Targeting inflammation to prevent and treat sensorineural hearing loss

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To the Editor: Sensorineural hearing loss (SNHL) is the most prevalent form of hearing loss. The pathogenesis of SNHL remains elusive, resulting in a lack of definitive and effective treatments for most SNHL types. There is substantial evidence that inflammation significantly contributes to SNHL progression. Various injurious agents damage tissues and cells, prompting macrophages to identify these agents and necrotic material and produce inflammatory mediators. Inflammatory mediators are transported to the cochlea through the bloodstream, where they activate resident macrophages and stimulate monocyte infiltration, thereby initiating cochlear inflammation. Inflammation triggers various pathological alterations within the cochlea, primarily characterized by diminished hair cells and synapses, reduced spiral neuron numbers, and compromised blood–labyrinth barrier (BLB) integrity [Supplementary Figure 1, http://links.lww.com/CM9/C342].[1] Thus, exploring the role of inflammation in SNHL provides distinct insights for its treatment.

Pathways of inflammation in SNHL research: Inflammation is a complex process regulated by multiple signaling pathways and cytokines [Supplementary Table 1, http://links.lww.com/CM9/C342]. The mitogen-activated protein kinase (MAPK) pathways are pivotal in cellular signaling and gene expression, transducing various extracellular stimuli into diverse intracellular responses, including apoptosis, inflammation, and differentiation. The classical MAPK pathways include extracellular signal-regulated protein kinase (ERK), c-Jun N-terminal kinase (JNK), and p38.

Toll-like receptor 4 (TLR-4) is a pattern-recognition receptor (PRR) responsible for recognizing and binding to pathogen-associated molecular patterns, such as lipopolysaccharides (LPS) or damage-associated molecular patterns (DAMPs), such as heat-shock proteins (HSPs), subsequently initiating downstream signaling pathways, such as nuclear factor-κB (NF-κB), which in turn promotes the production of proinflammatory molecules. Aside from its role in producing proinflammatory factors, the TLR pathway regulates the antigen-presenting function of macrophages.

NOD-like receptor (NLR) also serves as a PRR, initiating inflammasome assembly and regulating its composition. The NLR family pyrin domain-containing 3 (NLRP3) inflammasome processes interleukin (IL)-1 and IL-18 into their mature forms via caspase-1 activation, resulting in full activation of the downstream inflammation.

Sirtuins (SIRTs) are a group of nicotinamide adenine dinucleotide (NAD) dependent enzymes that function as deacetylases or adenosine diphosphate (ADP)-ribosyl transferases. SIRT1 is predominantly located in the nucleus, while SIRT3 is in mitochondria. Poly (ADP-ribose) polymerase (PARP)-1 is activated in response to DNA damage, facilitating DNA repair through the breakdown of NAD^+ into nicotinamide and ADP-ribose. Excessive activation of PARP-1 and heightened NAD^+ degradation during injury increase NAD^+ catabolism and lower intracellular NAD^+ levels, leading to a substantial decline in SIRT activity, augmented nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) deacetylation, increased inflammation, and heightened hearing loss. Restoring SIRT1 and SIRT3 expression and activity can reduce the level of inflammation and exhibit a protective effect on hearing by raising cellular NAD^+ levels.

NF-κB broadly refers to inducible dimeric transcription factors comprising various NF-κB/Rel family members. It can be activated by diverse stimuli, such as

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proinflammatory cytokines, LPS, viruses, and both physical and chemical stressors, inducing the expression of an extensive array of proteins such as cytokines, adhesion molecules, acute-phase response proteins, complements, and receptors. NF-κB also plays a pivotal role in antiviral responses induced by interferon genes.

According to the available literature, the PARP–SIRT pathway primarily contributes to age-related hearing loss (ARHL) and noise-induced hearing loss (NIHL), while the NLRP3 pathway is predominantly investigated in the pathogenesis of SNHL in patients with cryopyrin-associated periodic syndromes (CAPS, a kind of hereditary hearing loss [HHL]). In addition, the MAPK and TLR-4 pathways are implicated in various aspects of SNHL development. NF-κB acts as a central hub, coordinating multiple pathways that regulate cochlear inflammation and immune responses [Supplementary Figure 2, http://links.lww.com/CM9/C342].

