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REVIEW

Cochlear Inflammatory Microenvironment in Age-Related Hearing Loss: Mechanisms and Recent Advances

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Abstract: Age-related hearing loss (ARHL) is a common sensory disorder in older adults and a major public health concern that reduces quality of life and social functioning. Traditionally, ARHL has been associated with hair cell apoptosis, strial degeneration, spiral ganglion neuron loss, oxidative stress, and mitochondrial dysfunction. Recent studies suggest that dysregulation of the cochlear inflammatory microenvironment also contributes to its onset and progression. During aging, impaired immune regulation, weakened antioxidant defenses, blood-labyrinth barrier dysfunction, and persistent pro-inflammatory signaling disturb cochlear homeostasis and promote pathological remodeling, leading to injury of hair cells, synapses, and auditory neurons. In addition, systemic chronic low-grade inflammation, metabolic disturbances, and vascular dysfunction may further worsen cochlear inflammation. This review summarizes the structural basis, maladaptive remodeling, functional consequences, and potential therapeutic strategies of the cochlear inflammatory microenvironment in ARHL.

Keywords: age-related hearing loss, presbycusis, cochlear inflammation, inflammaging, oxidative stress

Introduction

ARHL is one of the most common sensory disorders in older adults and a major cause of communication difficulties and reduced quality of life.[1] Its prevalence increases with age and is associated with cognitive decline, depression, and dementia.[2–4] Although ARHL has traditionally been viewed as a consequence of cochlear degeneration, increasing evidence suggests that its development is influenced by multiple factors, including noise exposure, metabolic abnormalities, cardiovascular dysfunction, unhealthy lifestyles, and genetic susceptibility.[5,6] Many of these factors are closely linked to chronic low-grade inflammation, oxidative stress, microcirculatory dysfunction, and immune imbalance, suggesting that disruption of the cochlear inflammatory microenvironment may contribute importantly to auditory decline.[7] Recent studies further indicate that aging-related inflammatory remodeling of the cochlea, characterized by altered macrophage activity, persistent upregulation of pro-inflammatory mediators, and inflammasome activation, can disturb local homeostasis and accelerate hair cell and synaptic injury.[8–10] Emerging evidence from systemic inflammatory markers, multi-omics analyses, and population-based studies, together with the therapeutic promise of immunomodulatory approaches such as exosome-mediated M2 macrophage polarization, further highlights the importance of the cochlear inflammatory microenvironment in ARHL.[11,12] This review summarizes its cellular basis, molecular networks, and potential therapeutic strategies.

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Structural and Homeostatic Basis of the Cochlear Inflammatory Microenvironment

Structural Basis of the Cochlear Inflammatory Microenvironment

The cochlear inflammatory microenvironment is not defined by a single immune component, but by a local regulatory network composed of resident immune cells, the blood-labyrinth barrier (BLB), and cochlear cells including hair cells, supporting cells, spiral ganglion neurons, and lateral wall cells.[13–16] Under physiological conditions, these components interact to support immune surveillance, barrier integrity, molecular exchange, and intercellular communication, thereby maintaining cochlear homeostasis.[17] The cochlear inflammatory microenvironment therefore represents an integrated local system that links immune defense, barrier protection, and cellular homeostasis.[15–17]

Mechanisms Maintaining Homeostasis

Under physiological conditions, the cochlear inflammatory microenvironment is not completely quiescent, but remains in a low-activity and tightly regulated state that supports tissue homeostasis.[18,19] This balance is maintained in part by resident immune cells, particularly macrophages, which remain under physiological surveillance rather than persistent activation.[20] At the same time, the blood-labyrinth barrier preserves immune isolation and molecular selectivity, thereby limiting excessive inflammatory infiltration and maintaining the stability of the cochlear milieu.[21,22] In parallel, antioxidant buffering systems help prevent reactive oxygen species (ROS) accumulation and restrain ROS-triggered inflammatory amplification, while supporting cells and lateral wall structures contribute to ionic and metabolic homeostasis.[23] Together, these coordinated mechanisms allow the cochlea to preserve local immune balance and functional stability; once disrupted, the inflammatory microenvironment may shift from physiological defense toward pathological remodeling.[20–23]

Relationship Between the Cochlear Inflammatory Microenvironment and Age-Related Hearing Loss

