hair cells, spiral ganglion neurons, and glia, is both a target of immune attack and an active participant. Glial cells sense neural stress and release immune-modulating signals (e.g., ATP, chemokines), while neurons express receptors for cytokines (e.g., TNF- α) that directly alter synaptic function and survival. Damage in one compartment invariably perturbs the others, creating feed-forward loops that can either exacerbate injury or, if properly modulated, facilitate recovery. This review will dissect the components of this tripartite system, with a particular focus on the immune compartment as the central orchestrator of pathological outcomes in SNHL.

2. Core Cellular Components of the Cochlear Immune Microenvironment and Their Dynamic Responses in SNHL

Building on the systemic perspective of the “neuro-immune-vascular” unit, we first focus on the core cellular components within the cochlear immune microenvironment. These cells are not only executors of immune responses but also key regulators of cochlear damage and repair under various etiologies.

2.1. Resident Macrophages: Sentinels and Double-Edged Swords of Cochlear Immune Homeostasis

As the most abundant and extensively studied immune cell population in the cochlea, resident macrophages are widely distributed in key areas like the spiral ligament, spiral ganglion, and stria vascularis, serving as central sentinels for sensing environmental changes and initiating immune responses [12] [13]. Under physiological conditions, they predominantly exhibit a protective/surveillance phenotype (often classified as M2-like), actively maintaining cochlear immune quiescence and tissue homeostasis through continuous environmental sampling and timely clearance of apoptotic debris [14] [15]. Upon encountering damage from noise, ototoxic drugs, or aging, these sentinel cells are rapidly activated, and their phenotype can shift towards a pro-inflammatory direction (often classified as M1-like). This shift is not binary but exists along a dynamic continuum, leading to vastly different pathological outcomes. Polarized pro-inflammatory macrophages release large amounts of cytokines like TNF- α and IL-1 β , and reactive oxygen species (ROS), directly attacking healthy hair cells and neurons or disrupting their synaptic connections, thereby amplifying initial damage [15] [16]. Recent studies indicate that activation of resident macrophages is a key event leading to hair cell damage after noise exposure [16]. In presbycusis, the inherent im-

munosenescent phenotype of macrophages leads to diminished surveillance and sustained release of low-level inflammatory mediators, creating an “inflammaging” microenvironment that drives progressive hearing loss [17] [18]. Conversely, in later stages of injury or under specific signals, macrophages can enhance their phagocytic function and switch to a repair phenotype. Not only do they clean up the “battlefield,” recent evidence suggests they can actively secrete factors promoting the regeneration of inner hair cell ribbon synapses [19]. This timely reversion to a repair (M2-like) phenotype is crucial for controlling inflammation, promoting tissue remodeling, and maintaining stria vascularis function [13] [15]. In summary, cochlear resident macrophages play a dual, paradoxical role in SNHL progression. Whether the balance tilts towards damage or repair fundamentally depends on the dynamic regulation of their functional phenotypic continuum by local microenvironmental signals [15]. However, a significant experimental challenge lies in definitively distinguishing resident macrophages from those recruited from the periphery, as they often share surface markers and exhibit overlapping functions. This ambiguity complicates the precise attribution of their distinct roles in SNHL pathogenesis and may affect the interpretation of therapeutic strategies targeting specific macrophage subpopulations.

2.2. Other Resident Immune Cells: Important Participants and Unsolved Mysteries

Beyond macrophages, other resident immune cells exist within the cochlea. Although less numerous and evidence is still accumulating, they may play significant regulatory roles under specific pathological conditions. Research on mast cells is relatively established. They reside in areas like the spiral ligament in rodent cochleae [20]. In cisplatin-induced ototoxicity models, cochlear mast cell degranulation is observed; released mediators like histamine may exacerbate hearing loss by affecting BLB permeability or directly causing neurotoxicity [21]. Evidence is emerging for potential resident subsets of innate lymphoid cells (e.g., natural killer cells) in the cochlea [6] [22]. However, the origin and role of neutrophils are more complex. Traditionally considered recruited from peripheral blood during acute inflammation, a few studies suggest possible resident populations, though their function under homeostasis remains unknown [6]. Overall, compared to macrophages, current understanding of the precise functions, activation mechanisms, and interaction networks of these “non-mainstream” resident immune cells in SNHL remains limited [22]. Elucidating their exact roles will be an important direction for revealing the full picture of the cochlear immune microenvironment and discovering potential new intervention targets.

2.3. Peripheral Immune Cell Infiltration: Barrier Breakdown and Inflammation Amplification

Severe cochlear damage often compromises the structural and functional integrity of the BLB. The BLB, a precise barrier separating peripheral circulation from inner

ear fluids, is a prerequisite for large-scale infiltration of peripheral immune cells into cochlear compartments [23] [24]. Following BLB disruption, chemokines released by damaged cochlear cells create chemical gradients, guiding migration of neutrophils, monocytes, and T lymphocytes from the blood to the injury site. Key signals include C-C Motif Chemokine Ligand 2 (CCL2) for monocyte/macrophage recruitment, and the CX3CL1 (Fractalkine)-CX3CR1 axis, which binds to the receptor CX3CR1 on neurons and macrophages, playing a central role in neuro-immune communication and macrophage positioning [14] [25]. Following noise damage, adaptive immune cells, including CD4+ and CD8+ T cells, infiltrate the cochlea, forming a mixed innate and adaptive immune response [26]. These newly recruited cells, particularly monocytes/macrophages and T cells, significantly expand the scale and intensity of the local inflammatory response. They release copious inflammatory mediators that further disrupt inner ear homeostasis, attack remaining hair cells and neurons, and may initiate or amplify adaptive immune responses, potentially pushing acute injury towards chronic inflammation or autoimmune pathology, ultimately driving sustained hearing loss progression [14] [18] [25]. Therefore, maintaining BLB integrity or specifically blocking pathological immune cell infiltration (e.g., targeting key chemokines or their receptors) is considered a highly promising therapeutic strategy aimed at curbing the vicious cycle of inflammation at its source.