Diverse etiologies and inflammatory processes: Based on etiology, SNHL can be classified into age-related, noise-induced, viral, hereditary, and drug-induced hearing loss [Supplementary Figure 3, http://links.lww.com/CM9/C342]. ARHL is the most prevalent type of SNHL. Aging contributes to a reduction in immune system functionality and diminishes the body's capacity to regulate inflammation, resulting in increased levels of proinflammatory cytokines and decreased levels of anti-inflammatory cytokines. This imbalance facilitates chronic inflammation during tissue aging, ultimately culminating in the deterioration of tissue structure and the emergence of functional disorders.[2]

NIHL is the most prevalent form of SNHL after ARHL. Exposure to noise initially sparks an acute inflammatory reaction in the cochlea, with early proinflammatory mediator expression playing a critical role. Given that there are few clinical studies on the pathogenesis of NIHL, and most animal studies include models of acute acoustic injury from brief exposure to intense noise, there is a notable gap in understanding the cochlear inflammation in individuals exposed to prolonged noise and its progression.

It has consistently been shown that inflammation is evident in patients with some kinds of HHL, linking certain gene alterations to inflammatory processes [Supplementary Table 2, http://links.lww.com/CM9/C342]. Specifically, mutations in the collagen 4 (COL4) gene lead to Alport syndrome (AS), marked by progressive renal failure and hearing loss. In AS, cochlear damage stems from the thickening of the capillary basement membrane, especially in the stria vascular. The levels of inflammatory markers, including transcription factors, cytokines, chemokines, and chemokine receptors, were increased in AS mice compared to wild-type mice.

Inflammation increases the absorption of ototoxic drugs by the cochlea. It also causes capillary dilation and increased permeability of the BLB, enhancing ototoxic drug transport across the BLB, and upregulates the expression of transport channels for these drugs (e.g., transient receptor potential vanilloid 1 [TRPV1] channel) on hair cells. In addition, certain ototoxic drugs (e.g., cisplatin) can elicit inflammation by directly stimulating cytokine release or inducing cytokine synthesis.

Congenital cytomegalovirus (cCMV) infection is a leading cause of hearing loss among children globally. cCMV infection triggers an inflammatory reaction that compromises the integrity of BLB, promoting hematogenous dissemination of the virus to the cochlea. The development of hearing loss is promoted by direct cellular damage to the cochlea and the immune response to CMV.

Medications and techniques targeting inflammation: A number of drugs and techniques have been developed to mitigate SNHL through the inhibition of inflammation. The mechanism of action of current anti-inflammatory drugs for SNHL treatment is multifaceted and can be summarized as follows: (1) Regulation of inflammatory cytokine expression: This involves reducing the expression of proinflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor-α (TNF-α) while concurrently enhancing the expression of anti-inflammatory cytokines such as IL-10. (2) Inhibition of inflammatory signaling pathways: These drugs intervene in various cellular signaling pathways to block critical steps in the inflammatory response. (3) Regulation of enzyme activities: The formation of inflammatory mediators such as prostaglandins is diminished by inhibiting the activity of cyclooxygenase-2 (COX-2). (4) Indirect reduction of intracellular inflammation: This is achieved through various pathways, e.g., activation of the reduction of oxidative stress and the protection of mitochondria and the increase in heat shock response. A detailed classification of these drugs and their anti-inflammatory mechanisms is provided in Supplementary Table 3, http://links.lww.com/CM9/C342.

Among the drugs outlined, only glucocorticoids (GC) are widely used in treating SNHL and are recommended by guidelines for sudden SNHL. Several drugs are currently tested in clinical trials (e.g., anakinra, canakinumab, resveratrol) and have demonstrated hearing improvement in multiple studies. Other drugs remain in the basic research phase but have shown promising results in inflammation suppression and hearing protection at the animal level in various types of SNHL. Overall, anti-inflammatory drugs exhibit significant potential in the treatment of SNHL.

