JOURNAL OF ENZYME INHIBITION AND MEDICINAL CHEMISTRY
2025, VOL. 40, NO. 1, 2468853
https://doi.org/10.1080/14756366.2025.2468853

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS Check for updates

Ferroptosis and hearing loss: from molecular mechanisms to therapeutic interventions

Xingyi Lv, Chenyi Yang, Xianying Li, Yun Liu, Yu Yang, Tongyan Jin, Zhijian Chen, Jinjing Jia, Min Wang and Li Li

Department of Physiology, College of Medicine, Jiaxing University, Jiaxing, Zhejiang, China

ABSTRACT

Hearing loss profoundly affects social engagement, mental health, cognition, and brain development, with sensorineural hearing loss (SNHL) being a major concern. Linked to ototoxic medications, ageing, and noise exposure, SNHL presents significant treatment challenges, highlighting the need for effective prevention and regeneration strategies. Ferroptosis, a distinct form of cell death featuring iron-dependent lipid peroxidation, has garnered interest due to its potential role in cancer, ageing, and neuronal degeneration, especially hearing loss. The emerging role of ferroptosis as a crucial mediator in SNHL suggests that it may offer a novel therapeutic target for otoprotection. This review aims to summarise the intricate connection between ferroptosis and SNHL, offering a fresh perspective for exploring targeted therapeutic strategies that could potentially mitigate cochlear cells damage and enhance the quality of life for individuals with hearing impairments.

ARTICLE HISTORY
Received 27 August 2024
Revised 11 February 2025
Accepted 13 February 2025

KEYWORDS
Hearing loss; ferroptosis; otoprotection

Introduction

Hearing loss, a prevalent condition affecting millions globally, has attracted extensive research attention[1,2]. Various factors are implicated in auditory dysfunction especially sensorineural hearing loss (SNHL), with oxidative stress, hair cells (HCs) injury, spiral ganglion neuron (SGN) degeneration, and increased blood-labyrinth barrier (BLB) permeability standing out as major causes in hearing loss[3–5]. A core mechanism is the irreversible damage to cochlear HCs. Due to its limited regenerative capacity, this leads to permanent hearing decline. When chemicals or drugs enter cochlear HCs *via* diffusion or active transport, they can trigger inflammation, activate caspases, or generate reactive oxygen species (ROS), ultimately causing necrosis or programmed cell death (PCD). Additionally, ageing as a significant contributor to hearing impairment, largely due to mitochondrial dysfunction, leading to ROS accumulation and the depletion of intracellular antioxidants[6–8]. Genetic factors have also received increasing scrutiny in recent years, as mutations affecting key metabolic pathways or antioxidant defences can exacerbate cellular vulnerability to damage[9,10]. Certain medications, such as cisplatin and aminoglycoside, are known to be ototoxic, while prolonged noise exposure is another established risk factor for hearing loss[3,11].

Irrespective of the underlying cause, these factors collectively induce oxidative stress and inflammation in HCs, which play a crucial role in initiating ferroptosis, thereby contributing to hearing impairment.

Given the irreversible nature of most hearing losses, the urgent pursuit of protective or mitigating measures is paramount. Extensive research has been dedicated to PCD as a potential strategy to address hearing impairment, with apoptosis being the earliest and most extensively studied form[12]. Recently, ferroptosis, a newly recognised iron-dependent PCD characterised by lipid peroxidation, has garnered significant attention[13]. Ferroptosis is known for its critical role in neurologic disorders, organ dysfunctions, and tumour proliferation[14–17]. However, the links between ferroptosis and hearing loss are relatively unexplored.

In this review, we aim to summarise the recent findings which clarify the links between ferroptosis and hearing loss, shedding light on potential therapeutic avenues for mitigating hearing impairment. By synthesising existing literature and integrating recent discoveries, this review endeavours to provide a comprehensive understanding of the roles played by ferroptosis in the aetiology and progression of hearing loss.

A brief overview of ferroptosis

Ferroptosis, a novel form of PCD, was first proposed in 2012[13]. Its core reason lies in the iron-dependent abnormal accumulation of lipid peroxides. The mechanisms involve three key aspects: iron metabolism imbalance inducing harmful Fenton reactions that generate ROS[18]; disruption lipid metabolism by ROS, leading to produce membrane lipid peroxides[19]; and imbalances in the amino acid antioxidant system impeding the clearance of excess lipid peroxides. These factors interplay, collectively driving the initiation and progression of ferroptosis (Figure 1).

