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**Noise-induced cochlear inflammation**

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**Abstract**

Hearing loss is the most common sensory disability with considerable social and economic implications. According to recent World Health Organisation estimates, 360 million people worldwide suffer from moderate to profound hearing loss. Exposure to excessive noise is one of the major causes of sensorineural hearing loss, secondary only to age-related hearing loss (presbyacusis). Since cochlear tissues have limited abilities of repair and regeneration, this damage can be irreversible, leading to cochlear dysfunction and permanent hearing loss. Recent studies have shown that cochlear inflammation can be induced by noise exposure and contribute to the overall pathogenesis of cochlear injury and hearing loss. The cochlea is separated from the systemic circulation by the blood-labyrinth barrier, which is physiologically similar to the blood-brain barrier of the central nervous system. Because of this feature, the cochlea was originally considered an immunologically privileged organ. However, this postulate has been challenged by the evidence of an inflammatory response in the cochlea in the presence of bacterial or viral pathogens or antigens that can cause labyrinthitis. Although the main purpose of the inflammatory reaction is to protect against invading pathogens, the inflammatory response can also cause significant bystander injury to the delicate structures of the cochlea. The cochlear inflammatory response is characterised by the generation of proinflammatory mediators (cytokines, chemokines and adhesion molecules), and the recruitment of inflammatory cells (leukocytes). Here, we present an overview of the current research on cochlear inflammation, with particular emphasis on noise-induced cochlear inflammation. We also discuss treatment strategies aimed at the suppression of inflammation, which may potentially lead to mitigation of hearing loss.

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**Key words**: Cochlea; Inflammation; Noise; Hearing loss; Otoprotection

**Core tip**:Noise exposure, either occupational or recreational, is a major cause of sensorineural hearing loss in the industrialised world. Hearing loss is a devastating disability with considerable social and economic implications. Recent studies have demonstrated that an inflammatory response induced in the cochlea by noise exposure may contribute to the development of noise-induced hearing loss. Better understanding of the underlying inflammatory processes will help define pharmacological interventions that can potentially mitigate noise-induced cochlear inflammation and the associated hearing loss.

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**NOISE-INDUCED HEARING LOSS**

The human ear is an exquisitely sensitive organ, allowing us to perceive and distinguish among the myriad sounds around us, be they pleasurable, informative or damaging. Located within the inner ear is the cochlea, the specialised peripheral end organ of the auditory system, which mediates the transduction of sound waves into electrical nerve impulses that travel to the brain for central processing of auditory information. Unfortunately, this extreme sensitivity of the cochlea comes at a cost as it makes it highly susceptible to injury when exposed to loud sound. The consequence of this injury is the loss of hearing, which can be either temporary or permanent. Noise-induced hearing loss may result from either brief exposure to an intense “impulse” noise or sustained and repeated exposure to excessive sound levels (*i.e.,* continued exposure to high levels of noise over an extended period of time). The hearing loss from noise exposure is typically binaural (symmetric), and the severity of it is related to the intensity, frequency, duration and temporal characteristics (*e.g.,* impulse/impact, intermittent or continuous noise) of the noise exposure[1,2].

Excessive noise is the most common occupational and environmental health hazard. Dangerous levels of noise are generated in a large number of workplaces such as construction sites, mines, saw mills, military bases, and airports, among many others. Although usually associated with occupational exposure, noise-induced hearing loss is becoming increasingly prevalent in recreational settings. Many people, especially children and teenagers, voluntarily expose themselves to potentially injurious noise levels via portable music players, stereos, video games, rock concerts, and nightclubs. Other non-occupational sources of loud noise include firearms, power tools such as chain saws and drills, lawn mowers, and recreational vehicles such as motorcycles.

Noise-induced hearing loss is the second most common sensorineural hearing deficit, after age-related hearing loss (presbyacusis), and is the leading cause of preventable sensorineural hearing loss in the industrialised world[3]. According to recent global estimates released by the World Health Organisation (WHO, 2012), there are 360 million people worldwide (over 5% of the world’s population) with disabling hearing loss. Disabling hearing loss, as defined by WHO, is “hearing loss greater than 40 dB in the better hearing ear in adults and a hearing loss greater than 30 dB in the better hearing ear in children”. A significant proportion (16%) of the disabling hearing loss in the adult population in the world is attributed to occupational noise exposure[4]. In the United States, approximately 15% (26 million) of people between 20 to 69 years of age have high frequency hearing loss from overexposure to loud noise at work or during leisure activities. Hearing loss has considerable social and economic implications at both the individual and societal levels. This devastating sensory disability and the serious communication difficulties has a negative impact on the quality of life of the affected individual and can lead to feelings of loneliness, social isolation and depression.

Although it can be permanent and not fully treatable, noise-induced hearing loss is virtually 100 percent preventable. Obviously, the best preventive measure against noise-induced hearing loss is to completely avoid or minimise exposure to excessively noisy environments. When this is not possible, the only preventative measure available is the consistent and proper use of hearing protection devices such as earplugs and earmuffs. When used correctly, these protective devices can provide 20 to 40 dB of attenuation, however their use is often impractical in many settings and they are not completely effective in harsh environments, or because of incorrect use.

Avoiding or reducing modifiable risk factors associated with noise-induced hearing loss such as voluntary exposure to loud noise, non-use of hearing protection, cigarette smoking, lack of exercise, poor diet (low dietary intake of antioxidant-rich food), and poor oral health (tooth loss) may reduce the risk or delay the onset of this debilitating condition[5,6]. The presence of cardiovascular disease and diabetes are also major risk factors. In addition to these, several non-modifiable risk factors related to noise-induced hearing loss exist, particularly age and genetics[5]. Age plays the most significant role, with the risk typically increasing with advancing age. Furthermore, great genetic variability in the susceptibility to noise-induced hearing loss has been documented in both humans and mice[7].

The association between noise exposure and hearing loss was first recognised by the physician Sir Francis Bacon (1561 – 1626)[8]. In 1890, Habermann was the first to describe the cochlear histopathological features of noise-induced hearing loss from examining the temporal bones of an elderly ex-boilermaker[9]. However, it was not until 1907 that Wittmaack conducted the first experimental research of noise-induced deafness in animals[9,10]. Substantial insights into the pathophysiology of noise-induced cochlear injury were gained by Wittmaack’s experiments and the many others that followed, including Hallowell Davis’s systemic studies on guinea pigs and humans at Harvard University in 1943.

The cochlea sustains dramatic cellular injury following noise overexposure. The pathological consequences (pattern and extent) depend on the acoustic characteristics of the noise (*i.e.,* sound intensity, frequency and duration), age and genetics[10]. The two types of hearing loss from noise exposure - temporary and permanent hearing loss (also known as temporary and permanent threshold shift) - also vary in their mechanisms[11]. Noise exposure is known to produce a variety of structural changes to the various cells within the cochlea. The most vulnerable are sensory hair cells, particularly the outer hair cells, which have traditionally been the focus of most hearing loss studies. A major impact is on sensory hair cell stereocilia which can undergo mechanical damage during noise exposure. Other changes include the loss of outer hair cells, damage to the inner hair cell – auditory nerve synapse, swelling of the primary auditory neurones in the spiral ganglion, damage to the supporting cells, acute swelling of the stria vascularis, reduced cochlear blood flow and the loss of fibrocytes in the spiral ligament[2,11-15]. In addition, direct mechanical disruption of the cochlea can be induced by impulse noise exposure, *e.g.,* rupturing of the organ of Corti and its separation from the basilar membrane.

**COCHLEAR INFLAMMATION**

Cochlear inflammation has been implicated as a major etiologic factor in a range of conditions that cause hearing loss. These include acoustic trauma (noise-induced cochlear damage), otitis media (middle ear infection), meningitis, autoimmune inner ear disease, and ototoxicity (drug-induced inner ear damage, *e.g.,* aminoglycoside antibiotics, platinum-based chemotherapeutic agents)[16-23]. Labyrinthitis can also be evoked by cochlear surgery and the insertion of cochlear implants[24,25]. Pathogen-induced labyrinthitis as a consequence of otitis media or meningitis is usually associated with bacterial and viral infections. Labyrinthitis secondary to otitis media (tympanogenic labyrinthitis) primarily occurs by the spread of the infection from the middle ear into the inner ear through the three-layered round window membrane[18,22,26,27]. Meningogenic labyrinthitis most likely occurs by the spread of infection from the meninges into the perilymphatic space of the cochlea through the cochlear aqueduct[19,28,29]. Mycotic (fungal) labyrinthitis is rare, and is usually associated with systemic debilitating diseases and occurs by either the tympanogenic, meningogenic or hematogenic route[30].

