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Review

Advances in the Study of NOD–Like Receptors in Common Otological Diseases

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Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are integral components of the cytoplasmic pattern recognition receptors (PRRs) family, playing a crucial role in both innate immunity and inflammatory responses. Nucleotide-binding oligomerization domain–like receptors detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), activating multiple signaling pathways, including nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK), and triggering immune responses through inflammasome activation. The NLR family contains 5 distinguishable subfamily classifications. The development and progression of multiple ear-related disorders depend significantly on NOD1, NOD2, NLRP3, and NLRX1, among other specific members of the NLR family. The analysis investigates NLRs' interactions with ear pathologies, particularly focusing on NLRP3 functions in the development of otitis media along with its effect on cholesteatoma formation and hearing loss. In addition, this review evaluates targeted therapeutic strategies derived from NLRs research by developing a theoretical foundation that suggests new ways for advancing treatments for otological diseases.

KEYWORDS: Cholesteatoma, hearing loss, NOD-like receptors, NLRP3, otitis media

INTRODUCTION

Otological diseases such as otitis media, cholesteatoma, and hearing loss affect human health on a global scale. Their pathogenesis is often multifactorial. The scientific community agrees that disease development involves fundamental roles of both immune components and inflammatory mechanisms, although researchers have yet to determine their exact underlying causes. Pattern recognition receptors (PRRs) within cells, specifically nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs), have become major research subjects because these receptors direct innate immune and inflammatory responses. The innate pathogen pattern recognition system consists of NLRs, along with retinoic acid-inducible gene I-like receptors (RLRs), Toll-like receptors (TLRs), and C-type lectin receptors.[1] The immune response modulation through these receptors occurs when they detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).[2] Presently, scientists have noted 22 unique families of NLR proteins within human biological systems, primarily operating in dendritic cells, lymphocytes, neutrophils, monocytes, and macrophages. A recent study found the nod-like receptor (NLR) family pyrin domain-containing protein-3 (NLRP3) expression in macrophages in the resident tissue of the cochlea, and the role of NLR in otological diseases is attracting increasing attention.[3] Additionally, numerous studies show that NLRs serve as fundamental players in biological processes, including cell metabolism recognition, presentation of antigens, embryonic guidance, inflammatory regulation, cell death management, and adaptive immunity regulation.[4-6] Research investigations in NLRs have steadily grown in multiple scientific spheres, encompassing tumors, allergic diseases, and immune and inflammatory diseases.[6,7] This article examines the NLR family's involvement in otological disorders, focusing on NLRP3 inflammasome activation and its critical impact on disease progression. The study of NLRs' immunomodulatory functions in ear disorders allows researchers to create new targeted treatment methods for such conditions. This study did not involve human participants or animal subjects; therefore, ethics approval and informed consent were not required.

OVERVIEW OF NOD-LIKE RECEPTORS

Nod-like receptors function as cytoplasmic PRRs that belong to a specific group of cellular receptors. The typical structural characteristics of family members in this group include several conserved functional domains as the main components.[8] The NOD functions as a central fundamental structure with nucleotidease activity while being known as a nucleotide-binding oligomerization

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(NACHT) domain. It can promote the oligomerization of the NLR molecule by binding and hydrolyzing nucleotides. The C-terminal leucine-rich repeat (LRR) section in NLR proteins acts as the main component for pathogen detection together with immune system regulation functions. The effector domain in Nucleotide-binding oligomerization domain–like receptors proteins includes a combination of acidic transactivation domain (AD), baculovirus inhibitor repeat (BIR), and death effector domain, and caspase recruitment domain (CARD) and pyrin domain (PYD) as their main components.[9] Nucleotide-binding oligomerization domain–like receptors subfamilies comprise of 5 distinct classes based on their effector domains which include NLRA(NOD-like receptor subfamily A, acidic domain–containing), NLRB (subfamily B, BIR-containing), NLRC (subfamily C, CARD-containing), NLRP (pyrin domain-containing subfamily), and NLRX (subfamily X, lacking N-terminal domain homology) (Figure 1). The N-terminal part of NLRA possesses a CARD and also contains an AD. The N-terminal region remains controllable by different post-translational modifications, including acetylation, phosphorylation, and ubiquitination. The N-terminal domain of NLRB, which contains 3 BIRs, plays a role in host protection and cellular survival functions. The N-terminal of NLRC features either a single CARD domain or 2 CARD-like domains, while NOD1 (NLRC1) and NOD2 (NLRC2), together with NLRC3, NLRC4, and NLRC5, serve as the proteins associated with NLRC. NLRP includes an effector domain that contains the pyrin domain (PYD) while its related proteins are designated as NLRP1 through NLRP14. In some members, such as NLRP1, special structures such as the FIIND domain (function-to-find domain, a self-cleaving domain essential for inflammasome activation) are also found to further regulate the immune response. The NLRX subfamily is unique in that it includes just a single member, NLRX1, which stands apart from the other 4 subfamilies due to its lack of notable homology in the N-terminal domains. Interestingly, the N-terminal sequence of NLRX1 facilitates the targeting of the protein to the outer mitochondrial membrane.[4]