2.4. Glial Cells: Active Immunomodulators and Signal Amplifiers in the Cochlea

Cochlear glial cells (including supporting cells and spiral ganglion satellite glial cells) are far more than structural and nutritional support. Under injury conditions, they transform into active immunomodulatory hubs, profoundly shaping the local microenvironment through three primary functions: 1) As danger sensors and alarmin releasers: When hair cells are damaged or neurons are stressed, nearby glial cells rapidly sense danger signals via pattern recognition receptors (PRRs) and initiate local immune responses by releasing “alarm molecules” like ATP and glutamate [6] [27]. 2) As producers of inflammatory mediators: More importantly, they actively synthesize and release key inflammatory cytokines (e.g., IL-1 β , TNF- α) and chemokines (e.g., CCL2), becoming a significant source of inflammatory mediators within the cochlea [14]. As coordinators of intercellular communication: These mediators form the core communication network coordinating responses across different cell types. Specifically, supporting cells—directly contacting hair cells—primarily contribute to glutamate clearance and CCL2 secretion for macrophage recruitment [14]. Conversely, satellite glial cells—enveloping neuronal cell bodies—are more involved in direct neuro-immune crosstalk, modulating neuronal survival and macrophage activity through cytokine release, thereby establishing a tight “neuron-glia-immune cell” tripartite dialogue [28]. This complex, cell-type-specific interaction network significantly amplifies and finely tunes the immune response [25]. Additionally, glial cells (especially sup-

porting cells), by highly expressing glutamate transporters (e.g., GLAST), promptly clear excess excitatory neurotransmitter, preventing excitotoxic neuronal death while indirectly stabilizing the immune microenvironment, demonstrating their multifaceted protective regulatory functions [27].

In summary, the cochlear immune microenvironment in SNHL is a highly dynamic, tightly interacting complex system. The dual role of resident macrophages, pathological infiltration of peripheral immune cells, and active immunomodulation by glial cells are not isolated but interwoven into a regulatory network determining the fate of damage and repair. Therefore, future breakthroughs in therapeutic strategies will necessarily rely on a deeper understanding of this network and its underlying regulatory mechanisms. Targeting specific cells, signaling pathways, or intercellular dialogues within this microenvironment will lay the critical theoretical foundation and open promising new avenues for developing novel biological therapies capable of precisely intervening in disease progression and promoting endogenous repair.

2.5. Sex as a Biological Variable in Cochlear Immune Responses

A critical, yet often underexplored, dimension in cochlear immunology is the influence of sex as a biological variable [29]. Sex hormones, particularly estrogens and androgens, are potent modulators of innate and adaptive immune responses [29] [30]. Estrogen generally exhibits anti-inflammatory and neuroprotective effects, while testosterone and its metabolites can have more complex, context-dependent immunomodulatory roles [29]. These hormonal differences may underlie observed disparities in the prevalence, severity, or progression of certain forms of SNHL [29]. For instance, autoimmune inner ear disease shows a female predominance, suggesting a potential link between female sex hormones and dysregulated adaptive immunity [29]. In noise-induced hearing loss, some animal studies and human epidemiological data suggest potential differences in susceptibility or recovery between males and females, possibly mediated by differential inflammatory responses, antioxidant capacity, or vascular reactivity [29]. Furthermore, the phenomenon of “inflammaging” in presbycusis may be influenced by the distinct hormonal changes during menopause and andropause [29]. Future research must systematically incorporate sex-based analyses in animal models (using both male and female subjects) and in the interpretation of human clinical data. Elucidating sex-specific regulatory mechanisms within the cochlear immune microenvironment could reveal novel therapeutic targets and is essential for developing personalized, precision medicine approaches for SNHL [29].

3. Key Regulatory Signaling Pathways and Molecular Mechanisms in the Cochlear Immune Microenvironment

3.1. Classical Inflammatory Signaling Pathways

The NF- κ B signaling pathway is a core transcriptional hub responding to cochlear injury and driving inflammatory responses. It can be activated by various danger