Labyrinthitis usually affects the cochlea more severely than the vestibular system, resulting in adverse effects on cochlear function[26]. A well-documented complication of cochlear inflammation is partial or complete sensorineural hearing loss (SNHL). Pathological consequences that have been observed in animal models of cochlear inflammation include degeneration of hair cells of the organ of Corti, disruption of fibrocytes in the spiral ligament, loss of interdental cells of the spiral limbus, swelling of the stria vascularis, and vascular damage[26,31-33]. The disruption of the spiral ligament fibrocytes has been suggested as a major contributor to the inflammation-induced cochlear dysfunction[32,34]. Decreased immunostaining for gap junction protein connexin 26 in type I and type II fibrocytes and decreased Na+-K+-ATPase staining in type II fibrocytes, both of which are critical in the maintenance of cochlear homeostasis, were observed in a guinea pig model of labyrinthitis induced by inoculation of the protein antigen keyhole limpet hemocyanin (KLH) into the scala tympani[35]. In addition, reduced connexin 26 immunostaining in the spiral ligament was also demonstrated in a mouse model of otitis media induced by the transtympanic inoculation of viable *Streptococcus pneumoniae*[36].

Analogous to the central nervous system and the retina of the eye, the cochlea is separated from the systemic circulation by a blood-labyrinth barrier, which has similar physiological characteristics as the blood-brain barrier and the blood-retinal barrier. This barrier is important in maintaining the ionic composition of the cochlear fluid compartments, and is essential for the functional integrity of the cochlea[37]. Because of the existence of this blood-labyrinth barrier and the relative absence of resident tissue macrophages, the inner ear was originally considered an immunologically privileged organ, isolated from the immune system and protected from immune surveillance. However, this hypothesis has been refuted by research demonstrating that the inner ear is capable of rapidly generating an active inflammatory/immune response in the presence of antigens or pathogens. In addition, connections exist between the inner ear and the systemic lymphatic system through cervical lymph nodes[38].

Although the intended purpose of the immune response in the inner ear is to defend the hearing organ against invading pathogens and to clear cellular debris, the inflammatory response can also cause significant bystander injury to the delicate structures of the cochlea[37,39]. Because mammalian inner ear tissues have limited abilities of repair and regeneration (unlike avian auditory hair cells which have the capacity to regenerate), this damage is irreversible, leading to permanent hearing loss. Immune-related cochlear inflammation is increasingly recognised as a potential mechanism of inner ear disease and associated hearing loss. Systemic administration of immunosuppressive drugs (*e.g.,* corticosteroids) has been shown to effectively ameliorate some cases of idiopathic, rapidly progressive bilateral sensorineural hearing loss, implicating inner ear inflammation as an underlying mechanism of the hearing loss[40]. Histopathological studies of human temporal bones also support the hypothesis that a number of otological disorders are linked with inflammatory responses[41]. The severity of hearing impairment and the potential for recovery correlate with the extent of inflammation-induced tissue damage. Animal studies have demonstrated that the development of inflammation and hearing loss following an immunological challenge can be rapid, with the onset of hearing loss occurring at 12 to 15 h, and peaking at 24 to 48 h[42,43].

Regardless of the cause, the cochlear inflammatory response follows a similar course with three characteristic stages: an initial acute stage, a fibrotic stage, and an ossification stage[44]. The acute phase of cochlear inflammation, which lasts approximately 3 to 7 d, is characterised by the production of proinflammatory mediators such as cytokines and chemokines, an increased expression of adhesion molecules, the recruitment and infiltration of inflammatory cells such as polymorphonuclear leukocytes (mostly neutrophils), monocytes, macrophages and lymphocytes, and the breakdown of the blood-labyrinth barrier[31,44]. In the chronic stage of the cochlear inflammatory response, a fibrotic matrix is formed in the perilymphatic spaces, which later becomes calcified. This bony occlusion of the fluid-filled cochlear scalae, known as labyrinthitis ossificans, is most extensive in post-meningitis cases[45].

The cochlea itself can mount an immune response. Resident cells in the cochlea can express a range of inflammatory mediators, which are thought to play critical roles in the inflammatory response[46,47]. The cochlea communicates with the immune system *via* the systemic circulation. Entry of inflammatory cells occurs primarily through the spiral modiolar vein and its tributaries (collecting venules) situated at the base of the scala tympani[48]. Inflammatory cells accumulate in the perivascular space surrounding the spiral modiolar vein, and then stream into the scala tympani along the extravascular space of the collecting venules. Other areas where circulating inflammatory cells enter the cochlea include the blood vessels of the spiral ligament and the spiral ganglion. The lateral wall of the cochlea and the spiral ganglion represent the most permeable parts of the blood-labyrinth barrier, partly due to their high vascularisation[49,50].

The mammalian cochlea contains resident macrophages at normal/steady state[16,25,49,51]. These macrophages are phenotypically similar to the tissue macrophages in other organs of the body (*e.g.,* microglia of the central nervous system) and are found in small numbers predominantly in the spiral ligament and the spiral ganglion. Moreover, it was recently reported that a large number of perivascular resident macrophages (PVMs) are present in the stria vascularis surrounding the endothelial cells of the capillaries[52]. Data from radiation chimeras have shown that these resident macrophages in the cochlea form an exchanging and migratory population, supplied continuously from haematopoietic precursors in the bone marrow, andexhibiting slow turnover during steady-state conditions[25,49,52]. These haematopoietic precursors migrate into the cochlea and differentiate into tissue macrophages. Bromodeoxyuridine (BrdU) labelling has demonstrated that the marked increase in macrophage numbers in the cochlea following an insult such as noise exposure is not due to the proliferation of these resident cochlear macrophages, but rather occurs by the migration of macrophages from the vascular system[16,53].

The signals that initiate the recruitment and infiltration of inflammatory cells into the cochlea are still under scrutiny, and a wide range of soluble mediators (*e.g.,* cytokines, chemokines) may be involved. The sources of proinflammatory mediators in the cochlea include various resident cochlear cells types (*e.g.,* spiral ligament fibrocytes, supporting cells) and infiltrating leukocytes migrating from the cochlear vasculature. *In vitro* studies using cultured murine spiral ligament fibrocytes have shown that upon stimulation with proinflammatory cytokines, fibrocytes secrete a variety of inflammatory mediators such as TNF-α, IL-1β, IL-6, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-2 (MIP-2), keratinocyte-derived chemokine (KC), soluble intercellular adhesion molecule-1 (sICAM-1) and vascular endothelial growth factor (VEGF), which play important roles in the recruitment of inflammatory cells into the cochlea[32,33,47,54]. The secretion of sICAM-1 is compatible with an earlier study that reported strong ICAM-1 expression in the spiral ligament and spiral modiolar vein in the early phase of labyrinthitis induced by the inoculation of KLH into the scala tympani[55]. It is speculated that chemokines produced by the fibrocytes are presented to the surface of vascular endothelial cells via the process of transcytosis, which consequently attracts inflammatory cells. Fibrocytes, vascular endothelial cells, and inflammatory cells together may form networks interconnected by cytokines, chemokines and various other inflammatory mediators[32,47].

It is well documented that inhibition of TNF-α with the soluble TNF-α receptor-FC fusion protein Etanercept, given either systemically or directly into the cochlea, significantly attenuates the cochlear inflammatory response[56]. This suggests that TNF-α plays a major role in the development of cochlear inflammation. Studies on organ of Corti explants have shown that TNF-α alone, in the absence of antigens or pathogens, has the ability to induce the recruitment of inflammatory cells into the cochlea from the systemic circulation[57]. TNF-α is also expressed by infiltrating leukocytes, suggesting that it is likely involved in a positive feedback loop that further amplifies the recruitment of inflammatory cells. This is supported by the evidence that TNF-α inhibition can prevent the recruitment of inflammatory cells into the cochlea[56]. TNF-α can also induce nitric oxide synthesis by stimulating the expression of inducible nitric oxide synthase (iNOS), which can further aggravate inflammation and degeneration in the cochlea[58].

The expression of many proinflammatory mediators is mostly regulated by nuclear factor-kappa B (NF-κB)[23]. NF-κB comprises a family of inducible transcription factors that play a pivotal role in immune and inflammatory responses. Activation of NF-κB induces the transcription of cytokines such as TNF-α, IL-1β and IL-6, as well as iNOS, and the adhesion molecules, ICAM-1 and VCAM-1. NF-κB activation in the cochlea has been demonstrated following intraperitoneal injection of lipopolysaccharide (LPS)[59], suggesting that the cochlea can become immunologically active even after systemic administration of bacterial toxins. Cochlear activation of NF-κB has also been reported to occur following acoustic trauma (see the following section) and in cisplatin-induced ototoxicity[21].