The activation of the downstream signaling pathways of NLRs is fundamental in regulating inflammatory responses and innate immunity. It can activate multiple downstream signal transduction pathways, such as NF-κB signal transduction, MAPK signal transduction, and inflammatory body activation.[10] In NF-κB signal transduction, NLRs recognize PAMPs or DAMPs, further activating the IKK (IκB kinase) complex, which in turn promotes the phosphorylation and degradation of the IκB protein, ultimately leading to the transfer of the NF-κB dimer from the cytoplasm to the nucleus and the initiation of transcription of inflammation-related genes.[11] The MAPK signaling pathway plays a crucial role in governing various cellular activities, including proliferation, differentiation, and apoptosis, primarily by activating kinases like ERK, JNK (c-Jun N-terminal kinase), and p38.[12] Inflammasomes were first discovered in 2002.[13] They are cytoplasmic multiprotein complexes consisting of sensor proteins, adaptor proteins, and effector enzymes that aggregate in host cells in response to PAMPs or different types of stress. They undergo a series of processes to release cytokines in their active form into the extracellular space, ultimately promoting inflammatory responses, inflammatory body assembly, activation of the NF-κB pathway, and transcriptional activity.[2] NOD1, NOD2, and NLRP3 are among the NLRs that function as genuine PRRs and trigger pro-inflammatory responses. The structure and function of these 3 types of molecules will be described in detail below.

MAIN POINTS

- Nucleotide-binding oligomerization domain-(NOD)–like receptors are key regulators of inflammatory processes and host defense mechanisms.
- NOD1 and NOD2 pathways play significant roles in the progression of otitis media and cholesteatoma.
- Excessive NLRP3 activation contributes to chronic inflammation and tissue damage.
- Inhibitors of IL-1β, NLRP3, NOD1, and NOD2 show promise in treating inflammation-related ear conditions.
- NLRP3 activation is involved in various ear diseases, such as otitis media, cholesteatoma, and hearing loss.

NOD1 and NOD2

NOD1 and NOD2, the first recognized members of the intracellular PRR NLR family, are crucial for the innate immune response.[6] The CARD domains in NLR proteins allow signaling cascade progression, with NOD1 having 1 domain and NOD2 containing 2 domains, reflecting their different functional characteristics. NOD1 functions as a vital immune defense component. It can precisely recognize the gram-negative bacterial cell wall peptide γ-D-glutamyl-meso-diaminopimelic acid (iE-DAP). The exact recognition power of NOD1 gives this protein its specialized ability to fight infections of gram-negative bacteria while playing a vital role in defending the body against such pathogens.[14] The activation mechanism of NOD2 depends solely on muramyl dipeptide (MDP), which can be found in all peptidoglycans that exist within the cell walls of both gram-positive and gram-negative bacteria. This broad specificity enables NOD2 to detect a diverse array of bacterial species, positioning it as a key player in the body's general defense mechanism against bacterial invasions. NOD1 and NOD2 will oligomerize when they detect matched ligand molecules iE-DAP or MDP. Their oligomerization is a key step in signal transduction. The CARD domains within NOD1 and NOD2 function by bringing the receptor-interacting serine-threonine kinase 2 (RIPK2, also called RIP2 or RICK) adaptor protein into signaling pathways, which eventually activate IKK and transforming growth factor-β (TGF-β) activated kinase 1 (TAK1) downstream. Nuclear translocation of NF-κB and complex release occurs via the IKK complex, while TAK1 initiates the MAPK signaling network. These 2 signaling routes work in unison to promote higher expression of pro-inflammatory genes that include tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) and many others. This process kickstarts and intensifies the host's antimicrobial immune response, aiding in the elimination of invading pathogens and the promotion of overall health. The optimal function of immune balance depends on exact regulation of the NOD1 and NOD2 signaling pathways because improper pathway activation or mis-regulation initiates inflammatory diseases (Figure 2).