Aging-Driven Remodeling of the Cochlear Inflammatory Microenvironment

Aging weakens immune regulation, antioxidant defense, and vascular support, shifting the cochlear microenvironment from a low-activity, tightly controlled state toward persistent pro-inflammatory remodeling.[24,25] Early changes are often reflected in disruption of the BLB and lateral wall homeostasis.[26] Chronic low-grade inflammation, metabolic dysfunction, and oxidative stress can increase BLB permeability, impair tight junction integrity, and reduce microvascular support, thereby facilitating the effects of circulating inflammatory mediators on the cochlea.[27,28] In parallel, key molecules involved in ion transport, energy metabolism, and homeostatic maintenance are downregulated in the spiral ligament, stria vascularis, and lateral wall.[29] These alterations further weaken the capacity of the cochlea to preserve the endocochlear potential, ionic homeostasis, and local metabolic stability.[30] These findings suggest that the BLB is not only essential for cochlear homeostasis, but also serves as a critical interface through which systemic inflammation influences the local cochlear inflammatory microenvironment.[31,32] As this homeostatic foundation deteriorates, the stress-response threshold of multiple cochlear cell types is altered. Resident macrophages become more readily activated and tend to shift toward a pro-inflammatory phenotype, whereas supporting cells and lateral wall-associated cells show reduced capacity for barrier maintenance and metabolic support. Meanwhile, sensory and neural cells become increasingly vulnerable to persistent inflammatory and oxidative injury. Thus, aging does not induce isolated cellular abnormalities, but rather drives coordinated remodeling of the cochlear microenvironment involving immune, barrier, metabolic, and neurosensory components.[24,25] (Figure 1)

At the molecular level, this process is better understood as a coordinated inflammatory cascade centered on oxidative stress rather than as simple parallel activation of multiple pathways.[28,30] Declining Nrf2/Keap1 activity reduces ROS clearance, and accumulated ROS in turn activates NF-κB (nuclear factor kappa B) and MAPK signaling, promoting the expression of pro-inflammatory mediators such as IL-6, TNF-α, and IL-1β. ROS also facilitates NLRP3 (NOD-like receptor family pyrin domain containing 3) inflammasome assembly and caspase-1 activation, leading to the maturation