At present, it is technically impossible to positively identify inflammatory processes within the human inner ear. There are no well-defined detection methods available and diagnostic biopsy of the human cochlea is not feasible. To overcome this limitation, high field magnetic resonance imaging (MRI) techniques were recently developed by our group to quantitatively evaluate the development of cochlear inflammatory processes in a guinea pig model induced by the intratympanic injection of LPS[60]. For the first time, dynamic changes in cochlear vascular permeability following cochlear inflammation was quantified using dynamic contrast enhanced (DCE)-MRI and ultrasmall superparamagnetic iron oxide particles (USPIOs) were used to characterise the recruitment of macrophages into the cochlea. These methodologies therefore hold considerable potential as diagnostic tools for human inner ear diseases such as labyrinthitis and could also be used to quantitatively assess the efficacy of treatments for cochlear inflammation.

**NOISE-INDUCED COCHLEAR INFLAMMATION**

Recent years have advanced our understanding of the underlying mechanisms of noise-induced cochlear damage. One of the most compelling hypotheses postulates oxidative stress (the excessive formation of reactive oxygen species or free radicals) in the cochlea as a key mechanism of noise-induced hearing loss[10,14,61]. An increase in reactive oxygen species is also thought to be involved in age-related and drug-induced hearing loss (ototoxicity). Oxidative stress alters the redox balance of the cells, leading to the activation of cell death pathways (apoptosis and necrosis) in the cochlea and hearing loss.

Other studies, however, have implied the intrinsic involvement of inflammation in noise-induced cochlear tissue damage. Early ultrastructural studies in the noise-exposed mammalian cochlea have identified macrophage-like cells in the damaged organ of Corti, mainly in the tunnel of Corti and in the outer hair cell region, appearing five days after acoustic overstimulation[62,63]. These macrophages are likely involved in mopping up cell debris. The presence of transforming monocytes in the area and mononuclear leukocytes within the spiral lamina blood vessels suggested that these dendritic macrophages originated from blood-borne monocytes[63].

Several studies have demonstrated that after acoustic trauma, a large influx of inflammatory cells from the vasculature can be observed in the cochlea, generally peaking between 2 and 7 d after exposure to traumatic noise, and diminishing thereafter[16,17,64-66]. Inflammatory cells within the cochlea were identified immunohistochemically using their cell surface markers CD45, a receptor tyrosine phosphatase present on all hematopoietic/bone marrow-derived leukocytes or F4/80, a marker of activated macrophages and monocytes. The study by Tornabene *et al*[17] showed that CD45-positive cells increased from an average of 0.3 cells/section in the non-exposed cochlea to a maximum of 88 cells/section at 2 and 4 d after noise exposure. These infiltrating cells were localised predominantly in the spiral ligament, particularly in the inferior region among type I and type IV fibrocytes and in the region adjacent to the bony cochlear capsule among type III fibrocytes, and in the perilymph-filled spaces of the scala tympani and scala vestibuli[16,17,64,65]. Leukocytes were also observed within the spiral limbus, another region known to be susceptible to acoustic injury, and in the spiral ganglion[16,64,65]. A few cells were also found in the stria vascularis and the perivascular spaces of the modiolus[17,67]. This recruitment of macrophages to the cochlea following excessive stimuli is similar to what occurs in other sensory organs, such as the retina of the eye. Thus, exposure to damaging light causes an infiltration of inflammatory cells to the light-damaged region of the retina[68].

BrdU labelling has demonstrated that these inflammatory cells migrate from the vasculature, and it appears that most of these cells enter the cochlea through the blood vessels of the lateral wall[16]. The lateral wall is highly vascularised, and the spiral ligament is the site where the large majority of inflammatory cells can be found. Immunostaining with other monocyte/macrophage markers (CD68, CX3CR1, Iba-1) demonstrated that the vast majority of these infiltrating cells are derived from the monocyte/macrophage lineage, with a small number representing other leukocytes such as T and B lymphocytes[16,25]. Hirose *et al*[16] coined the term “cochlear macrophage” for those inflammatory cells, to indicate an inducible exchanging population of phagocytic cells that respond to acoustic injury.

The recruitment and extravasation of these inflammatory cells into the cochlea is mediated by cytokines (*e.g.,* TNF-α, IL-1β, IL-6), chemokines (*e.g.,* MCP-1, MCP-5, MIP-1β) and cell adhesion molecules (*e.g.,* ICAM-1, PECAM-1), which are upregulated immediately after noise exposure[17,46,69-71]. Fujioka *et al*[46] demonstrated an upregulation of the proinflammatory cytokines TNF-α, IL-1β and IL-6 in the noise-damaged cochlea as early as three hours after noise exposure. IL-6 immunoreactive cells were observed initially in the lower and lateral regions of the spiral ligament, specifically in the cytoplasm of type IV and III fibrocytes, then throughout the spiral ligament and even in the stria vascularis[46]. Double labelling with NeuN, a neuronal marker, showed IL-6 expression in the spiral ganglion neurons 12-24 h after noise exposure. IL-6 upregulation in the noise-exposed cochlea likely contributes to cochlear injury, as the inhibition of IL-6 suppressed cochlear inflammation and mitigated the hearing loss[64]. Chemokines that are chemotactic for macrophages such as monocyte chemoattractant protein-1 (MCP-1/CCL2), monocyte chemoattractant protein-5 (MCP-5/CCL12), and macrophage inflammatory protein-1β (MIP-1β/CCL4) are upregulated in the noise-exposed cochlea two hours following acoustic trauma[17]. The early expression of chemokines suggests that resident cochlear cells may be responsible for this upregulation.

Intercellular adhesion molecule-1 (ICAM-1/CD54) is a vascular adhesion molecule that plays a critical role in mediating temporary adhesion/immobilisation of leukocytes to vascular endothelial cells in preparation for extravasation. Increased expression of ICAM-1 at the protein level is seen 24 h after noise exposure, reaching a maximum at two and four days, and returning to basal levels by 14 d[17]. This elevated expression is seen chiefly in the vascular endothelial cells and fibrocytes occupying the root region of the spiral ligament, and less intensely in the region of the spiral ligament adjacent to the cochlear bony capsule. The endosteal cells lining the scala tympani and scala vestibuli and capillaries of the stria vascularis also show increased ICAM-1 immunolabelling. Upregulation of ICAM-1 at the mRNA level is first observed two hours after noise exposure. The increased ICAM-1 expression in these cells regulates and directs the extravasation and cellular infiltration of inflammatory leukocytes. Results from our recent study on ICAM-1 expression following acute noise exposure in mice are compatible with these findings (see Figure 1). Other adhesion molecules that show increased expression following noise exposure include P-selectin, platelet-endothelial cell-adhesion molecule-1 (PECAM-1) and vascular cell adhesion molecule-1 (VCAM-1)[72,73]. Shi *et al*[72] demonstrated that the expression of these adhesion molecules is modulated by poly(ADP-ribose) polymerase-1 (PARP-1), a DNA repair enzyme. They suggested that noise activates PARP-1 in capillary endothelial cells of the spiral ligament and stria vascularis, which may act through NF-κB to regulate the expression of adhesion proteins in the lateral wall.

The expression of many proinflammatory mediators that participate in the acute inflammatory response is broadly regulated by the transcription factor NF-κB. Apart from its pivotal role in immune and inflammatory responses, NF-κB is also implicated in a range of processes such as cell survival, apoptosis, development, differentiation and cell growth[74]. NF-κB comprises a family of five inducible transcription factors, p50/p105 (NF-κB1), p52/p100 (NF-κB2), p65 (RelA), RelB, and c-Rel[75]. They exist as hetero- or homo-dimeric complexes, with the p50/p65 hetero-dimer being the predominant form. In quiescent cells, NF-κB is expressed in the cytoplasm in a latent form, with an inhibitory protein (IκB) bound to the dimer. Upon stimulation, the inhibitory protein is degraded, activating the NF-κB dimer, which then translocates to the nucleus where it binds to the promoters of its target genes. NF-κB activation in the cochlea has been demonstrated following noise exposure[73,76,77]. Following a two hour exposure of mice to traumatic noise (124 dB SPL), translocation of p65 and p50 to the nucleus of fibrocytes in the lateral wall was observed, indicating NF-κB activation[76]. Prominent nuclear localisation of NF-κB occurred two hours after noise exposure, but the nuclear immunostaining subsided after 72 h, suggesting an early response of NF-κB to acoustic overstimulation.