signals like oxidative stress and cytokines, leading to widespread upregulation of pro-inflammatory mediators. In noise-induced hearing loss, damage-associated molecular patterns (DAMPs) can initiate NF- κ B signaling via the Toll-Like Receptor 4 (TLR4)/MyD88 axis, causing massive production of cytokines like TNF- α and IL-1 β , directly exacerbating inflammatory damage [31]. Research also reveals the synergistic effect of CD38 with NF- κ B as a key mechanism promoting post-noise cochlear inflammation, while specific inhibitors (e.g., apigenin) exert protective effects by blocking this pathway [32]. In the context of presbycusis, cumulative oxidative stress (e.g., ROS) can persistently activate the ROS/NF- κ B pathway, promoting senescent phenotypes in auditory cells; antioxidants (e.g., vitamin C) can delay aging processes by inhibiting this pathway [33]. Notably, strong positive feedback regulation exists between the NF- κ B pathway and its downstream products. For example, TNF- α , a key product driven by NF- κ B, not only directly induces hair cell apoptosis and synaptopathy [34] [35] but can also reactivate NF- κ B in an autocrine/paracrine manner, forming a self-amplifying pro-inflammatory loop that continuously worsens hearing damage. Drugs like dexamethasone effectively mitigate TNF- α -mediated hair cell damage by inhibiting NF- κ B signaling [36]. Thus, targeting the NF- κ B pathway is considered a potential strategy for intervening in the inflammatory process of SNHL.

The NLRP3 inflammasome is a key molecular platform sensing intracellular danger signals and initiating pyroptosis and IL-1 β maturation/release, playing a significant role in connecting various damaging factors to cochlear inflammatory injury. In noise- and drug-induced hearing loss, accumulated oxidative stress and mitochondrial dysfunction in the cochlea release signals like ROS and mtDNA, directly assembling and activating the NLRP3 inflammasome. Its activation leads to caspase-1 cleavage/activation, processing pro-IL-1 β into mature IL-1 β , and inducing pyroptosis, collectively exacerbating damage to hair cells and spiral ganglion neurons [37]-[39]. Notably, mitochondrial dysfunction is considered a common upstream event for NLRP3 activation, with released components (e.g., mtDNA) serving as direct triggers, revealing the intrinsic link between energy metabolism dysregulation and innate immune activation [40]. This pathway is finely regulated. The oxidative stress sensor TXNIP can promote NLRP3 and NF- κ B activation, while inhibiting TXNIP alleviates subsequent damage [41]. Conversely, in presbycusis, Sestrin2 exerts endogenous protective effects by inhibiting NLRP3 inflammasome activity [42]. In summary, the NLRP3 inflammasome pathway integrates damage signals from multiple etiologies, serving as a key node driving cochlear inflammation and cell death. Therefore, targeting NLRP3 inflammasome assembly or activation has become a highly promising therapeutic strategy for intervening in SNHL [38] [42].

Beyond NLRP3, other inflammasome sensors like AIM2 (which detects cytosolic DNA) and NLRC4 (activated by bacterial flagellin and type III secretion system components) are also expressed in the inner ear, though their roles in sterile injury models of SNHL are less defined and may be context-dependent. The acti-

vation triggers for NLRP3 in the cochlea are particularly linked to the pathophysiology of SNHL. Critically, the specific DAMPs and their cellular sources vary across etiologies, leading to distinct patterns of inflammasome activation. In noise trauma, the massive release of ATP from damaged hair cells and supporting cells acts as a primary DAMP, which predominantly activates the P2X7 receptor on resident macrophages and glial cells, triggering potassium efflux and NLRP3 assembly [39]. Concurrently, oxidative stress and mitochondrial dysfunction in these same cell types generate ROS and release mitochondrial DNA (mtDNA), further amplifying NLRP3 activation [40]. In contrast, in ototoxic drug injury, direct drug-induced mitochondrial damage occurs primarily within sensory epithelial cells and spiral ganglion neurons. This intracellular damage leads to ROS and mtDNA release that can activate the inflammasome within these very cells, establishing autocrine and paracrine damage pathways [43]. Such cell-type- and etiology-specific activation patterns underscore the complexity of targeting the NLRP3 inflammasome, as therapeutic strategies may need to be tailored to the predominant cellular source of inflammation in each SNHL subtype.

3.2. Innate Immune Recognition and Signaling

The cochlear innate immune system collaboratively achieves danger recognition and initial response through PRRs and the complement system.

TLR4 can recognize endogenous DAMPs (e.g., heat shock proteins, hyaluronan fragments) released by tissue damage and exogenous pathogen-associated molecular patterns (e.g., bacterial lipopolysaccharide). Various inner ear cells (e.g., endolymphatic sac fibroblasts) express TLRs and produce abundant cytokines and chemokines upon ligand stimulation, initiating local inflammation. Under pathological conditions, stimuli like noise or LPS can specifically activate TLR4 signaling in the cochlea. This signaling, via downstream pathways like NF- κ B, drives infiltration of inflammatory cells like neutrophils and significantly increases BLB permeability, thereby amplifying inflammatory damage [43]–[45]. Studies show that inhibiting TLR4 signaling significantly reduces cochlear inflammation and improves hearing function [46].

The complement system, as another important innate immune arm, can be activated at injury sites, directly attacking target cells via membrane attack complex formation or recruiting/activating more immune cells via anaphylatoxins (e.g., C5a), amplifying the inflammatory response alongside the TLR pathway. Its specific regulatory network in SNHL is being elucidated [47]. Thus, the complement system and TLR pathways synergistically form the foundation of cochlear innate immune responses. Precise regulation of their balance may become a novel target for future hearing loss interventions.

3.3. Cytokine/Chemokine Networks

Cytokines and chemokines constitute the most crucial intercellular communication language within the cochlear immune microenvironment. Through complex

network interactions, they finely regulate the recruitment, activation, and functional polarization of immune cells, fundamentally determining the direction of the inflammatory process (acute resolution, chronicity, or tissue repair).