A crucial aspect of this regulation is the dynamic balance of iron within the cell. In normal conditions, iron is primarily acquired from

CONTACT Min Wang wangmin3826@zjxu.edu.cn Department of Physiology, College of Medicine, Jiaxing University, 118 Jiahang Road, Jiaxing, Zhejiang, 314000, China; Li Li lily7588@163.com Department of Physiology, College of Medicine, Jiaxing University, 118 Jiahang Road, Jiaxing, Zhejiang, 314000, China

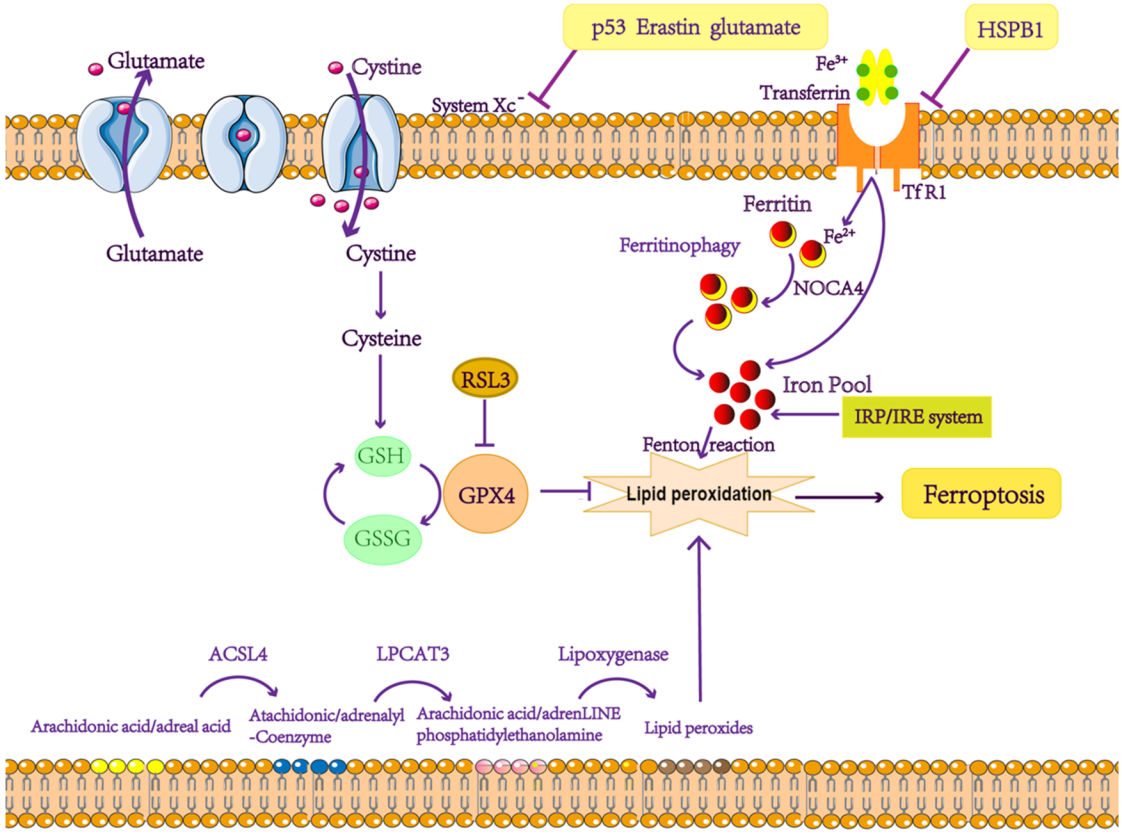

Figure 1. The key molecular pathways of ferroptosis. (Drawn by Y.C., X.Li., Y.L., and Y.Y.).

the intestine *via* TF/TfR (iron transporters)[20,21], followed by reduction to ferrous ions by STEAP3 at the cell membrane[22], and then imported into the cytosolic iron pool by transporter proteins, such as DMT1 or ZIP8/14. Once within the cell, ferrous ions are either utilised by IRP1/2 proteins (iron regulatory proteins)[23,24] or stored in Ferritin[20,21]. Excess ferrous ions are exported by Ferroportin. Disruptions in any of these processes can lead to imbalanced iron homeostasis. Abnormal accumulation of ferrous ions generates ROS, particularly hydroxyl radicals *via* the Fenton reaction, which trigger lipid peroxidation and ultimately induce ferroptosis[25]. As an iron chelator, Deferoxamine (DFO) directly reduces ROS accumulation by chelating ferrous ions, thereby inhibiting ferroptosis[26].

Lipid peroxidation also plays a pivotal role in ferroptosis, particularly through the peroxidation of membrane polyunsaturated fatty acids (PUFAs). Catalysed by ferrous ions, PUFAs form lipid peroxides, such as 4-HNE and MDA, which damage cellular membranes and contribute to cellular collapse. Lipid metabolic enzymes, such as lysophosphatidylcholine acyltransferase 3 (LPCAT3)[27], acyl-CoA synthetase long-chain family member 4 (ACSL4), and arachidonate lipoxygenases (ALOXs)[28], regulate the synthesis and peroxidation of PUFA-containing phospholipids (PUFA-PLs) in the cell membrane, leading to iron-dependent lipid peroxidation and cell death. Notably, ACSL4 accelerates the esterification of PUFAs into acyl-CoA, exacerbating membrane lipid peroxidation and functioning as a critical driver in the progression of ferroptosis[29].