As mentioned earlier, a large population of PVMs exist in the stria vascularis, however, these cells are not found elsewhere in the cochlea, including the spiral ligament[52]. The PVMs play an important role in regulating the integrity of the intrastrial fluid-blood barrier by modulating the expression of tight- and adherens-junction proteins between the endothelial cells via the secretion of pigment epithelium growth factor (PEDF)[78,79]. The integrity of the barrier is critical for establishing and maintaining the endocochlear potential and preventing the entry of toxic substances into the cochlea[80]. Exposure to excessive noise leads to breakdown and increased permeability of the blood-labyrinth barrier by causing PVMs to change morphology and detach from strial capillaries and also by causing a significant downregulation of PEDF production and tight junction protein expression[81]. Similar to the cochlea, the retina of the eye contains perivascular macrophages, which also contribute to the maintenance of the blood-retinal barrier[82]. Recent evidence has demonstrated that bone marrow-derived cells (BMDCs) are recruited to the stria vascularis during the first week after acoustic injury to repair and restore the noise-damaged blood vessels[83]. These cells promote angiogenesis and neovascularisation, differentiating into PVMs, pericytes and endothelial cells and integrating into the strial blood vessels by four weeks after noise exposure. This recruitment is mediated by an intrinsic (iNOS)-dependent stromal cell-derived factor-1α (SDF-1α) signalling pathway. Blocking the activity of iNOS or SDF-1α significantly reduced both the number of infiltrating BMDCs and the capillary density (vascular repair) in the stria vascularis of the noise-exposed cochlea.

Similar to noise-induced hearing loss, oxidative stress and inflammation are major contributing factors to cisplatin-induced ototoxicity. Cisplatin has been shown to increase the expression of inflammatory mediators such as inducible nitric oxide synthase (iNOS), cyclo-oxygenase-2 (COX-2) and TNF-α, which are downstream targets of the transcription factor, signal transducer and activator of transcription-1 (STAT1)[84]. Cisplatin-induced activation of STAT1 is dependent on ROS generation through NOX3, a member of the NOX family of superoxide-generating nicotinamide adenine dinucleotide phosphate (NADPH) oxidases. NOX3 is expressed almost exclusively in the inner ear and serves as the primary source of ROS generation in the cochlea[85]. siRNA-mediated gene silencing of NOX3 mitigates cisplatin-induced hearing loss, demonstrating a key role of NOX3 in the development of cisplatin-mediated ototoxicity[86]. In contrast to these findings, recent data from our group showed that exposure to noise results in a significant down-regulation of NOX3 in the cochlea[87]. We propose that the reduction in NOX3 may represent an endogenous protective mechanism to reduce oxidative stress in the noise-exposed cochlea. These studies provide evidence that NOX3 is involved in the development of noise- and cisplatin-induced cochlear injury, albeit in a different way.

The exact role inflammatory cells play once recruited to the noise-damaged cochlea remains unclear. It is possible that the inflammatory response exacerbates the cellular damage in the cochlea by causing bystander tissue injury. It has also been suggested that the recruitment of inflammatory cells following acoustic injury is part of a wound healing response, given that infiltrating cells are largely observed in the region of the spiral ligament where noise-induced fibrocyte loss is most evident[16,17,49,69]. Leukocytes may play a critical role in promoting repair by removing cellular debris created by the primary insult. These cells may contribute to the repair process by changing the local environment via the secretion of chemical mediators such as cytokines and growth factors. Inflammatory leukocytes could function along with resident fibrocytes of the spiral ligament to regulate repair of the noise-damaged cochlear structures. It has been speculated that the fibrocytes initiate the local inflammatory process[65]. These cells express similar cytokines, chemokines and adhesion molecules, and also respond to signals used by leukocytes for cell-cell signalling. Cochlear fibrocytes can perhaps be considered facultative resident macrophages, serving some functions normally performed by circulating macrophages.

**TREATMENT STRATEGIES FOR MITIGATING NOISE-INDUCED COCHLEAR INFLAMMATION**

At the present time, there is no cure for noise-induced hearing loss, or any other types of hearing loss. The only therapeutic intervention for the hearing impaired is the use of hearing devices such as hearing aids that amplify sound or cochlear implants. A cochlear implant is a neural prosthesis that functions by electrically stimulating residual spiral ganglion neurons, the primary auditory neurons of the cochlea.

Corticosteroids (glucocorticoids) are widely used in the treatment of numerous acute and chronic inflammatory diseases, and have also long been used in the management of sensorineural hearing loss of various causes, including noise-induced hearing loss. Corticosteroids are typically administered systemically, either intravenously or orally. Appropriate doses of steroids supress excessive inflammation, but are unable to completely recover the associated hearing loss. Higher doses, on the other hand, can be deleterious to cochlear function in the long term and are often accompanied by a wide range of adverse side effects[88]. Glucocorticoids exert their actions by binding to and activating soluble cytoplasmic glucocorticoid receptors, which translocate to the nucleus and bind to specific DNA sites, culminating in the downregulation of proinflammatory cytokines and adhesion molecules[89]. Experiments have demonstrated that dexamethasone, a popular glucocorticoid, suppresses TNF-α-induced inflammatory mediator release from cultured spiral ligament fibrocytes[54]. The otoprotective effects of steroids may be mediated through the actions of NF-κB, as glucocorticoids are shown to be potent inhibitors of NF-κB activation via the induction of the IκBα inhibitory protein[90]. Local routes of steroid delivery have been developed without the unfavourable side effects. Direct infusion of dexamethasone into the perilymphatic space using osmotic mini-pumps has been reported to show protective effects against noise-induced injury in the guinea pig cochlea[91]. Intratympanic administration of steroids have also shown good therapeutic efficacy[92].

From our existing knowledge of the underlying mechanisms and pathways of the cochlear inflammatory response, rational therapeutic approaches can be devised to supress the inflammation and reduce cochlear injury. It is speculated that there are networks in the cochlea among inflammatory cells, fibrocytes and vascular endothelial cells, which are interconnected by various proinflammatory mediators (chemokines, cytokines, and adhesion molecules)[47]. Appropriate control of these networks could potentially attenuate the inflammatory reaction in the cochlea. Because of their early expression in the inflammatory response and their role in recruiting inflammatory cells into the cochlea, targeting chemokines/cytokines through direct inhibition may represent an effective novel therapeutic strategy.

Satoh *et al*[56] examined the therapeutic potential of anti-TNF-α therapy and showed that blocking the activity of TNF-α using Etanercept, a soluble TNF-α receptor-FC fusion protein, significantly attenuated the cochlear inflammatory response (reduced inflammatory cell infiltration and cochlear fibrosis) in an animal model of immune-mediated labyrinthitis induced by immunisation with keyhole limpet hemocyanin (KLH). A further study showed that neutralisation of TNF-α using Etanercept markedly decreased the expression and secretion of proinflammatory cytokines (TNF-α, IL-1β and IL-6) in the cochlea after cisplatin injection[21].

Another potential treatment strategy would be to block IL-6 signalling in the cochlea. It is interesting in this regard that specific humanised neutralising antibodies against IL-6 have recently been used clinically with promising effects in patients with rheumatoid arthritis and inflammatory bowel disease. In fact, a recent study by Wakabayashi *et al*[64] showed that inhibition of IL-6 with IL-6 receptor neutralising antibody (MR16-1) resulted in a dramatic suppression of the cochlear inflammatory response (reduced infiltration of inflammatory cells) and significantly improved hearing function in noise-exposed mice.

Recently, Nakamoto *et al*[70] showed that administration of geranylgeranylacetone (GGA), an anti-ulcer drug, suppressed the expression of proinflammatory cytokines (IL-6 and IL-1β) in the noise-exposed cochlea and also improved auditory function. GGA activates heat shock transcription factor 1 (HSF1), which induces the expression of heat shock proteins (Hsps). HSF1 is also known to directly or indirectly regulate cytokine expression, such as inhibiting the expression of IL-6 and IL-1β. GGA can also reduce inflammation in other organs (*e.g.,* liver) without apparent side effects even at large doses. GGA may therefore provide a novel beneficial strategy for the prevention of noise-induced hearing loss.

The role of antioxidants in noise-induced hearing loss has been the subject of extensive research. Antioxidants have been demonstrated to provide a protective effect in the cochlea by restoring the redox balance. A recent study examined the effects of antioxidant treatment on the inflammatory response in the cochlea following noise exposure[67]. This study reported that antioxidant treatment not only reduced markers of oxidative stress, but also significantly reduced the infiltration of inflammatory cells into the cochlea. This finding suggests an anti-inflammatory role of antioxidants in the cochlea.