Dynamic Balance of Pro- and Anti-inflammatory Factors: The core pro-inflammatory network centered on TNF- α , IL-1 β , and Interleukin-6 (IL-6) is key to driving acute inflammation and secondary damage. TNF- α and IL-1 β synergistically amplify inflammation and directly induce apoptosis and synaptopathy [34] [35]. IL-6 plays a particularly unique role; its mediation of “inflammatory aging” after noise damage is closely related to presbycusis pathogenesis (e.g., upregulation of Cav1.3 channels in inner hair cells) [48]. Antagonizing this network (e.g., using IL-6 signal blockers [49] or IL-1 receptor antagonists [50]) effectively reduces hearing loss. In contrast, anti-inflammatory/repair factors represented by Interleukin-10 (IL-10) and Transforming Growth Factor-beta (TGF- β) are responsible for limiting excessive inflammation, promoting repair, and regulating macrophage polarization towards a repair phenotype [51] [52]. The strength and spatiotemporal dynamic balance between pro- and anti-inflammatory signals directly determine whether the injury outcome leads to repair or chronic inflammation/fibrosis.

Precise Navigation and Functional Regulation by Chemokines: Chemokines provide precise navigation for immune cell migration. CCL2 (MCP-1) is the primary signal recruiting monocytes/macrophages. The function of the CX3CL1 (Fractalkine)-CX3CR1 axis is more multifaceted: under homeostasis, it maintains macrophage quiescence and participates in synaptic homeostasis [53]. After injury, glycolytic reprogramming (via LDHA) in stria vascularis endothelial cells can upregulate CX3CL1, subsequently activating CX3CR1+ macrophages and promoting their shift towards a pro-inflammatory phenotype, exacerbating inflammation [54]. The pathological importance of this axis is corroborated in humans: CX3CR1 gene polymorphisms are associated with increased risk of worsened hearing loss after noise exposure [55]. This reveals the critical role of a “metabolism-chemokine-immunity” cross-scale regulatory axis in SNHL.

3.4. Metabolic and Epigenetic Regulation

The functional state of immune cells is not only driven by external signals but also profoundly regulated by their intrinsic metabolic status and epigenetic modifications. These two mechanisms together form the basis of immune cell functional plasticity, providing a new perspective for understanding the cochlear immune microenvironment.

Immune cell activation is accompanied by profound metabolic reprogramming. For instance, pro-inflammatory (M1) macrophages rely on glycolysis for rapid energy supply, whereas a shift towards oxidative phosphorylation is associated with anti-inflammatory, pro-repair (M2) polarization. Research reveals that in noise-induced hearing loss, enhanced glycolysis (mediated by LDHA) in stria vascularis endothelial cells regulates macrophage function via metabolites (e.g., lactate) and

signaling molecules (e.g., CX3CL1), forming a key “metabolism-immune dialogue” [54]. Mitochondrial dysfunction and consequent oxidative stress are not only culprits of cell damage but also key upstream events activating immune signals like the NLRP3 inflammasome [38]. Additionally, increased noise susceptibility due to connexin 30 (Cx30) deficiency is also closely related to cochlear redox and lactate imbalance [56]. Downregulation of core metabolic regulatory pathways like Peroxisome Proliferator-Activated Receptors (PPARs) is involved in the pathological process of noise damage [57]. These findings suggest that targeting specific metabolic pathways may become a new strategy for intervening in SNHL.

Epigenetic mechanisms (e.g., non-coding RNAs, DNA methylation) can persistently alter gene expression patterns, participating in age-related and acquired hearing loss. MicroRNAs (miRNAs) like miR-34a are upregulated during aging and oxidative stress, promoting hair cell death by targeting various protective genes [58] [59]. The role of long non-coding RNAs (lncRNAs) in cochlear development and injury is also emerging [59]. DNA methylation changes have been systematically reviewed as potential contributors to hearing loss, possibly affecting long-term expression patterns of immune- and stress-related genes [60]. Single-cell and transcriptomic technologies (e.g., single-cell transcriptomic atlas [10] and systematic transcriptome analysis [61]) provide systematic evidence, finely revealing changes in the expression profiles of immune-related genes in the cochlea after aging or noise exposure. These studies indicate that epigenetic regulation may “solidify” acute inflammatory responses into chronic inflammation or senescent phenotypes.

In summary, the regulation of the cochlear immune microenvironment is a multi-layered, highly networked dynamic process. From danger signal recognition (e.g., TLRs), to core pathway initiation (e.g., NF- κ B, NLRP3), to precise communication via cytokines/chemokines, all are ultimately shaped by deep-seated cellular metabolic reprogramming and epigenetic modifications. These layers are not isolated but interwoven into complex cascades and feedback networks: e.g., metabolic oxidative stress can activate NLRP3 and NF- κ B, leading to pro-inflammatory factor production and altered chemokine expression, recruiting and reprogramming immune cells; while prolonged inflammatory states may be fixed via epigenetic mechanisms, contributing to “inflammaging.” Therefore, future breakthroughs in therapeutic strategies depend on deciphering this complex network and identifying its key nodes (e.g., CD38, Sestrin2, CX3CR1), subsequently developing precise immune-modulating therapies targeting specific pathways, cell subsets, or intercellular dialogues (e.g., specific inhibitors, cytokine antagonists, metabolic modulators), opening promising new directions for preventing and treating SNHL.