NLRP3

One of the most important exemplars of the NLR protein group is NLRP3. The structure of this protein contains an N-terminal PYD, a central NACHT domain, and a C-terminal LRR domain. The NLRP3 protein associates with itself to construct a large macromolecular structure by interacting with apoptosis-associated speck-like protein (ASC), which also contains a CARD and procaspase-1 cysteine protease. In fact, this complicated assembly is commonly known as

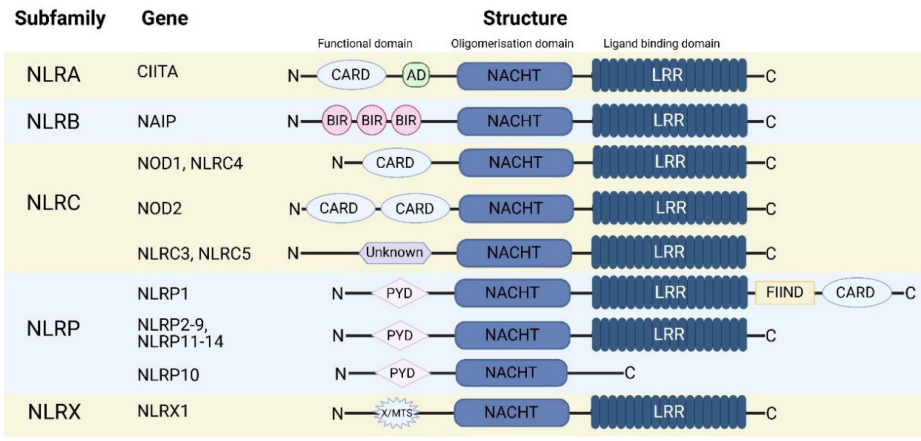

Figure 1. Structures of nod-like receptor subfamilies.

the NLRP3 inflammasome. There are 2 stages in the activation process of the canonical NLRP3 inflammasomes: initiation and activation.[15] In the first phase, activation of NLRP3 depends on the PRRs, which recognize PAMPs or DAMPs; this leads to elevated NLRP3 and pro-IL-1β mRNA and protein levels, mediated by NF-κB or alternative transcription factors. The second phase involves identifying NLRP3 using various PAMPs and DAMPs. These triggers initiate a chain of cellular responses, such as the outflow of potassium ions, destruction of mitochondrial function, release of reactive oxygen species, release of mitochondrial DNA, lysosome bursting, and more.[16] These ultimately give rise to the assembly and activation of NLRP3 inflammasomes. In addition, NEK7 is also activated and serves as a key regulatory factor in the activation of the NLRP3 inflammasome. It promotes the aggregation of NLRP3 and the formation of the inflammasome by binding to the LRR domain of NLRP3. At the same time, NEK7 has been found to be associated with cellular responses such as potassium efflux, mitochondrial dysfunction, reactive oxygen species generation, and lysosomal rupture.[17] The PYD domain of NLRP3 is essential for recruiting the ASC adaptor protein upon NLRP3 inflammasome activation and for the formation of the NLRP3 inflammasome complex. This complex then facilitates the cleavage of inactive procaspase-1, transforming it into its active form, caspase-1. Once its family member caspase-1 is activated and initiates the inflammatory cascade, it cleaves pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18. At the same time, the activated caspase-1 cleaves the C-terminal end of gasdermin D (GSDMD), the pyroptosis protein, breaking its N-terminal portion. This piece of GSDMD-N is then free and moves to the cell membrane, binding with lipids like cardiolipin, effectively creating holes in the membrane. These holes are usually 10-14 nm in diameter, large enough to release cytokines (IL-1β, IL-18)