Extensive evidence from *in vitro* and *in vivo* studies has demonstrated the strong anti-inflammatory potential of adenosine, a ubiquitous signalling molecule and neuromodulator, in a range of tissues[93-98], Adenosine exerts its anti-inflammatory action by influencing almost all aspects of the immune response[99]. The A2A receptor, reported to be the crucial receptor involved in the suppression of inflammation, is a promising target for the treatment of inflammatory conditions. Selective A2A receptor agonists have been used successfully in the therapy of sepsis, inflammatory bowel disease, skin inflammation and arthritis[98], and a similar effect could be postulated in the cochlea. In addition, A2A receptor agonists have been reported to suppress neuroinflammation in animal models[99]. In the mammalian (rat) cochlea, A2A receptors are expressed in the inner hair cells and supporting Deiters’ cells of the organ of Corti, spiral ligament, spiral ganglion neurons, and blood vessels[100]. This broad distribution suggests an important role of A2A receptors in the cochlea. The systemic administration of exogenous adenosine is limited by its peripheral side effects[97]. An alternative approach for augmenting the availability and actions of endogenous adenosine that has received increasing attention in recent years is the inhibition of adenosine kinase[94,101,102]. Adenosine kinase inhibitors, such as ABT-702, have demonstrated excellent efficacy in animal models of acute and chronic inflammation[101,103,104], and may have considerable therapeutic potential in cochlear inflammation. Adenosine kinase is extensively distributed in the adult cochlea[105,106], and may have a critical role in the regulation of adenosine signalling under physiological and pathological conditions.

**CONCLUSION**

The cochlea responds to trauma and infection like organs elsewhere in the body by eliciting an inflammatory response. Exposure to excessive noise triggers a cochlear inflammatory response that is characterised by an initial upregulation of numerous proinflammatory mediators and adhesion molecules by various resident cochlear cell types, followed by the rapid recruitment and infiltration of inflammatory cells into the cochlea from the systemic circulation. Much has been learned over the years of the noise-induced inflammatory process in the cochlea from animal models, but the exact mechanisms by which noise elicits this response is still unclear. The noise-induced inflammatory response may be involved in propagating cellular damage in the cochlea, but there is also a possibility that it may be involved in reparative processes. The mechanism and importance of this response in the noise-injured cochlea requires further exploration. With deeper knowledge of the underlying cochlear inflammatory response, we can explore and develop novel therapeutic interventions to protect cochlear tissues from inflammation-induced injury and noise-induced hearing loss.

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**REFERENCES**

1 **Thorne PR**, Ameratunga SN, Stewart J, Reid N, Williams W, Purdy SC, Dodd G, Wallaart J. Epidemiology of noise-induced hearing loss in New Zealand. *N Z Med J* 2008; **121**: 33-44 [PMID: 18791626]

2**Henderson D**, Hu B, Bielefeld E. Patterns and mechanisms of noise-induced cochlear pathology. In: Schacht J, Popper A and Fay R: Auditory Trauma, Protection, and Repair. New York: Springer, 2008: 195-217

3 **Kopke RD**. Pharmacological approaches to the prevention and treatment of cochlear injury due to noise. *Audiological Medicine* 2007; **5**: 66-80 [DOI: 10.1080/16513860601181046]

4 **Nelson DI**, Nelson RY, Concha-Barrientos M, Fingerhut M. The global burden of occupational noise-induced hearing loss. *Am J Ind Med* 2005; **48**: 446-458 [PMID: 16299704 DOI: 10.1002/ajim.20223]

5 **Daniel E**. Noise and hearing loss: a review. *J Sch Health* 2007; **77**: 225-231 [PMID: 17430434 DOI: 10.1111/j.1746-1561.2007.00197.x]

6 **Trivedi M**, Pingle S. Noise-induced hearing loss (NIHL): risk factors, genes and associated proteins. *Asiatic J Biotechnology Resources* 2013; **4**: 1-6

7 **Gong T-W**, Lomax M. Genes that influence susceptibility to noise-induced hearing loss. In: Le Prell CG, Henderson D, Fay RR and Popper AN: Noise-Induced Hearing Loss. New York: Springer, 2012: 179-203

8 **Hawkins JE**. Sketches of otohistory. Part 1: otoprehistory: how it all began. *Audiol Neurootol* 2004; **9**: 66-71 [PMID: 14981354 DOI: 10.1159/000075997]

9 **Hawkins JE**, Schacht J. Sketches of otohistory. Part 10: noise-induced hearing loss. *Audiol Neurootol* 2005; **10**: 305-309 [PMID: 16103641 DOI: 10.1159/000087347]

10 **Talaska AE**, Schacht J. Mechanisms of noise damage to the cochlea. Audiological Medicine 2007; **5**: 3-9 [DOI: 10.1080/16513860601158887]

11 **Wang Y**, Hirose K, Liberman MC. Dynamics of noise-induced cellular injury and repair in the mouse cochlea. *J Assoc Res Otolaryngol* 2002; **3**: 248-268 [PMID: 12382101 DOI: 10.1007/s101620020028]

12 **Thorne PR**, Duncan CE, Gavin JB. The pathogenesis of stereocilia abnormalities in acoustic trauma. *Hear Res* 1986; **21**: 41-49 [PMID: 3957794 DOI: 10.1016/0378-5955(86)90044-4]

13 **Hu BH**, Henderson D, Nicotera TM. Involvement of apoptosis in progression of cochlear lesion following exposure to intense noise. *Hear Res* 2002; **166**: 62-71 [PMID: 12062759 DOI: 10.1016/S0378-5955(02)00286-1]

14 **Henderson D**, Bielefeld EC, Harris KC, Hu BH. The role of oxidative stress in noise-induced hearing loss. *Ear Hear* 2006; **27**: 1-19 [PMID: 16446561 DOI: 10.1097/01.aud.0000191942.36672.f3]

15 **Hu B**. Noise-induced structural damage to the cochlea. In: Le Prell CG, Henderson D, Fay RR and Popper AN: Noise-Induced Hearing Loss. New York: Springer, 2012: 57-86

16 **Hirose K**, Discolo CM, Keasler JR, Ransohoff R. Mononuclear phagocytes migrate into the murine cochlea after acoustic trauma. *J Comp Neurol* 2005; **489**: 180-194 [PMID: 15983998 DOI: 10.1002/cne.20619]

17 **Tornabene SV**, Sato K, Pham L, Billings P, Keithley EM. Immune cell recruitment following acoustic trauma. *Hear Res* 2006; **222**: 115-124 [PMID: 17081714 DOI: 10.1016/j.heares.2006.09.004]

18 **Trinidad A**, Ramírez-Camacho R, García-Berrocal JR, Verdaguer JM, Daza R. Labyrinthitis secondary to experimental otitis media. *Am J Otolaryngol* 2009; **26**: 226-229 [PMID: 15991087 DOI: 10.1016/j.amjoto.2005.01.003]

19 **Cayé-Thomasen P**, Worsøe L, Brandt CT, Miyazaki H, Ostergaard C, Frimodt-Møller N, Thomsen J. Routes, dynamics, and correlates of cochlear inflammation in terminal and recovering experimental meningitis. *Laryngoscope* 2009; **119**: 1560-1570 [PMID: 19504554 DOI: 10.1002/lary.20260]

20 **Gloddek B**, Lassmann S, Gloddek J, Arnold W. Role of S-100beta as potential autoantigen in an autoimmune disease of the inner ear. *J Neuroimmunol* 1999; **101**: 39-46 [PMID: 10580812 DOI: 10.1016/S0165-5728(99)00131-9]

21 **So H**, Kim H, Lee JH, Park C, Kim Y, Kim E, Kim JK, Yun KJ, Lee KM, Lee HY, Moon SK, Lim DJ, Park R. Cisplatin cytotoxicity of auditory cells requires secretions of proinflammatory cytokines via activation of ERK and NF-kappaB. *J Assoc Res Otolaryngol* 2007; **8**: 338-355 [PMID: 17516123 DOI: 10.1007/s10162-007-0084-9]

22 **Kawauchi H**, DeMaria TF, Lim DJ. Endotoxin permeability through the round window. *Acta Otolaryngol Suppl* 1989; **457**: 100-115 [PMID: 2648753 DOI: 10.3109/00016488809138892]

23 **So H**, Kim H, Kim Y, Kim E, Pae HO, Chung HT, Kim HJ, Kwon KB, Lee KM, Lee HY, Moon SK, Park R. Evidence that cisplatin-induced auditory damage is attenuated by downregulation of pro-inflammatory cytokines via Nrf2/HO-1. *J Assoc Res Otolaryngol* 2008; **9**: 290-306 [PMID: 18584244 DOI: 10.1007/s10162-008-0126-y]

24 **Backhouse S**, Coleman B, Shepherd R. Surgical access to the mammalian cochlea for cell-based therapies. *Exp Neurol* 2008; **214**: 193-200 [PMID: 18773894 DOI: 10.1016/j.expneurol.2008.08.002]