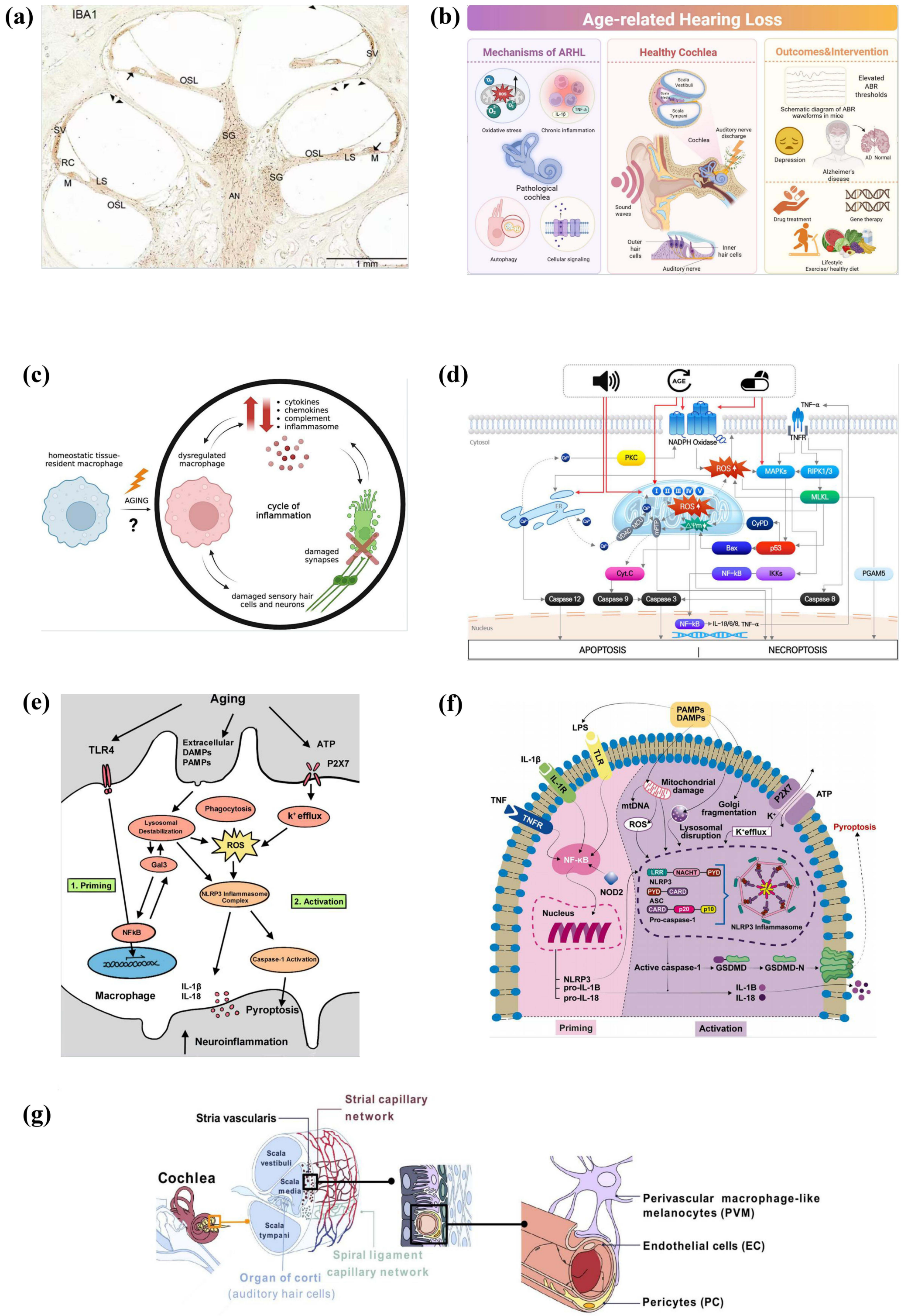

Figure 1 Structural basis and major pathogenic mechanisms of the cochlear inflammatory microenvironment in ARHL. This composite figure summarizes the structural basis and representative pathogenic mechanisms of the cochlear inflammatory microenvironment in ARHL. (**a**) Representative cochlear histology showing the major anatomical structures of the cochlea. Arrows and arrowheads indicate the labeled regions highlighted in the image.[27] (**b**) Schematic overview of ARHL, including age-related cochlear alterations and their representative functional consequences.[31] (**c**) Proposed inflammatory cycle linking macrophage dysregulation, inflammatory mediator release, and progressive injury to hair cells, synapses, and auditory neurons.[30] (**d**) Oxidative stress- and inflammation-related signaling pathways involved in cochlear degeneration.[28] (**e** and **f**) Schematic models illustrating the priming and activation of the NLRP3 inflammasome in response to aging-related stress and inflammatory stimulation.[27,32] (**g**) Structural organization of the BLB, including endothelial cells, pericytes, and perivascular macrophage-like melanocytes.[33]

Abbreviations: AN, auditory nerve; OSL, osseous spiral lamina; SG, spiral ganglion; SV, stria vascularis; LS, lateral sulcus; RC, root cell region; M, basilar membrane; IBA1, ionized calcium-binding adapter molecule 1, a marker of macrophages.

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and release of IL-1β and IL-18.[32] In addition, NF-κB upregulates NLRP3 and related precursor molecules, thereby priming inflammasome activation, while persistently elevated inflammatory cytokines further stimulate JAK/STAT signaling and amplify inflammatory transcriptional responses.[33] Together, ROS accumulation, cytokine release, and immune cell activation form a self-reinforcing positive feedback loop that progressively aggravates the cochlear inflammatory microenvironment. (Figure 2)

Impact of Inflammatory Microenvironment Remodeling on Cochlear Structure and Function

A persistent pro-inflammatory microenvironment ultimately leads to progressive structural and functional damage in the cochlea.[34] Chronic inflammation and mitochondrial dysfunction may reinforce each other, promoting excessive ROS accumulation, calcium dyshomeostasis, and endoplasmic reticulum stress, which may in turn activate programmed cell death pathways, such as apoptosis and pyroptosis, thereby compromising sensory epithelial integrity and accelerating hair cell injury.[35,36] At the same time, impaired lateral wall homeostasis, disrupted ion recycling, and insufficient metabolic support further weaken the cochlea's capacity to buffer and repair injury.[37,38] Beyond the sensory epithelium, inflammatory remodeling also affects the synaptic-neural unit. Ribbon synapse damage, persistent oxidative stress, and pro-inflammatory stimulation together promote spiral ganglion neuron degeneration, contributing to hidden hearing loss and worsening neural deficits.[39] In parallel, injury to the stria vascularis and the associated microvascular system may