4. Therapeutic Strategies Targeting the Immune Microenvironment and Intervention Research Advances

4.1. Therapeutic Strategies: From Broad-Spectrum Anti-Inflammation to Precise Immune Modulation

Based on an in-depth understanding of the regulatory mechanisms of the cochlear

immune microenvironment, the core objective of intervention strategies is evolving from traditional broad-spectrum anti-inflammation towards precise immune modulation targeting specific cells, pathways, or molecules, aiming to maximize therapeutic efficacy and minimize side effects.

Glucocorticoids: The Cornerstone and Limitations of Broad-Spectrum Anti-Inflammation

Glucocorticoids (e.g., dexamethasone), by broadly inhibiting inflammatory factors and stabilizing vascular barriers, remain first-line drugs for SNHL (especially sudden sensorineural hearing loss). Their protective mechanisms are clear, e.g., directly antagonizing TNF- α -induced hair cell apoptosis [36]. In cochlear implantation (CI), local release of dexamethasone from electrode arrays has been shown to dose-dependently reduce insertion trauma, neurodegeneration, and fibrosis [62]; dexamethasone-eluting implants demonstrate reduced inflammation and foreign body response in both preclinical and clinical studies [63]. However, their “broad-spectrum” nature also constitutes a major limitation. Systemic use has significant side effects and limited inner ear penetration; intratympanic injection improves local concentration but faces issues like uneven distribution, short retention, and perforation risk. A meta-analysis supports the efficacy of intratympanic injection, but optimal protocols remain unstandardized [64]. More critically, systemic versus local administration differentially affects the cochlear perilymph proteome [65], suggesting complex action networks and potential unintended effects. Therefore, developing more precise, controllable local delivery systems is key to optimizing their application.

Specific Targeted Therapies: The Dawn of Precise Intervention

Targeting innate immune sensors: The NLRP3 inflammasome is a core target. Its inhibitors alleviate inflammation and neuronal degeneration in noise- and drug-induced deafness models [38] [66], while the endogenous protein Sestrin2 exerts protective effects in presbycusis by inhibiting NLRP3 [67]. Targeting key inflammatory mediators: TNF- α antagonists (e.g., etanercept) can prevent noise-induced hearing loss by improving microcirculation [68] and show efficacy in cases of autoimmune inner ear disease [69] [70]. IL-6/JAK/STAT pathway inhibitors effectively suppress post-noise inflammation and improve hearing [49], also a potential strategy for mitigating cisplatin ototoxicity [71]. Targeting upstream signaling and metabolic reprogramming: Inhibiting the TLR4/NF- κ B pathway (e.g., a possible mechanism of hyperbaric oxygen [72]) or correcting inflammation triggered by mitochondrial dysfunction [73] represents new intervention ideas from the source. Network pharmacology and multi-omics technologies are accelerating the discovery and validation of more potential targets (e.g., CD38, CX3CR1). Currently, local precise delivery of glucocorticoids and the development of novel specific targeted drugs are two parallel and complementary paths. Future ideal strategies will require precise diagnosis of a patient’s specific etiology (e.g., noise, aging, autoimmune) and the individualized state of their cochlear immune microenvironment, to selectively modulate key nodes (e.g., NLRP3, specific

cytokines, metabolic pathways), thereby achieving a paradigm shift from “inhibiting all inflammation” to “remodeling immune homeostasis.” This will bring truly precise medical breakthroughs to SNHL prevention and treatment.

4.2. Immune Modulation and Repair-Promotion Strategies: From Passive Suppression to Active Remodeling

Moving beyond mere anti-inflammatory suppression, next-generation therapeutic strategies aim to actively intervene and remodel the cochlear immune microenvironment, reprogramming it from a destructive inflammatory state to a repair-conducive state supporting tissue protection and regeneration. This is primarily achieved by functionally regulating key immune cells, leveraging paracrine effects of cells, and developing precise delivery technologies.

Targeting Key Immune Cell Functions

Regulating the phenotype of resident macrophages is a core direction. In noise injury, activated macrophages contribute to hair cell damage [16]. Therefore, promoting their polarization from pro-inflammatory (M1) to anti-inflammatory/repair (M2) phenotype becomes crucial. Studies use molecules like IL-4 or PPAR γ agonists to directly induce M2 polarization. A more targeted strategy involves local delivery of soluble Fractalkine (CX3CL1) peptides, which, by acting on CX3CR1+ macrophages, effectively promotes repair of inner hair cell ribbon synapses after noise damage [74]. This marks a deepening of therapeutic goals from suppressing inflammation to “immune re-education” and specific neuroprotection.

Harnessing Paracrine Effects of Stem Cells for Immune Modulation

The core mechanism of mesenchymal stem cell (MSC) therapy is shifting from “cell replacement” to “cell-free” paracrine regulation. MSCs and their secreted extracellular vesicles (EVs) can actively modulate the immune microenvironment, e.g., inducing macrophage M2 polarization, suppressing excessive inflammation, and providing trophic support. For example, exosomes from umbilical cord-derived MSCs can rescue outer hair cell loss in cisplatin-injected mice [75]; MSCs and EVs carrying Apelin are being explored for treating presbycusis [76]. Genetically modified MSCs can enhance specific functions [77]. This cell-free strategy centered on exosomes overcomes many challenges of cell transplantation, with its fundamental advantage lying in potent immunomodulatory and tissue repair capabilities [78] [79]. However, significant regulatory and manufacturing hurdles remain, including standardization of exosome isolation, characterization, scalable production, and quality control, which must be addressed before clinical translation.