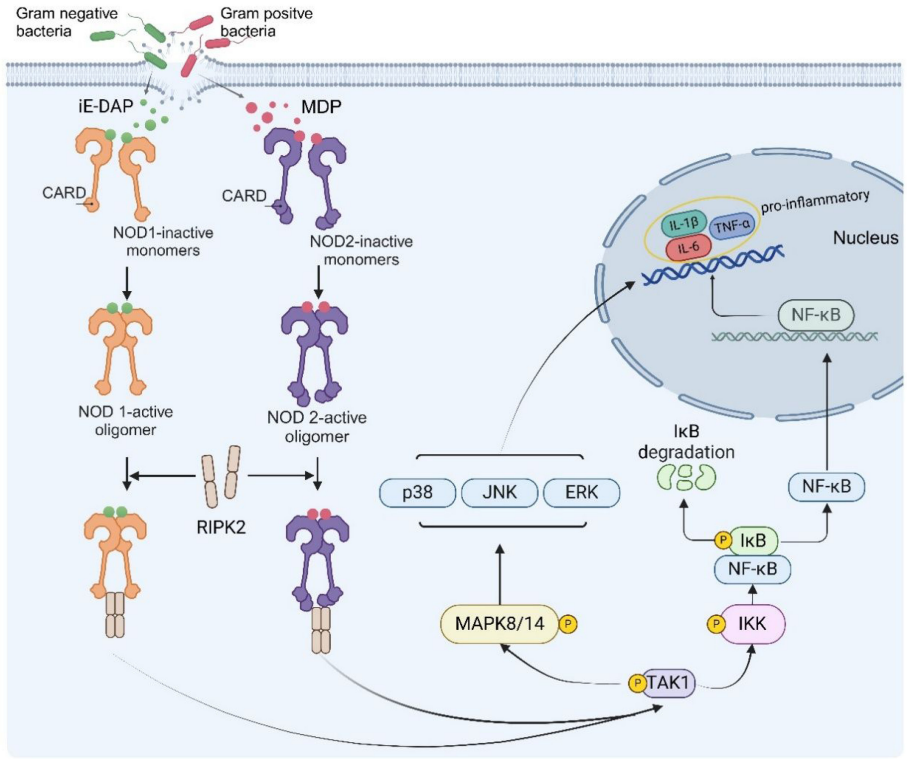

Figure 2. NOD1 and NOD2 signaling pathway.

from the cell to the outside. As the holes in the membrane expand, normal cell permeability is impaired, and more intracellular water enters the cell, leading to increased cell volume. This expansion can cause damage to the cell membrane and finally lead to cell lysis. Following cell lysis, mature inflammatory mediators like IL-1β and IL-18 are discharged into the extracellular environment, prompting nearby cells to heighten their inflammatory responses and boosting the immune system's vigilance against pathogens. While these cytokines play a crucial role in initiating a robust immune response and are fundamental to the body's defense mechanisms, excessive activation can lead to chronic inflammation and potential tissue damage[18] (Figure 3).

NOD-LIKE RECEPTOR AND EAR DISEASES

Nod-Like Receptor and Otitis Media

Otitis media, often just called OM, is a catch-all term for a spectrum of middle ear infections and inflammatory conditions. This encompasses everything from the sudden onset of acute otitis media to otitis media with effusion (OME). Additionally, diseases such as chronic suppurative otitis media are included, which are associated with symptoms like ear discharge and/or perforation. Multiple researchers agree that different factors contribute to the development of these conditions, although specific causes remain unclear. Bacterial or viral infections, allergic responses, Eustachian tube dysfunction, and middle ear physiological, immune, and pathological conditions are considered contributing factors. Both genetic and environmental factors contribute significantly to the development of this condition.[19]