Furthermore, the cellular clearance of lipid peroxides is essential for preventing ferroptosis. The GPX4 pathway plays a pivotal role in this defence by reducing intracellular oxidative stress. GPX4, located in mitochondria, cytoplasm, and nucleus, utilises glutathione (GSH) as a cofactor to reduce lipid peroxides to non-toxic lipid alcohols, thereby maintaining membrane lipid homeostasis. Inactivation of GPX4 leads to the accumulation of lipid peroxides, causing membrane rupture and cell death[30–33]. Concurrently, cells import cystine from the extracellular environment *via* the cystine-glutamate antiporter (System Xc^-), a vital precursor for GSH synthesis[34]. Consequently, disruption of GSH synthesis by ferroptosis inducers like erastin[34–36], which indirectly inactivates GPX4, and Ras-selective lethal 3 (RSL3)[37,38], which directly inactivates GPX4 independently of system Xc^-, exacerbates ferroptosis. Conversely, Ferrostatin-1, a highly selective ferroptosis inhibitor, demonstrates immense anti-ferroptotic effect by inhibiting lipid peroxidation induced by the Fenton reaction, thereby protecting membrane lipids from damage and effectively inhibiting ferroptosis[39]. Additionally, other glutathione-independent antioxidant systems, such as the NAD(P)H-FSP1-CoQ10 axis[40] and the DHFR-BH4-GCH1 axis[41], also participate in lipid peroxide clearance and ferroptosis inhibition.

After elucidating the intricate mechanisms underlying ferroptosis, it is crucial to acknowledge the involvement of ferroptosis in various diseases, such as cancer, neurodegeneration, ischaemia-reperfusion injury, as well as hearing loss[14–17]. Accumulating evidence suggests that oxidative stress and lipid peroxidation play critical roles in the pathogenesis of hearing disorders. For instance, mutations in genes encoding proteins involved in iron metabolism and GSH synthesis have been associated with SNHL[42–44]. Thus, understanding the regulation mechanisms of ferroptosis and its interplay with hearing loss is essential for elucidating the underlying causes of hearing loss and developing potential therapeutic strategies. Thus, the research on ferroptosis holds transformative potential for medical interventions.

The links between ferroptosis and hearing loss

There is substantial evidence showing that ferroptosis is closely correlated with hearing loss since the concept of ferroptosis was proposed. In this section, we reviewed the current existing studies which clarified the significant roles of ferroptosis in the onset of various types of hearing loss, including drug-induced hearing loss, age-related hearing loss, noise-induced hearing loss, and otitis-media-induced hearing loss. These studies have not only highlighted the widespread impact of ferroptosis on auditory dysfunction but also laid the groundwork for a deeper understanding of the underlying mechanisms.

Here, the key molecular pathways involved in ferroptosis and hearing loss, which have emerged from these studies, are summarised in Figure 2.

Ferroptosis in drug-induced hearing loss

In this section, we systematically reviewed the existing studies of the most frequently used drugs that exhibited ototoxicity through