25 **Okano T**, Nakagawa T, Kita T, Kada S, Yoshimoto M, Nakahata T, Ito J. Bone marrow-derived cells expressing Iba1 are constitutively present as resident tissue macrophages in the mouse cochlea. *J Neurosci Res* 2008; **86**: 1758-1767 [PMID: 18253944 DOI: 10.1002/jnr.21625]

26 **Cureoglu S**, Schachern PA, Rinaldo A, Tsuprun V, Ferlito A, Paparella MM. Round window membrane and labyrinthine pathological changes: an overview. *Acta Otolaryngol* 2005; **125**: 9-15 [PMID: 15799567 DOI: 10.1080/00016480410022534]

27 **MacArthur CJ**, Trune DR. Mouse models of otitis media. *Curr Opin Otolaryngol Head Neck Surg* 2006; **14**: 341-346 [PMID: 16974149 DOI: 10.1097/01.moo.0000244193.97301.d7]

28 **Klein M**, Koedel U, Kastenbauer S, Pfister HW. Nitrogen and oxygen molecules in meningitis-associated labyrinthitis and hearing impairment. *Infection* 2008; **36**: 2-14 [PMID: 18084715 DOI: 10.1007/s15010-007-7153-1]

29 **Merchant SN**, Gopen Q. A human temporal bone study of acute bacterial meningogenic labyrinthitis. *Am J Otol* 1996; **17**: 375-385 [PMID: 8817013]

30 **Meyerhoff WL**, Paparella MM, Oda M, Shea D. Mycotic infections of the inner ear. *Laryngoscope* 1979; **89**: 1725-1734 [PMID: 502694 DOI: 10.1288/00005537-197911000-00003]

31 **Barkdull GC**, Vu C, Keithley EM, Harris JP. Cochlear microperfusion: experimental evaluation of a potential new therapy for severe hearing loss caused by inflammation. *Otol Neurotol* 2005; **26**: 19-26 [PMID: 15699715 DOI: 10.1097/00129492-200501000-00005]

32 **Ichimiya I**, Yoshida K, Hirano T, Suzuki M, Mogi G. Significance of spiral ligament fibrocytes with cochlear inflammation. *Int J Pediatr Otorhinolaryngol* 2000; **56**: 45-51 [PMID: 11074115 DOI: 10.1016/S0165-5876(00)00408-0]

33 **Moon SK**, Park R, Lee HY, Nam GJ, Cha K, Andalibi A, Lim DJ. Spiral ligament fibrocytes release chemokines in response to otitis media pathogens. *Acta Otolaryngol* 2006; **126**: 564-569 [PMID: 16720438 DOI: 10.1080/00016480500452525]

34 **Ichimiya I**, Yoshida K, Hirano T, Suzuki M, Mogi G. Aspects of cochlear lateral wall inflammation. Audiological Medicine 2004; **2**: 179-181 [DOI: 10.1080/1651386410018187]

35 **Ichimiya I**, Kurono Y, Hirano T, Mogi G. Changes in immunostaining of inner ears after antigen challenge into the scala tympani. *Laryngoscope* 1998; **108**: 585-591 [PMID: 9546275 DOI: 10.1097/00005537-199804000-00023]

36 **Ichimiya I**, Suzuki M, Hirano T, Mogi G. The influence of pneumococcal otitis media on the cochlear lateral wall. *Hear Res* 1999; **131**: 128-134 [PMID: 10355610 DOI: 10.1016/S0378-5955(99)00025-8]

37 **Harris JP**, Ryan AF. Fundamental immune mechanisms of the brain and inner ear. *Otolaryngol Head Neck Surg* 1995; **112**: 639-653 [PMID: 7777346 DOI: 10.1016/S0194-5998(95)70170-2]

38 **Yimtae K**, Song H, Billings P, Harris JP, Keithley EM. Connection between the inner ear and the lymphatic system. *Laryngoscope* 2001; **111**: 1631-1635 [PMID: 11568618 DOI: 10.1097/00005537-200109000-00026]

39 **Ma C**, Billings P, Harris JP, Keithley EM. Characterization of an experimentally induced inner ear immune response. *Laryngoscope* 2000; **110**: 451-456 [PMID: 10718437 DOI: 10.1097/00005537-200003000-00024]

40 **Ryan AF**, Harris JP, Keithley EM. Immune-mediated hearing loss: basic mechanisms and options for therapy. *Acta Otolaryngol Suppl* 2002; 38-43 [PMID: 12211356 DOI: 10.1080/00016480260094965]

41 **Keithley EM**, Chen MC, Linthicum F. Clinical diagnoses associated with histologic findings of fibrotic tissue and new bone in the inner ear. *Laryngoscope* 1998; **108**: 87-91 [PMID: 9432073 DOI: 10.1097/00005537-199801000-00016]

42 **Keithley EM**, Woolf NK, Harris JP. Development of morphological and physiological changes in the cochlea induced by cytomegalovirus. *Laryngoscope* 1989; **99**: 409-414 [PMID: 2538687 DOI: 10.1288/00005537-198904000-00010]

43 **Kesser BW**, Hashisaki GT, Spindel JH, Ruth RA, Scheld WM. Time course of hearing loss in an animal model of pneumococcal meningitis. *Otolaryngol Head Neck Surg* 1999; **120**: 628-637 [PMID: 10229585 DOI: 10.1053/hn.1999.v120.a92772]

44 **Schramm HM**. The role of the osteoimmune axis in the inflammation of the inner auditory ear and with regard to the putative anticarcinogenetic principle: part 2. *Inflamm Allergy Drug Targets* 2010; **9**: 120-129 [PMID: 20402646 DOI: 10.2174/187152810791292818]

45 **Xu HX**, Joglekar SS, Paparella MM. Labyrinthitis ossificans. *Otol Neurotol* 2009; **30**: 579-580 [PMID: 19300296 DOI: 10.1097/MAO.0b013e31819fe81c]

46 **Fujioka M**, Kanzaki S, Okano HJ, Masuda M, Ogawa K, Okano H. Proinflammatory cytokines expression in noise-induced damaged cochlea. *J Neurosci Res* 2006; **83**: 575-583 [PMID: 16429448 DOI: 10.1002/jnr.20764]

47 **Yoshida K**, Ichimiya I, Suzuki M, Mogi G. Effect of proinflammatory cytokines on cultured spiral ligament fibrocytes. *Hear Res* 1999; **137**: 155-159 [PMID: 10545642 DOI: 10.1016/S0378-5955(99)00134-3]

48 **Harris JP**, Fukuda S, Keithley EM. Spiral modiolar vein: its importance in inner ear inflammation. *Acta Otolaryngol* 1990; **110**: 357-365 [PMID: 2284910 DOI: 10.3109/00016489009122560]

49 **Sato E**, Shick HE, Ransohoff RM, Hirose K. Repopulation of cochlear macrophages in murine hematopoietic progenitor cell chimeras: the role of CX3CR1. *J Comp Neurol* 2008; **506**: 930-942 [PMID: 18085589 DOI: 10.1002/cne.21583]

50 **Sato E**, Shick HE, Ransohoff RM, Hirose K. Expression of fractalkine receptor CX3CR1 on cochlear macrophages influences survival of hair cells following ototoxic injury. *J Assoc Res Otolaryngol* 2010; **11**: 223-234 [PMID: 19936834 DOI: 10.1007/s10162-009-0198-3]

51 **Lang H**, Ebihara Y, Schmiedt RA, Minamiguchi H, Zhou D, Smythe N, Liu L, Ogawa M, Schulte BA. Contribution of bone marrow hematopoietic stem cells to adult mouse inner ear: mesenchymal cells and fibrocytes. *J Comp Neurol* 2006; **496**: 187-201 [PMID: 16538683 DOI: 10.1002/cne.20929]

52 **Shi X**. Resident macrophages in the cochlear blood-labyrinth barrier and their renewal via migration of bone-marrow-derived cells. *Cell Tissue Res* 2010; **342**: 21-30 [PMID: 20838812 DOI: 10.1007/s00441-010-1040-2]

53 **Ladrech S**, Wang J, Simonneau L, Puel JL, Lenoir M. Macrophage contribution to the response of the rat organ of Corti to amikacin. *J Neurosci Res* 2007; **85**: 1970-1979 [PMID: 17497672 DOI: 10.1002/jnr.21335]

54 **Maeda K**, Yoshida K, Ichimiya I, Suzuki M. Dexamethasone inhibits tumor necrosis factor-alpha-induced cytokine secretion from spiral ligament fibrocytes. *Hear Res* 2005; **202**: 154-160 [PMID: 15811707 DOI: 10.1016/j.heares.2004.08.022]

55 **Suzuki M**, Harris JP. Expression of intercellular adhesion molecule-1 during inner ear inflammation. *Ann Otol Rhinol Laryngol* 1995; **104**: 69-75 [PMID: 7530436]