Pathologists understand OM through the chronic inflammatory reaction, as both the innate and adaptive immune systems work together to produce this pattern. The immune system activation, together with the inflammatory regulatory mechanism of the host, represents the most important factors that lead to chronic otitis media pathogenesis.[20] The investigation of Kim et al[21] revealed that patients with recurrent OME experienced declining NOD1 and NOD2 expression levels, which supports the potential involvement of the NOD pathway in OME development. Other research findings revealed increased NOD2 expression levels in the middle ear mucosa of patients with chronic otitis media.[22] Lee et al[23] discovered that NOD1 and NOD2 mutation-carrier mice were more vulnerable to non-typeable *Haemophilus influenzae* infection compared to C57BL/6 wild-type mice, resulting in persistent middle ear inflammation. Specifically, the middle ear inflammatory responses of NOD1-deficient mice progressed differently from NOD2-deficient mice, with both exhibiting delayed neutrophil-mediated inflammation, while NOD1-deficient mice had slower bacterial clearance.[23] Data obtained from NOD receptor-deficient mice showed delayed bacterial clearance and reduced immune cell infiltration in the middle ear as the main outcome. These findings collectively demonstrate the NOD pathway's significance in otitis media development and progression. It was also found that in OME model rats, NLRP3 inflammasomes mediate the immune response through the NF-κB signaling pathway, thereby promoting the production of IL-6 and CXCL1 (chemokines for neutrophil migration and infiltration, which are associated with inflammatory responses), and the application of IL-6 inhibitors significantly reduced the production of these inflammatory factors.[24] This result affirms NLRP3's pivotal regulatory influence in the pathology of OM. In summary, the impact of innate immune signals in the host's defensive response is obvious. It can therefore be inferred that IL-6 inhibitors and NLRP3 inhibitors have great therapeutic potential for reducing the inflammatory response

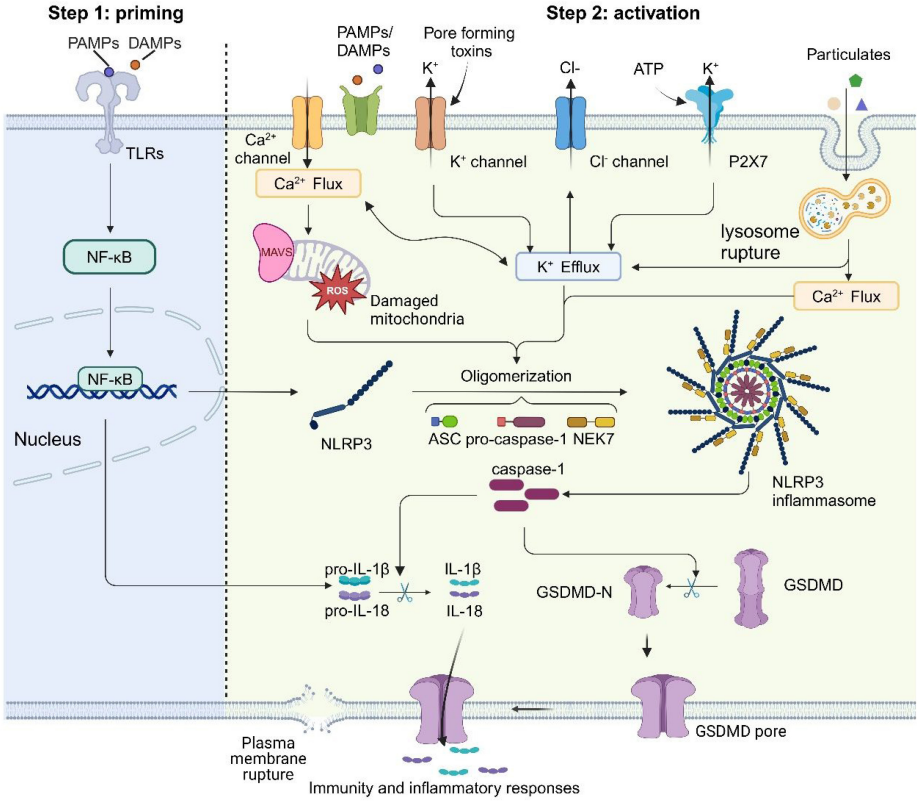

Figure 3. Mechanisms of NLRP3 inflammasome activation.

associated with OM, but this finding still needs to be verified in large-scale clinical trials.