Developing Nanocarriers for Precise Targeted Delivery

The clinical translation of the above strategies highly depends on technologies capable of efficiently and precisely delivering therapeutic molecules (e.g., inducing factors, exosomes, gene editors, specific inhibitors) to cochlear target cells. Nanocarriers play a pivotal role here. They can be used to deliver antioxidants [80], gene therapy vectors [81] [82], and various immunomodulatory drugs.

Through surface functionalization, nanoparticles can achieve targeted delivery to cochlear inflammatory sites or specific cell types (e.g., macrophages), significantly improving efficacy and reducing systemic exposure risks. This enabling technology is key to translating many promising molecules (e.g., NLRP3 inhibitors [37]) into viable therapies. The integration of microfluidics and biosensing further advances the application of theranostics in inner ear diseases [83].

In summary, by targeting cell function, utilizing paracrine regulation, and developing advanced delivery systems, auditory research is moving towards a precision therapy era of “actively remodeling the cochlear immune microenvironment.” However, these strategies still face common challenges regarding targeting efficiency, long-term safety, and clinical translation pathways. Future breakthroughs will depend on finer resolution of the immune microenvironment and deep integration of interdisciplinary technologies in delivery, regulation, and monitoring.

4.3. Immunological Enhancement in Clinical Application: The Example of Cochlear Implantation

Intervention Goal One: Inhibiting Fibrosis and Protecting Residual Hearing

Cochlear implantation (CI) is the ultimate treatment for severe SNHL, but the surgical trauma itself triggers significant cochlear immune inflammation, leading to residual hearing loss, fibrous tissue encapsulation of electrodes, and secondary damage to spiral ganglion neurons, thereby limiting its ultimate efficacy. Therefore, intervening in the post-CI pathological process from an immune microenvironment perspective is key to achieving enhanced efficacy and reduced harm. Post-CI, immune cells like macrophages rapidly aggregate, driving the early foreign body response and fibrosis process [52], which is central to increased electrode impedance, reduced electrical stimulation efficiency, and damage to residual hair cells. In response, local immunomodulation strategies are crucial. Dexamethasone-eluting electrodes have become a benchmark solution, effectively reducing inflammation, fibrosis, and protecting hearing [62] [63]. Future optimization may lie in combination therapies, e.g., co-applying M2 macrophage polarization inducers, targeted anti-fibrotic drugs (delivered via nanocarriers), or stem cell products with immunomodulatory functions, to more precisely remodel the post-operative microenvironment and maximize preservation of low-frequency residual hearing.

Intervention Goal Two: Promoting Neuronal Survival and Optimizing the Neural Interface

The number and health of spiral ganglion neurons directly determine CI speech recognition performance. Therefore, protecting neurons from implantation-related inflammation and aging processes is another key goal. This includes inhibiting neuroinflammation mediated by pathways like the NLRP3 inflammasome [63] and addressing age-related neuronal degeneration. Emerging strategies like Senolytic (senescent cell-clearing) therapy have shown potential in animal models

for delaying age-related hearing loss and improving cochlear aging phenotypes [84]. In the context of cochlear implantation, Senolytic therapy could be envisioned as a pre-implantation strategy to rejuvenate the cochlear microenvironment in older patients, or as a post-implantation adjunct to mitigate inflammation and cellular senescence triggered by surgical trauma. Furthermore, through gene therapy (e.g., VEGFA165 gene therapy improving BLB function [85]) or combined delivery of neurotrophic factors and immunomodulators, the aim is to create a local microenvironment supporting neuronal survival and regeneration, thereby enhancing long-term rehabilitation outcomes for CI recipients.

Immune Modulation—The Thread Throughout SNHL Treatment Evolution

Throughout this review, strategies targeting the cochlear immune microenvironment are undergoing profound evolution: from broad-spectrum anti-inflammation (e.g., systemic steroids) to local precise modulation (e.g., CI drug-elution), to active repair/remodeling (e.g., stem cells, immune re-education). The immunological “enhancement” of CI, a mature therapy, is a vivid embodiment and clinical testing ground of this evolutionary trajectory. Future breakthroughs rely on: First, utilizing single-cell omics to dissect the heterogeneity of cochlear immune responses across different etiologies, disease stages, and individuals. Second, developing sequential, combinatorial personalized intervention regimens. Third, promoting clinical translation of enabling technologies like nanodelivery and gene editing. Ultimately, through precise immune modulation, we may not only treat hearing loss but also protect and repair inner ear function, ushering in a new era for SNHL prevention and treatment.

5. Challenges and Future Perspectives

5.1 Core Challenges

Despite significant progress in cochlear immunology research, its complexity and uniqueness pose multiple challenges, hindering in-depth mechanistic understanding and clinical translation of therapies.

Spatiotemporal Heterogeneity and Dynamic Plasticity of Immune Cells.