56 **Satoh H**, Firestein GS, Billings PB, Harris JP, Keithley EM. Tumor necrosis factor-alpha, an initiator, and etanercept, an inhibitor of cochlear inflammation. *Laryngoscope* 2002; **112**: 1627-1634 [PMID: 12352677 DOI: 10.1097/00005537-200209000-00019]

57 **Keithley EM**, Wang X, Barkdull GC. Tumor necrosis factor alpha can induce recruitment of inflammatory cells to the cochlea. *Otol Neurotol* 2008; **29**: 854-859 [PMID: 18636025 DOI: 10.1097/MAO.0b013e31818256a9]

58 **Khan M**, Szczepek AJ, Haupt H, Olze H, Mazurek B. Expression of the proinflammatory cytokines in cochlear explant cultures: influence of normoxia and hypoxia. *Neurosci Lett* 2010; **479**: 249-252 [PMID: 20561939 DOI: 10.1016/j.neulet.2010.05.072]

59 **Adams JC**. Clinical implications of inflammatory cytokines in the cochlea: a technical note. *Otol Neurotol* 2002; **23**: 316-322 [PMID: 11981388 DOI: 10.1097/00129492-200205000-00015]

60 . Markers of cochlear inflammation using MRI. *J Magn Reson Imaging* 2013; : [PMID: 23589173 DOI: 10.1002/jmri.24144]

61 **Ohlemiller KK**, Wright JS, Dugan LL. Early elevation of cochlear reactive oxygen species following noise exposure. *Audiol Neurootol* 1999; **4**: 229-236 [PMID: 10436315 DOI: 10.1159/000013846]

62 **Fredelius L**. Time sequence of degeneration pattern of the organ of Corti after acoustic overstimulation. A transmission electron microscopy study. *Acta Otolaryngol* 1988; **106**: 373-385 [PMID: 3207005 DOI: 10.3109/00016488809122260]

63 **Fredelius L**, Rask-Andersen H. The role of macrophages in the disposal of degeneration products within the organ of corti after acoustic overstimulation. *Acta Otolaryngol* 1990; **109**: 76-82 [PMID: 2309562 DOI: 10.3109/00016489009107417]

64 **Wakabayashi K**, Fujioka M, Kanzaki S, Okano HJ, Shibata S, Yamashita D, Masuda M, Mihara M, Ohsugi Y, Ogawa K, Okano H. Blockade of interleukin-6 signaling suppressed cochlear inflammatory response and improved hearing impairment in noise-damaged mice cochlea. *Neurosci Res* 2010; **66**: 345-352 [PMID: 20026135 DOI: 10.1016/j.neures.2009.12.008]

65 **Tan BT**, Lee MM, Ruan R. Bone-marrow-derived cells that home to acoustic deafened cochlea preserved their hematopoietic identity. *J Comp Neurol* 2008; **509**: 167-179 [PMID: 18461607 DOI: 10.1002/cne.21729]

66 **Discolo CM**, Keasler JR, Hirose K. Inflammatory cells in the mouse cochlea after acoustic trauma. In: Abstract 166 Session J10. Noise injury: mechanisms. Proceedings of the 27th Association for Research in Otolaryngology (ARO) MidWinter Meeting; 23 Febuary 2004; Daytona Beach, Florida, USA

67 **Du X**, Choi CH, Chen K, Cheng W, Floyd RA, Kopke RD. Reduced formation of oxidative stress biomarkers and migration of mononuclear phagocytes in the cochleae of chinchilla after antioxidant treatment in acute acoustic trauma. *Int J Otolaryngol* 2011; **2011**: 612690 [PMID: 21961007 DOI: 10.1155/2011/612690]

68 **Rutar M**, Provis JM, Valter K. Brief exposure to damaging light causes focal recruitment of macrophages, and long-term destabilization of photoreceptors in the albino rat retina. *Curr Eye Res* 2010; **35**: 631-643 [PMID: 20597649 DOI: 10.3109/02713681003682925]

69 **Ohlemiller KK**. Recent findings and emerging questions in cochlear noise injury. *Hear Res* 2008; **245**: 5-17 [PMID: 18790034 DOI: 10.1016/j.heares.2008.08.007]

70 **Nakamoto T**, Mikuriya T, Sugahara K, Hirose Y, Hashimoto T, Shimogori H, Takii R, Nakai A, Yamashita H. Geranylgeranylacetone suppresses noise-induced expression of proinflammatory cytokines in the cochlea. *Auris Nasus Larynx* 2012; **39**: 270-274 [PMID: 21794995 DOI: 10.1016/j.anl.2011.06.001]

71 **Jo MH**, Kim CJ, Koh SH, Nam GS, Jeong HM, Lee JH, Lee SH. Expression and distribution of tumor necrosis factor-alpha in mice cochlea exposed to noise. Korean J Otorhinolaryngol-Head Neck Surg 2010; **53**: 527-533 [DOI: 10.3342/kjorl-hns.2010.53.9.527]

72 **Shi X**, Nuttall AL. Expression of adhesion molecular proteins in the cochlear lateral wall of normal and PARP-1 mutant mice. *Hear Res* 2007; **224**: 1-14 [PMID: 17184942 DOI: 10.1016/j.heares.2006.10.011]

73 **Yamamoto H**, Omelchenko I, Shi X, Nuttall AL. The influence of NF-kappaB signal-transduction pathways on the murine inner ear by acoustic overstimulation. *J Neurosci Res* 2009; **87**: 1832-1840 [PMID: 19185019 DOI: 10.1002/jnr.22018]

74 **Denk A**, Wirth T, Baumann B. NF-kappaB transcription factors: critical regulators of hematopoiesis and neuronal survival. *Cytokine Growth Factor Rev* 2000; **11**: 303-320 [PMID: 10959078 DOI: 10.1016/S1359-6101(00)00009-5]

75 **Ghosh S**, May MJ, Kopp EB. NF-kappa B and Rel proteins: evolutionarily conserved mediators of immune responses. *Annu Rev Immunol* 1998; **16**: 225-260 [PMID: 9597130 DOI: 10.1146/annurev.immunol.16.1.225]

76 **Masuda M**, Nagashima R, Kanzaki S, Fujioka M, Ogita K, Ogawa K. Nuclear factor-kappa B nuclear translocation in the cochlea of mice following acoustic overstimulation. *Brain Res* 2006; **1068**: 237-247 [PMID: 16376312 DOI: 10.1016/j.brainres.2005.11.020]

77 **Adams JC**, Seed B, Lu N, Landry A, Xavier RJ. Selective activation of nuclear factor kappa B in the cochlea by sensory and inflammatory stress. *Neuroscience* 2009; **160**: 530-539 [PMID: 19285117 DOI: 10.1016/j.neuroscience.2009.02.073]

78 **Zhang W**, Dai M, Fridberger A, Hassan A, Degagne J, Neng L, Zhang F, He W, Ren T, Trune D, Auer M, Shi X. Perivascular-resident macrophage-like melanocytes in the inner ear are essential for the integrity of the intrastrial fluid-blood barrier. *Proc Natl Acad Sci U S A* 2012; **109**: 10388-10393 [PMID: 22689949 DOI: 10.1073/pnas.1205210109]

79 **Neng L**, Zhang F, Kachelmeier A, Shi X. Endothelial cell, pericyte, and perivascular resident macrophage-type melanocyte interactions regulate cochlear intrastrial fluid-blood barrier permeability. *J Assoc Res Otolaryngol* 2013; **14**: 175-185 [PMID: 23247886 DOI: 10.1007/s10162-012-0365-9]

80 **Juhn SK**, Hunter BA, Odland RM. Blood-labyrinth barrier and fluid dynamics of the inner ear. *Int Tinnitus J* 2001; **7**: 72-83 [PMID: 14689642]

81 Perivascular macrophage-like melanocyte responsiveness to acoustic trauma--a salient feature of strial barrier associated hearing loss. *FASEB J* 2013; [PMID: 23729595 DOI: 10.1096/fj.13-232892]

82 **Mendes-Jorge L**, Ramos D, Luppo M, Llombart C, Alexandre-Pires G, Nacher V, Melgarejo V, Correia M, Navarro M, Carretero A, Tafuro S, Rodriguez-Baeza A, Esperança-Pina JA, Bosch F, Ruberte J. Scavenger function of resident autofluorescent perivascular macrophages and their contribution to the maintenance of the blood-retinal barrier. *Invest Ophthalmol Vis Sci* 2009; **50**: 5997-6005 [PMID: 19608545 DOI: 10.1167/iovs.09-3515]