NLR and Cholesteatoma

Cholesteatoma is a cystic non-tumor lesion of the temporal bone. It is destructive in nature and is usually considered to be the end-stage manifestation of chronic ear infections.[25] The continued growth of this lesion can lead to a series of serious complications, such as the destruction of the temporal bone structure, hearing loss, vertigo, facial nerve palsy, and intracranial infection. Currently, surgical removal is the only treatment option, but the risk of recurrence in patients after surgery is still high, up to 61%.[26] Therefore, exploring new treatment strategies has become a key issue that needs to be urgently addressed.

While various immune mechanisms contribute to the pathogenesis of cholesteatoma, the involvement of PRRs remains incompletely understood. Earlier research indicates that the mRNA expression levels of NLRP3, ASC, and caspase-1 in cholesteatoma tissues are markedly elevated compared to healthy control groups.[27] Sangal and colleagues[28] demonstrated that patients suffering from cholesteatoma exhibited a markedly higher incidence of mutations activating the CARD8 gene compared to healthy control groups. Furthermore, those with mutations in the CARD8 gene experienced greater levels of bone degradation. This finding suggests that the loss of NLRP3 and CARD8 gene polymorphisms that activate inflammasomes may regulate the severity of osteolytic damage caused by cholesteatoma. In addition, numerous studies have demonstrated that NOD2 mRNA and protein expression levels are markedly elevated in cholesteatoma samples compared to skin tissue from the external auditory canal. The evidence indicates that the interplay between NLRs-mediated innate immune signals and their associated target molecules could significantly influence the formation and progression of cholesteatoma.[29] Consequently, modulating inflammation driven by the NOD2 and NLRP3 inflammasome may emerge as a novel approach for addressing cholesteatoma.

NLR and Hearing Loss

Hearing loss has become a public health issue that requires urgent attention. According to statistics, the number of people affected by hearing impairment has exceeded 1.5 billion worldwide.[30] Of all hearing impairments, sensorineural hearing loss (SNHL) is the most common. The World Health Organization forecasts its global incidence surpassing 630 million by 2030.[31] It occurs due to a range of factors that cause damage to the inner ear, including genetics, noise exposure, aging, toxins, and cancer. Recently, inflammation has also been highlighted as a potential factor in the pathogenesis of hearing loss.[32] Research indicates that the inner ear harbors a stable population of macrophages, which, upon activation by tissue damage, play a pivotal role in orchestrating the inflammatory process through the increased production and secretion of pro-inflammatory mediators.[33] Nucleotide-binding oligomerization domain–like receptor inflammasomes, pro-inflammatory multiprotein assemblies, assemble within stimulated macrophages and potentially contribute to SNHL pathogenesis.