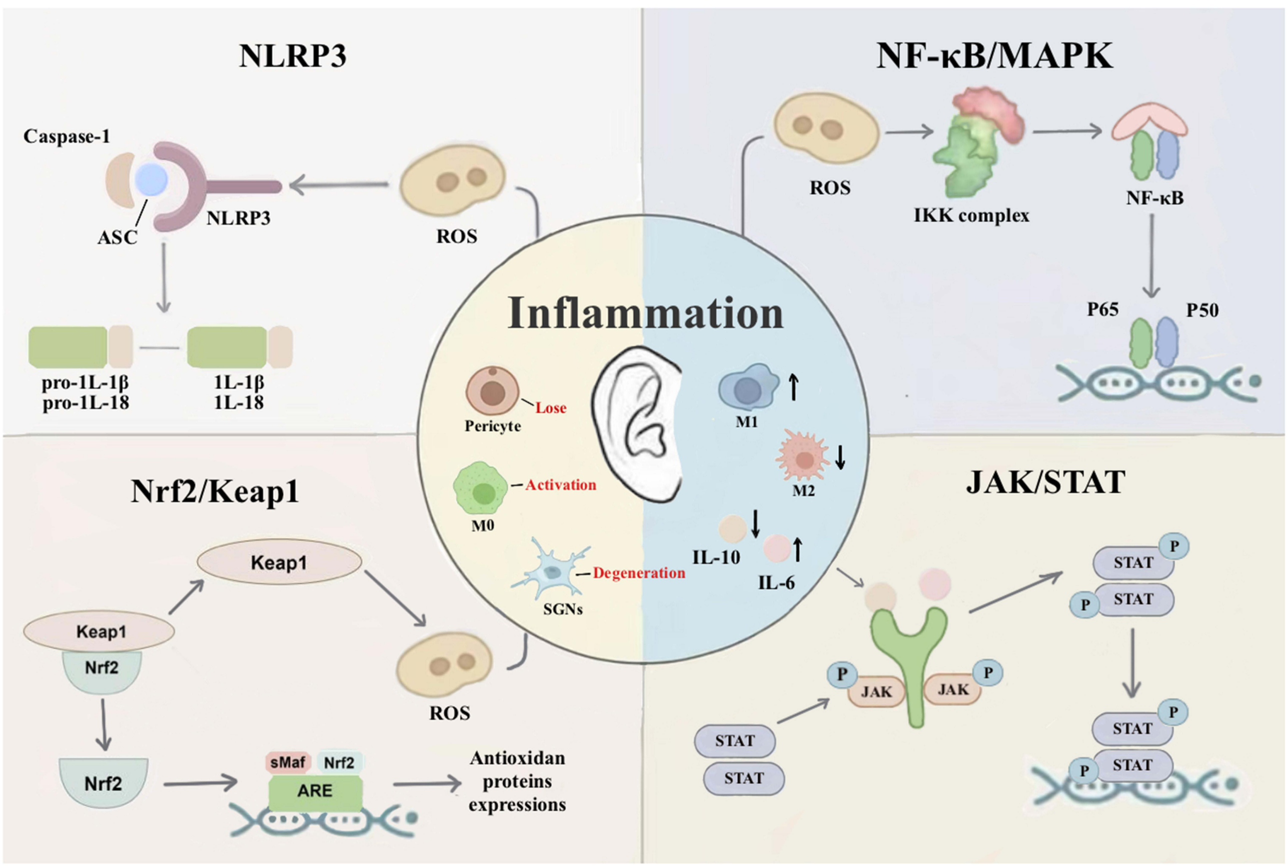

Figure 2 Crosstalk among oxidative stress, inflammatory signaling pathways, and cellular responses in the cochlear inflammatory microenvironment during aging. This schematic illustrates the interplay among oxidative stress, inflammatory signaling pathways, and cellular responses in the aging cochlea. Reduced Nrf2/Keap1 activity weakens antioxidant defense and promotes ROS accumulation. Excess ROS activates NF-κB/MAPK signaling, facilitates NLRP3 inflammasome activation, and amplifies downstream inflammatory responses. Persistent inflammatory signaling may further engage the JAK/STAT pathway, forming a self-reinforcing inflammatory network. These changes are associated with pericyte loss, macrophage polarization imbalance, increased IL-6, reduced IL-10, and degeneration of spiral ganglion neurons, thereby contributing to disruption of cochlear homeostasis and progression of ARHL. Upward and downward arrows indicate relative increase and decrease only for IL-6 and IL-10, respectively; all other arrows indicate general pathway flow or interaction and have no additional specific meaning.