83 **Dai M**, Yang Y, Omelchenko I, Nuttall AL, Kachelmeier A, Xiu R, Shi X. Bone marrow cell recruitment mediated by inducible nitric oxide synthase/stromal cell-derived factor-1alpha signaling repairs the acoustically damaged cochlear blood-labyrinth barrier. *Am J Pathol* 2010; **177**: 3089-3099 [PMID: 21057001 DOI: 10.2353/ajpath.2010.100340]

84 **Kaur T**, Mukherjea D, Sheehan K, Jajoo S, Rybak LP, Ramkumar V. Short interfering RNA against STAT1 attenuates cisplatin-induced ototoxicity in the rat by suppressing inflammation. *Cell Death Dis* 2011; **2**: e180 [PMID: 21776018 DOI: 10.1038/cddis.2011.63]

85 **Bánfi B**, Malgrange B, Knisz J, Steger K, Dubois-Dauphin M, Krause KH. NOX3, a superoxide-generating NADPH oxidase of the inner ear. *J Biol Chem* 2004; **279**: 46065-46072 [PMID: 15326186 DOI: 10.1074/jbc.M403046200]

86 **Mukherjea D**, Jajoo S, Kaur T, Sheehan KE, Ramkumar V, Rybak LP. Transtympanic administration of short interfering (si)RNA for the NOX3 isoform of NADPH oxidase protects against cisplatin-induced hearing loss in the rat. *Antioxid Redox Signal* 2010; **13**: 589-598 [PMID: 20214492 DOI: 10.1089/ars.2010.3110]

87 Noise-induced changes in expression levels of NADPH oxidases in the cochlea. *Hear Res* 2013; **304C**: 145-152 [PMID: 23899412 DOI: 10.1016/j.heares.2013.07.012]

88 **Abi-Hachem RN**, Zine A, Van De Water TR. The injured cochlea as a target for inflammatory processes, initiation of cell death pathways and application of related otoprotectives strategies. *Recent Pat CNS Drug Discov* 2010; **5**: 147-163 [PMID: 20167005 DOI: 10.2174/157488910791213121]

89 **Vandevyver S**, Dejager L, Tuckermann J, Libert C. New insights into the anti-inflammatory mechanisms of glucocorticoids: an emerging role for glucocorticoid-receptor-mediated transactivation. *Endocrinology* 2013; **154**: 993-1007 [PMID: 23384835 DOI: 10.1210/en.2012-2045]

90 **Auphan N**, DiDonato JA, Rosette C, Helmberg A, Karin M. Immunosuppression by glucocorticoids: inhibition of NF-kappa B activity through induction of I kappa B synthesis. *Science* 1995; **270**: 286-290 [PMID: 7569976 DOI: 10.1126/science.270.5234.286]

91 **Takemura K**, Komeda M, Yagi M, Himeno C, Izumikawa M, Doi T, Kuriyama H, Miller JM, Yamashita T. Direct inner ear infusion of dexamethasone attenuates noise-induced trauma in guinea pig. *Hear Res* 2004; **196**: 58-68 [PMID: 15464302 DOI: 10.1016/j.heares.2004.06.003]

92 **Zhou Y**, Zheng H, Shen X, Zhang Q, Yang M. Intratympanic administration of methylprednisolone reduces impact of experimental intensive impulse noise trauma on hearing. *Acta Otolaryngol* 2009; **129**: 602-607 [PMID: 18815936 DOI: 10.1080/00016480802342424]

93 **Bours MJ**, Swennen EL, Di Virgilio F, Cronstein BN, Dagnelie PC. Adenosine 5'-triphosphate and adenosine as endogenous signaling molecules in immunity and inflammation. *Pharmacol Ther* 2006; **112**: 358-404 [PMID: 16784779 DOI: 10.1016/j.pharmthera.2005.04.013]

94 **Cronstein BN**. Adenosine, an endogenous anti-inflammatory agent. *J Appl Physiol* 1994; **76**: 5-13 [PMID: 8175547]

95 **Cunha RA**. Neuroprotection by adenosine in the brain: From A(1) receptor activation to A (2A) receptor blockade. *Purinergic Signal* 2005; **1**: 111-134 [PMID: 18404497 DOI: 10.1007/s11302-005-0649-1]

96 **Fredholm BB**. Adenosine, an endogenous distress signal, modulates tissue damage and repair. *Cell Death Differ* 2007; **14**: 1315-1323 [PMID: 17396131 DOI: 10.1038/sj.cdd.4402132]

97 **Haskó G**, Cronstein BN. Adenosine: an endogenous regulator of innate immunity. *Trends Immunol* 2004; **25**: 33-39 [PMID: 14698282 DOI: 10.1016/j.it.2003.11.003]

98 **Jacobson KA**, Gao ZG. Adenosine receptors as therapeutic targets. *Nat Rev Drug Discov* 2006; **5**: 247-264 [PMID: 16518376 DOI: 10.1038/nrd1983]

99 **Chen JF**, Pedata F. Modulation of ischemic brain injury and neuroinflammation by adenosine A2A receptors. *Curr Pharm Des* 2008; **14**: 1490-1499 [PMID: 18537672 DOI: 10.2174/138161208784480126]

100 **Vlajkovic SM**, Abi S, Wang CJ, Housley GD, Thorne PR. Differential distribution of adenosine receptors in rat cochlea. *Cell Tissue Res* 2007; **328**: 461-471 [PMID: 17285327 DOI: 10.1007/s00441-006-0374-2]

101 **Boyle DL**, Kowaluk EA, Jarvis MF, Lee CH, Bhagwat SS, Williams M, Firestein GS. Anti-inflammatory effects of ABT-702, a novel non-nucleoside adenosine kinase inhibitor, in rat adjuvant arthritis. *J Pharmacol Exp Ther* 2001; **296**: 495-500 [PMID: 11160636]

102 **Rosengren S**, Bong GW, Firestein GS. Anti-inflammatory effects of an adenosine kinase inhibitor. Decreased neutrophil accumulation and vascular leakage. *J Immunol* 1995; **154**: 5444-5451 [PMID: 7730646]

103 **Jarvis MF**, Yu H, Kohlhaas K, Alexander K, Lee CH, Jiang M, Bhagwat SS, Williams M, Kowaluk EA. ABT-702 (4-amino-5-(3-bromophenyl)-7-(6-morpholinopyridin-3-yl)pyrido[2, 3-d]pyrimidine), a novel orally effective adenosine kinase inhibitor with analgesic and anti-inflammatory properties: I. In vitro characterization and acute antinociceptive effects in the mouse. *J Pharmacol Exp Ther* 2000; **295**: 1156-1164 [PMID: 11082453]

104 **Kowaluk EA**, Mikusa J, Wismer CT, Zhu CZ, Schweitzer E, Lynch JJ, Lee CH, Jiang M, Bhagwat SS, Gomtsyan A, McKie J, Cox BF, Polakowski J, Reinhart G, Williams M, Jarvis MF. ABT-702 (4-amino-5-(3-bromophenyl)-7-(6-morpholino-pyridin- 3-yl)pyrido[2,3-d]pyrimidine), a novel orally effective adenosine kinase inhibitor with analgesic and anti-inflammatory properties. II. In vivo characterization in the rat. *J Pharmacol Exp Ther* 2000; **295**: 1165-1174 [PMID: 11082454]

105 **Vlajkovic SM**, Guo CX, Dharmawardana N, Wong AC, Boison D, Housley GD, Thorne PR. Role of adenosine kinase in cochlear development and response to noise. *J Neurosci Res* 2010; **88**: 2598-2609 [PMID: 20648650]

106 **Vlajkovic SM**, Guo CX, Telang R, Wong AC, Paramananthasivam V, Boison D, Housley GD, Thorne PR. Adenosine kinase inhibition in the cochlea delays the onset of age-related hearing loss. *Exp Gerontol* 2011; **46**: 905-914 [PMID: 21846498 DOI: 10.1016/j.exger.2011.08.001]

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**Figure 1** **Intercellular adhesion molecule-1 immunolabeling in the spiral ligament of the cochlear basal turn in C57BL/6 mice.** A: In the non-noise exposed cochlea, intercellular adhesion molecule-1 (ICAM-1) was expressed by type IV fibrocytes and vascular endothelial cells in the lowest region of the spiral ligament; B: Mice exposed to traumatic noise (100 dB SPL, 8-16 kHz) for 24 h showed increased expression of ICAM-1, peaking at 24 h following acoustic trauma. ICAM-1 immunolabeling became more intense and expanded to cover a much greater area in the inferior region of the spiral ligament. ICAM-1 immunoexpression was determined by immunoperoxidase histochemistry and photomicrographs of mid-modiolar cochlear sections were taken with a digital light microscope (Nikon Eclipse 80i) at 40X magnification. SL: Spiral ligament; SM: Scala media. Scale bars = 50 µm.