Cryopyrin-Associated Periodic Syndromes

The *NLRP3* gene produces the NLRP3 protein, a central element of the NLRP3 inflammasome. A key player in the body's innate immune defenses, the NLRP3 inflammasome plays a pivotal role in triggering caspase-1 activation and orchestrating the release of pro-inflammatory cytokines, specifically IL-1β and IL-18, when faced with microbial invasions or cellular injury. Research indicates it is critical in numerous inflammatory and degenerative conditions. Variations in the *NLRP3* gene are closely related to autoimmune inflammatory diseases of various organs. These illnesses are grouped under the term cryopyrin-associated periodic syndromes (CAPS), encompassing several disorders such as chronic infantile neurological cutaneous and articular syndrome NOMID (neonatal-onset multisystem inflammatory disease), Muckle-Wells syndrome (MWS), and familial cold autoinflammatory syndrome (FCAS). Cryopyrin-associated periodic syndrome is a genetic autoinflammatory disorder resulting from an acquired mutation in the *NLRP3* gene. Hearing loss frequently occurs as a symptom of this condition. Research indicates that hearing loss occurs in roughly 76% of NOMID patients, 86% of those with NOMID/MWS, 33% with MWS, and 25% with FCAS.[34] More recent work hints that, in a specific subset of autoinflammatory conditions (DFNA34), hearing loss might be the only noticeable symptom.[35] Several studies have examined the link between CAPS-induced hearing loss and *NLRP3* gene mutations. Ji-Hyun et al[36] experimentally confirmed that in a transgenic mouse model with NLRP3 mutant (D301N) specifically expressed in CX3CR1-positive macrophages, significant hearing loss was observed after intraperitoneal injection of lipopolysaccharide, and this pathological process could be significantly alleviated by inhibitors of the IL-1 signaling pathway (interleukin-1 receptor antagonist,IL-1Ra) and NLRP3-specific inhibitors (MCC950).[37] In addition, the research team of Yehree successfully constructed the first animal model that showed quantifiable hearing loss in cochlear tissue accompanied by *Nlrp3* overexpression. The researchers created a novel genetically modified mouse model by breeding *Nlrp3*^{D301NneoR} mutant mice with *Gfi1*^{Cre} (growth factor independent transcription inhibitor 1) knock-in mice, which specifically activates the mutated *Nlrp3* gene in cochlear cells and hematopoietic cells. The experimental results showed that the *Nlrp3* gene was significantly overexpressed in this mouse model, and the mice exhibited severe to profound hearing loss at postnatal day 20, while the normal phenotype mice did not show significant hearing loss.[38] This shows that *NLRP3* gene variants associated with CAPS may be an important direct factor in triggering inflammation-related hearing loss in the periphery, and it is hoped that NLRP3 inhibitors can be used to reduce hearing loss.

Noise-Induced Hearing Loss

Noise-induced hearing loss (NIHL), the second leading acquired hearing deficit, results from extended loud sound exposure, inducing sensorineural deafness. It is reported that over 12% of the global population experiences noise-induced hearing loss.[39] The mechanisms behind noise-induced hearing loss involve complex, incompletely understood interactions of various factors. However, an inflammatory response is considered to be one of the key factors leading to NIHL. In their experimental study, Sai et al[40] revealed that the levels of caspase-1 and cleaved NLRP3 mRNA and protein in the cochlea were markedly elevated in the group exposed to noise compared to the control group. Research data indicates the NLRP3 inflammasome pathway serves as a key factor in the protective mechanisms that occur with noise-induced cochlear damage. Studies indicate that mice exposed to noise display heightened expression levels of NLRP3 protein in spiral ganglion neurons as well as inner hair cells and outer hair cells, in comparison to silent condition mice. Given the

evidence, it is pretty clear that NLR inflammasomes are key players in the development of noise-induced hearing loss (NIHL). In addition, the Mizushima team found that compared with control mice exposed to noise, mice in the experimental group that had macrophages and monocytes depleted by injection of liposomes containing clodronic acid and then exposed to noise had less hearing loss.[41] Research activity is highly focused on drug development for the NLR inflammasome pathway because this pathway offers innovative opportunities in preventing and managing NIHL.

Age-Related Hearing Impairment

Age-related hearing Impairment, or presbycusis, describes auditory decline stemming from systemic degeneration during aging. Research indicates that a buildup of reactive oxygen species can initiate NLRP3 inflammasome activation. This activation process may be a major factor in how age-related hearing loss develops.[42] Experimental data reveal that NLRP3 protein, active caspase-1, and interleukins IL-1β and IL-18 are markedly elevated in the inner ear of aged mice compared to younger mice.[43] In addition, Feng et al's[44] in vitro aging model study further verified the close correlation between the activation of NLRP3 inflammasomes and cochlear synaptic damage, and that this process may accelerate the progression of age-related hearing impairment. Aside from NLRP3, it turns out that NLRX1 also plays a significant role in the development of age-related hearing loss. Apparently, NLRX1 kicks off the JNK signaling pathway, which then controls apoptosis, or cellular destruction, in the cochlear hair cells. In a study involving an aged mouse model, increased NLRX1 expression triggered a significant increase in pro-apoptotic markers (namely p-JNK, Bax, and Caspase-3) within the cochlea.[12] Concurrently, the amount of the anti-apoptotic protein Bcl-2 was notably reduced. This imbalance shifted the balance toward apoptosis in cochlear hair cells, ultimately compromising auditory function. Thus, NLRP3 and NLRX1 likely advance presbycusis via distinct pathways.