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reduce local perfusion, impair oxygen supply and ion transport, and ultimately decrease the endocochlear potential, thereby exacerbating auditory dysfunction. Overall, inflammatory activation, oxidative stress, metabolic imbalance, and microcirculatory disturbance are not isolated events, but rather interconnected processes that jointly drive ARHL progression across the sensory epithelium, synapses, neurons, and vascular-related structures.[40]

Importantly, cochlear inflammation does not occur in isolation. Aging-related systemic inflammation and metabolic dysfunction may further amplify local injury through BLB impairment and microcirculatory dysfunction.[41] This also suggests that systemic interventions targeting inflammatory burden, metabolic homeostasis, and vascular function may help delay ARHL progression by indirectly improving the local cochlear microenvironment.[42]

Therapeutic Strategies Targeting the Cochlear Inflammatory Microenvironment

Pharmacological Therapy and Targeting of Inflammatory Pathways

Pharmacological strategies are an important means of modulating the cochlear inflammatory microenvironment, primarily by suppressing pro-inflammatory signaling, reducing oxidative stress, and limiting inflammatory amplification.[43] Current evidence suggests that inhibition of NF-κB, MAPK, and the NLRP3 inflammasome, or enhancement of Nrf2/Keap1-mediated antioxidant defense, can reduce the release of inflammatory mediators and the accumulation of ROS, thereby alleviating persistent cochlear inflammatory injury.[44] These strategies aim to restore the balance between pro-inflammatory and antioxidant signaling at the molecular level, providing a basis for subsequent cellular and tissue protection.[44,45] Representative pharmacological candidates include anti-inflammatory agents such as NSAIDs and glucocorticoids, which have demonstrated anti-inflammatory potential in preclinical studies.[46,47] Nevertheless, their specific therapeutic value in ARHL has not yet been clearly established.[48] (Figure 3)

Regulation of the Immune Microenvironment and Cellular Protection

Beyond direct inhibition of inflammatory pathways, restoration of local immune homeostasis and enhancement of cellular protection represent important therapeutic directions.[49,50] During aging, resident immune cells are more prone to persistent activation and maintenance of a pro-inflammatory state, whereas the capacities of supporting cells, lateral wall-associated cells, and the neurosensory unit to maintain homeostasis and repair injury gradually

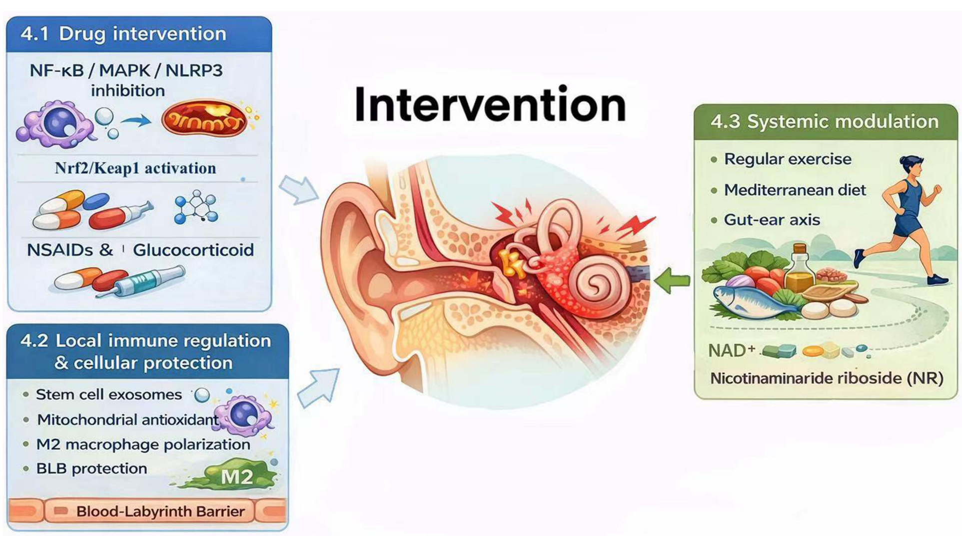

Figure 3 Potential intervention strategies targeting the cochlear inflammatory microenvironment in age-related hearing loss. This figure summarizes potential therapeutic strategies targeting the cochlear inflammatory microenvironment in ARHL. These approaches include pharmacological modulation of pro-inflammatory and antioxidant pathways, local immune regulation and cellular protection, and systemic interventions that may indirectly alleviate cochlear inflammation by improving inflammatory, metabolic, and vascular status. Together, these strategies aim to restore microenvironmental balance and reduce cochlear inflammatory injury. In this schematic, the arrows from the three panels toward the center indicate that all three categories represent potential intervention approaches for ARHL; differences in arrow color are used only for visual separation and do not imply distinct mechanistic meanings.