Cochlear immune cells, especially macrophages, exhibit distinct phenotypes and functions across different regions and pathological phases. Their highly plastic phenotypes (e.g., M1/M2) are precisely and dynamically regulated by the local microenvironment [12] [15]. Single-cell studies have revealed novel subsets (e.g., CD74+CD14+ macrophages) [86], but their origin, function, and regulatory networks remain a “black box.” How to analyze their evolutionary trajectories and interactions with auditory cells at high spatiotemporal resolution is key to understanding the “double-edged sword” nature of immunity.

Complex Regulation and Monitoring Difficulties of the BLB. The BLB is the gatekeeper controlling immune infiltration [8] [23], but the dynamic patterns of its permeability, fine regulatory molecules, and role in chronic inflammation remain unclear. Current research methods, such as contrast-enhanced magnetic resonance imaging (MRI) and tracer studies in animal models, provide some in-

sights but are limited in resolution and clinical applicability. The lack of non-invasive, real-time technologies to monitor human BLB function, coupled with species differences between animal models and humans, severely impedes related research and clinical translation [24].

The Translational Gap from Animal Models to Clinical Application. Immune responses in rodent cochleae differ from humans [20] [22]. Most immunomodulatory strategies effective in animals (e.g., specific inhibitors, stem cell therapies) face bottlenecks like low inner ear targeting efficiency and unknown long-term safety, making clinical translation challenging [78] [79] [87].

Insufficient Integration of Multi-Etiology Mechanisms. SNHL has diverse causes, yet current research often focuses on single models, lacking comparative integration of immune response characteristics and commonalities across etiologies. Aging (inflammaging) as a common background and how it synergizes with specific injuries to exacerbate immune dysregulation urgently requires systematic elucidation [18] [58].

5.2. Future Directions

Addressing these challenges requires interdisciplinary integration and innovation in technological methods, pushing research from phenomenological description to mechanistic understanding and precise intervention.

Direction 1: Developing Cross-Scale Integrative Studies to Map High-Resolution Spatiotemporal Cochlear Immune Atlases. To fully address the spatiotemporal heterogeneity and dynamic plasticity, future research must move beyond single-modality approaches. The integration of multi-omics technologies is paramount. This involves combining single-cell and *spatial* transcriptomics [25] to not only identify cell subsets but also map their precise anatomical locations and neighborhood interactions within the complex cochlear architecture. Coupling this with proteomic analyses of cochlear fluids (perilymph) and tissues will provide crucial information on the actual effector proteins and post-translational modifications driving immune responses [14]. Furthermore, metabolomic profiling can reveal the real-time metabolic states of immune and auditory cells, linking pathways like glycolysis or oxidative phosphorylation directly to functional phenotypes (e.g., M1 vs. M2 macrophages) [14]. Building upon foundational single-cell atlases [10], the synergistic analysis of these layered datasets through advanced bioinformatics will enable the construction of comprehensive, high-resolution spatiotemporal atlases of the cochlear immune microenvironment across different etiologies and disease stages. Such atlases will precisely define novel cell states, decipher their activation trajectories and intercellular communication networks (e.g., neuron-glia-immune dialogue via ligand-receptor pairing analysis) [14] [25], and ultimately identify the key molecular switches that drive the critical transition from harmful inflammation to productive repair.

Direction 2: Innovating Precise Targeted Delivery Technologies to Bridge the Translational Gap. To overcome delivery and translation hurdles, vigorous

development of nanocarriers, biomaterials, and novel gene delivery systems (e.g., adeno-associated virus, AAV) [80] [82] [87] is essential. The goal is to develop intelligent delivery platforms capable of targeting specific cochlear cells or regions, such as nanoparticles responsive to inflammatory signals for spatiotemporally specific delivery of NLRP3 inhibitors [37], pro-repair factors (e.g., IL-4), or protective genes (e.g., Sestrin2). Integration with microfluidics and biosensing enables theranostics [83].

Direction 3: Exploring Novel Strategies for Immune Reprogramming and Synergistic Repair. To move beyond mere suppression, future therapies should focus on actively remodeling the immune microenvironment. This includes: using soluble CX3CL1 peptides to modulate neuron-macrophage dialogue for synaptic repair [74]; applying cell-free agents like mesenchymal stem cell exosomes (MSC-EVs) for multi-target synergistic modulation [75] [78]; exploring Senolytics to delay cochlear “inflammaging” in the context of aging [84]. For CI, combining immunomodulation strategies with local sustained-release technologies can synergistically protect residual hearing and neurons [52].

Direction 4: Promoting Biomarker Discovery and Personalized Medical Practice. To achieve precision medicine, systematic screening of immune-related proteins, metabolites, or nucleic acids in cochlear perilymph as biomarkers is first needed [67], for early diagnosis and immune phenotyping. Building on this, studying the association between human immune gene polymorphisms (e.g., CX3CR1 [55]) and hearing loss susceptibility/treatment response can provide genetic bases for patient risk stratification. Ultimately, combining individual biomarker profiles and genetic features could guide the selection of personalized treatment strategies, e.g., precise intervention targeting specific inflammatory pathways (e.g., choosing TNF- α antagonists [69] [70]).