Vestibular Schwannoma

Moreover, vestibular schwannoma (VS) is the fourth most prevalent intracranial tumor, closely associated with the Schwann cells of the vestibular nerve, and may result in hearing impairment.[45] Research has consistently demonstrated that the activity of 7 key genes linked to inflammasome pathways—*CASP1, PYCARD, IL-18, NLRP3, NAIP, NLRC4,* and *AIM2*—is markedly elevated in VS tumor samples compared to healthy tissue.[46] This upregulation highlights a clear distinction between diseased and normal conditions, underscoring the potential role of these genes in the tumor's inflammatory response. Concurrently, NLRP3 and IL-1β activation in VS tissue was elevated compared to controls with typical auditory function. Based on these findings, it is speculated that blocking the activation of NLRP3 inflammasomes could represent a significant, innovative treatment strategy against VS, notably addressing auditory impairment, moving forward.

In essence, NLRP3 appears to be a pivotal player in the development and progression of numerous conditions, ranging from CAPS to NIHL, ARHL, and even VS. Its involvement highlights its significance in the underlying mechanisms of these diverse pathologies. There may be an association between NLRP3 overexpression and hearing function damage. It is noteworthy that existing pharmacological studies have confirmed that targeting and inhibiting the NLRP3 inflammasome-related signaling pathway (e.g., using drugs such as Oridonin,[47] anti-IL-1β antibodies,[48] and MCC950[37]) can significantly reduce hearing damage caused by inflammatory responses. Therefore, using appropriate interventions to regulate the NLRP3 inflammasome may provide new research directions for the prevention and treatment of deafness.

Nod-Like Receptor and Others

Currently, ear diseases still affect the health of a large proportion of people. As a result, studying their pathological mechanisms thoroughly and refining treatment strategies is essential. In addition to the above diseases, there are some other ear diseases that may be related to NLR. Research on Meniere's disease revealed elevated IL-1β and TNF-α levels in certain patients, suggesting chronic inflammation.[49] In a study using a mouse model with endolymphatic hydrops triggered by lipopolysaccharide, researchers observed that the mice exhibited worsened vestibular issues alongside heightened inflammasome activity. Research showed that inhibiting NLRP3 blocked the development of these symptoms.[47] Furthermore, findings from a study on noise-triggered tinnitus revealed that mice subjected to auditory stress displayed increased levels of TLR4, NLRP3, NF-κB, caspase-1, and IL-1β, suggesting that such stimuli may trigger neuroinflammatory responses in the hippocampus. Evidence suggests that the antidepressant medication lofepramine effectively relieves pain from noise-induced tinnitus symptoms, while other treatments have proven ineffective. By influencing the TLR4/NF-κB/NLRP3/caspase-1/IL-1β signaling pathway, it successfully reduces neuroinflammation associated with this condition, providing significant relief to patients suffering from tinnitus.[50] To put it briefly, the NLR family, with NLRP3 as its primary member, functions as an essential factor driving ear disorder development and progression. Future medical treatments for such conditions may become possible with this new understanding.

CONCLUSION

The developmental processes of ear diseases remain complex, and researchers need further investigation to better understand their mechanisms. Among the studies on the mechanisms of diseases involving NLRs, inflammasomes are the most frequently studied, with NLRP3 inflammasomes demonstrating a pro-inflammatory role. Several studies have provided new molecular target drugs that can be used to reduce pathological inflammation caused by pathogens, which can improve ear symptoms. Specifically, NLRP3 inhibitors and IL-1β antagonists show promise in early detection of minor auditory impairment. Unfortunately, the specific mechanism of NLR in ear disease is not yet fully understood, and these drugs are still in the animal testing stage. Their reliability and safety in humans depend on further clinical research in the future.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: N/A.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.B., B.X.; Design – P.B., B.X.; Supervision – P.B., B.X.; Funding – P.B.; Literature Search –L.Z.; Writing – L.Z.; Critical Review – P.B., B.X.

Declaration of Interests: The authors have no conflicts of interest to declare.

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