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decline, together promoting cochlear degeneration.[51] Therefore, strategies aimed at regulating immune cell function, restoring local microenvironmental homeostasis, and enhancing tissue protection may help reduce injury to hair cells, supporting cells, and spiral ganglion neurons.[52] Several emerging approaches, including stem cell exosome-based therapy, mitochondrial antioxidant support, macrophage polarization, and preservation of blood-labyrinth barrier integrity, are supported mainly by preclinical evidence, and their clinical applicability in ARHL remains uncertain.[53,54]

Systemic Inflammation Control and Integrated Interventions

Beyond local pharmacological treatment and immune microenvironment modulation, systemic regulation of inflammation and metabolism may also help improve the cochlear inflammatory microenvironment.[55,56] Aging-related chronic low-grade inflammation, metabolic dysfunction, and vascular decline can further amplify cochlear inflammation by impairing blood-labyrinth barrier stability, cochlear microcirculation, and local immune homeostasis.[57] Reducing systemic inflammatory burden and improving metabolic and vascular status may therefore provide indirect protection against local cochlear injury.[56] Recent studies suggest that long-term nicotinamide riboside supplementation may delay hearing loss progression in aged mice, possibly by increasing NAD+ levels, improving mitochondrial function, and reducing oxidative stress and chronic inflammation.[58] In addition, regular physical activity, the Mediterranean diet, and modulation of the gut–inner ear axis have attracted growing interest as potential systemic interventions.[59,60] Although these approaches may indirectly benefit the cochlear inflammatory microenvironment by alleviating chronic inflammation and metabolic dysfunction, evidence specific to ARHL is still insufficient, and their clinical relevance remains to be clarified.[61]

Future Directions and Challenges

Current evidence indicates that, despite growing interest in the cochlear inflammatory microenvironment, precise intervention for ARHL still faces several major challenges.[62,63] First, there is a lack of real-time, sensitive, and reproducible methods for dynamic monitoring of cochlear inflammation, barrier integrity, and metabolic status.[64] Current imaging techniques, including MRI, 3D-FLAIR, and DCE-MRI, can help assess blood-labyrinth barrier permeability and local fluid changes, but remain limited in spatial resolution and early detection of inflammatory alterations.[65] Future efforts may integrate circulating inflammatory biomarkers, multi-omics profiling, and imaging evaluation to establish more effective strategies for early screening and stratification of ARHL.[66] Second, most current interventions still target a single pathway or isolated process, making it difficult to address the complex coexistence of barrier dysfunction, oxidative stress, immune imbalance, and cellular degeneration within the cochlear inflammatory microenvironment.[67] Future studies should therefore further clarify its layered features and dynamic evolution, while promoting the development of targeted delivery systems, nanomedicine-based approaches, and combination therapies to improve local treatment efficacy and translational potential.[68]

Conclusion

Overall, the cochlear inflammatory microenvironment is closely involved throughout the onset and progression of ARHL and contributes substantially to degenerative injury of hair cells, synapses, and auditory neurons. With the accumulation of immunosenescence and chronic low-grade inflammation, pro-inflammatory signaling in the cochlea becomes persistently enhanced, whereas antioxidant defense and barrier protection gradually decline, driving the microenvironment from physiological homeostasis toward pathological remodeling. In recent years, a range of anti-inflammatory, antioxidant, and immunomodulatory strategies have shown potential to delay auditory aging in experimental studies, including inhibition of pro-inflammatory pathways such as NF-κB and the NLRP3 inflammasome, enhancement of Nrf2/Keap1-mediated antioxidant defense, and exosome-based modulation of local immune status. Further clarification of the layered features and dynamic changes of the cochlear inflammatory microenvironment, together with advances in precise monitoring, targeted delivery, and combination interventions, may provide a stronger foundation for the early prevention and treatment of ARHL.

Abbreviations

ARHL, age-related hearing loss; BLB, blood-labyrinth barrier; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor family pyrin domain containing 3; ROS, reactive oxygen species.

Disclosure

The authors report no conflicts of interest in this work.

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