In addition to the drugs themselves, drug delivery technologies have undergone rich and diverse developments. Numerous techniques have been devised and implemented to address the issue of low drug concentrations reaching the inner ear after systemic administration across the BLB. Intratympanic injections of GC are widely utilized for patients with contraindications to systemic GC or those experiencing incomplete recovery following initial treatment. Conversely, round window injections are primarily employed in gene therapy and remain in the clinical trial phase.[3] Nanomaterials have emerged as a current research focus within the field of drug delivery. It has been shown that nanomaterials loaded with anti-inflammatory drugs, when administered via the round window or tympanic cavity, can significantly enhance drug concentrations in the inner ear and subsequently improve hearing. Although

these nanomaterials are not yet used in clinical practice, ongoing advancements in technology and pharmaceutical research are expected to refine their ability to load and release drugs more precisely, thereby offering safer and more effective anti-inflammatory treatments. Furthermore, research suggests that direct administration of drugs to specific acupuncture points may effectively alleviate hearing issues in the inner ear. Given that many of the anti-inflammatory drugs discussed are derived from herbal extracts, this exploration not only provides valuable insights for enhancing the treatment efficacy of SNHL but also reinforces the discovery of traditional Chinese medicine remedies and therapeutic approaches.

Challenges and future prospects: The cochlea is intricately structured, housing cells that are functionally distinct. Research on SNHL related to inflammation has primarily concentrated on hair cells, with relatively less attention given to fibroblasts, marginal cells, and spiral ganglion neurons. Research on other cells, such as supporting cells, is even more scarce. A detailed examination of the interactions, functions, and roles of these cell types in the inflammatory process is crucial for advancing our understanding and treatment of SNHL. Future studies should encompass more cell types, aiming to comprehensively decipher the pathogenesis of SNHL and identify viable therapeutic strategies.

The challenge of acquiring clinical cochlea specimens has historically impeded precise inflammation measurement in living human cochlea, consequently obstructing the validation of findings from animal studies. Recent research suggests that assessing cochlea inflammation is feasible by measuring cytokine levels in perilymph fluid[4] and analyzing cochlea macrophages through high-resolution imaging.[5] These advancements appear promising in addressing the previously mentioned challenges. Nevertheless, the clinical utility of these novel methods necessitates thorough investigations into their sensitivity and specificity. Moreover, the development and application of additional innovative techniques are essential for a more comprehensive assessment of cochlea inflammation and its pathological manifestations.

Although anti-inflammatory drugs have shown considerable potential in treating SNHL, our understanding of their anti-inflammatory mechanisms is still relatively limited. Most research to date has focused on assessing the impact of these drugs on inflammatory markers, with insufficient exploration of their specific underlying mechanisms. Particularly at the molecular level, there is scant knowledge as to how these drugs modulate the inflammatory response and protect hearing via specific molecular pathways. Consequently, future research should concentrate on elucidating the molecular actions of these drugs to develop more precise and effective treatments for SNHL. Such efforts will enhance our comprehension of drug functionality within biological systems and could unveil novel therapeutic targets, thereby propelling forward the research on treatments for SNHL.

Despite significant advances in drug delivery technologies for the inner ear, several challenges persist. These include potential trauma from procedural manipulations, limited drug residence time within the inner ear, uneven drug distribution, and the sluggish pace of technological translation. The introduction of nanotechnology represents a pivotal shift in the inner-ear drug delivery, offering enhanced precision in drug localization and release control. This technology enables the direct delivery of highly concentrated drugs to targeted areas within the ear. Future efforts in SNHL therapy will likely focus on further refining these nanotechnologies. Such advancements aim to achieve more precise control over drug release and prolonged effects, thereby reducing the frequency of administration and enhancing the safety and effectiveness of treatments.

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Conflicts of interest

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