In conclusion, cochlear immune microenvironment research is at a critical turning point from “cognitive understanding” to “precise modulation.” Overcoming current challenges and seizing future directions require integrating immunology, neuroscience, bioengineering, and clinical medicine to map the human cochlear immune landscape, innovate spatiotemporally precise intervention tools, and ultimately develop personalized treatment strategies based on biomarkers and immune phenotyping. This represents not only an academic breakthrough but also offers new hope for millions of SNHL patients, moving from “delaying decline” to “promoting repair.”

5.3. Key Research Questions to Bridge the Translational Gap

To effectively translate the promising concept of cochlear immune modulation into clinical reality, future research must prioritize answering several pivotal questions:

Human Translation: What are the definitive similarities and differences between the rodent and human cochlear immune microenvironments across different etiologies of SNHL? Can we develop reliable human *in vitro* models (e.g., us-

ing perilymph biomarkers, organoids) or non-invasive imaging techniques to validate preclinical findings?

Spatiotemporal Dynamics: What are the exact temporal sequences and spatial distributions of immune cell activation, phenotype switching, and communication events that define the transition from acute, reparative inflammation to chronic, destructive inflammation in the cochlea?

Precision Targeting: How can we design delivery systems that not only cross the BLB but also selectively target specific cell populations (e.g., pro-inflammatory macrophages, senescent cells, specific glial subtypes) within the cochlea with high efficiency and minimal off-target effects?

Personalized Immunology: Can we identify a panel of biomarkers (genetic, proteomic, metabolic) from accessible biofluids that accurately reflect the individual's cochlear immune status, enabling etiology-specific diagnosis and tailored immunomodulatory therapy?

Synergistic Repair: How can we best combine immunomodulatory strategies (e.g., NLRP3 inhibition, macrophage reprogramming) with regenerative approaches (e.g., neurotrophic factor delivery, hair cell regeneration cues) to not only halt degeneration but also actively promote structural and functional repair of the inner ear?

Addressing these questions requires sustained interdisciplinary collaboration. By leveraging cutting-edge technologies in omics, imaging, bioengineering, and data science, the field can overcome current challenges and usher in a new era of precision medicine for SNHL, moving decisively from merely delaying hearing decline to actively promoting inner ear repair.

6. Conclusions

This review demonstrates that the cochlear immune microenvironment is a core regulatory unit in the pathogenesis and development of sensorineural hearing loss. This system is highly dynamic and multilayered. It encompasses diverse cell types including resident immune cells (e.g., macrophages), peripherally infiltrating immune cells, and glial cells, along with complex cytokine networks, signaling pathways (e.g., NF- κ B, NLRP3 inflammasome), and structural elements like the blood-labyrinth barrier (BLB), collectively forming a “neuro-immune-vascular” interactive network. In SNHL induced by various etiologies, this microenvironment exhibits significant spatiotemporal heterogeneity and functional plasticity, capable of driving inflammatory damage while also holding potential for promoting repair and homeostasis restoration. Therefore, in-depth analysis of the dynamic regulatory mechanisms of the cochlear immune microenvironment is not only key to understanding SNHL pathology but also provides a crucial theoretical basis for developing targeted therapeutic strategies. Current therapeutic approaches are undergoing a fundamental shift from traditional “broad-spectrum anti-inflammation” to “precise immune modulation.” While traditional anti-inflammatory drugs like glucocorticoids have some efficacy, their non-specific ac-

tions and local delivery challenges limit their clinical prospects. Future therapeutic directions should focus on targeted modulation of specific immune cell functions (e.g., macrophage phenotype polarization), intervention at key signaling nodes (e.g., NLRP3 inflammasome, CX3CR1/CX3CL1 axis), or using cell-free agents like stem cell exosomes to actively remodel the immune microenvironment. Combining these with clinical scenarios like cochlear implantation for immunological enhancement further highlights the potential of precise immune modulation in improving therapeutic outcomes, protecting residual hearing, and promoting neural repair. Achieving a paradigm upgrade from “inhibiting inflammation” to “rebuilding immune homeostasis” will be the core breakthrough point for next-generation SNHL treatment strategies.

Furthermore, incorporating an understanding of sex-specific immune modulation, as influenced by hormonal milieus, will be crucial for developing truly personalized therapeutic regimens. Advancing this field requires interdisciplinary collaboration and deep integration of new technologies. Cutting-edge technologies such as single-cell and spatial transcriptomics, *in vivo* imaging, nanocarrier-based targeted delivery systems, microfluidics, and biosensing provide unprecedented tools for mapping high-resolution spatiotemporal cochlear immune atlases, deciphering intercellular communication networks, and achieving precise drug delivery and real-time monitoring. Simultaneously, multi-omics studies integrating systems biology and clinical samples hold promise for discovering biomarkers for early diagnosis and phenotyping, propelling personalized medicine practice. Only through synergistic innovation across immunology, neuroscience, bioengineering, and clinical medicine can we overcome the core challenges in mechanistic understanding, delivery technology, and clinical translation. As outlined in Section 5.3, addressing five pivotal translational questions—human translation, spatiotemporal dynamics, precision targeting, personalized immunology, and synergistic repair—will be paramount. By systematically pursuing answers to these questions with cutting-edge interdisciplinary approaches, we can ultimately achieve the paradigm shift from “delaying hearing decline” to “promoting inner ear repair,” bringing new therapeutic hope to hundreds of millions of SNHL patients worldwide.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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