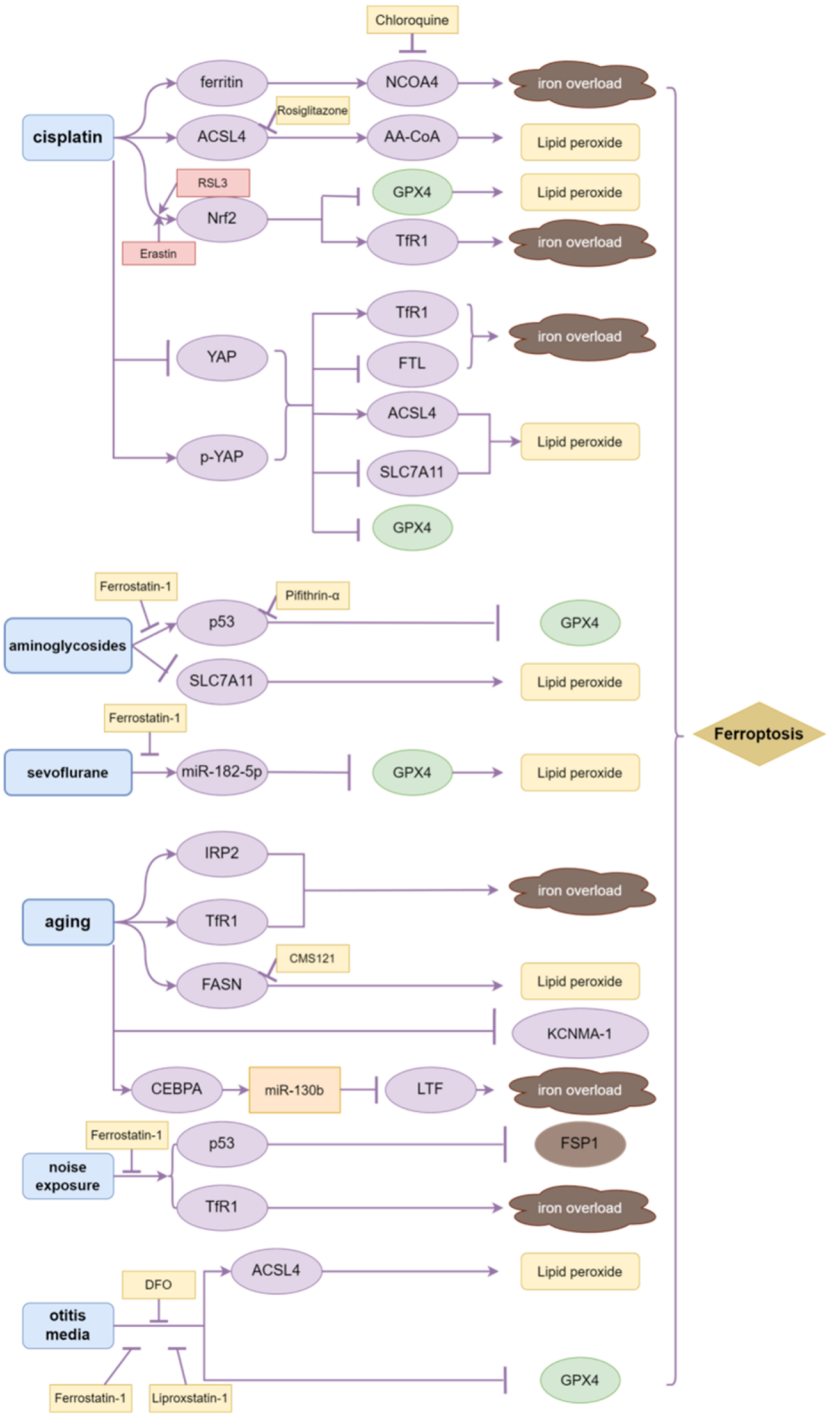

Figure 2. Key molecular pathways involved in ferroptosis and hearing loss. The key molecular pathways in hearing loss caused by cisplatin, aminoglycosides, sevoflurane administration, ageing, noise exposure, and otitis media were summarised. (Drawn by T.J., Z.C., and J.J.).

ferroptosis and their mechanisms to lead to hearing dysfunction, including platinum-based anti-cancer drug, aminoglycoside antibiotics, and anaesthetics.

Cisplatin, an anti-cancer drug

Cisplatin, a well-known chemotherapeutic drug, has been used for the treatment of numerous malignant cancers including bladder, head and neck, lung, ovary, and testis[45]. Attributed to its severe side effects, among which nephrotoxicity and ototoxicity are the main ones, the large scale of clinical application is limited[46].

The prevailing view today is that apoptosis is the primary mechanism leading to cisplatin-induced hearing loss[11]. However, inhibiting apoptosis in animal models only partially reversed cisplatin-induced hearing loss, suggesting that the exact mechanisms behind cisplatin-induced ototoxicity are still not fully understood. When cisplatin is taken up by the HCs, it triggers oxidative stress and the release of inflammatory cytokines, which contribute to excessive ROS production and ultimately lead to ferroptosis[47].

Jian et al.[21] observed pro-ferroptotic alterations, such as lipid peroxidation and impaired antioxidant capacity, in the cochlea of C57BL/6 mice and HEI-OC1 cell lines following cisplatin damage. Additionally, the application of chloroquine to block the autophagy pathway significantly alleviated cisplatin-induced ferroptosis, indicating a close relationship between this form of cell death and autophagy. This specific autophagy, known as ferritinophagy, is mediated by nuclear receptor coactivator 4 (NCOA4)[48]. Intracellular irons are stored in ferritin, which can be translocated into autolysosomes in the mediation of NCOA4, to release free irons. This process is crucial for maintaining intracellular iron homeostasis[49]. However, excessive degradation of ferritin results in the release of too much free iron, leading to ferroptosis. Consistent with this, their study showed that cisplatin activated ferritinophagy in HEI-OC1 cells, evidenced by increased expressions of NCOA4 and LC3II (autophagy marker), and altered FTH-LAMP-1 colocalization upon cisplatin exposure[21]. Therefore, drugs which target NCOA4 may offer potential therapeutic value in the future.

Moreover, another key player in initiating ferroptosis is ACSL4, a key enzyme in arachidonic acid metabolic pathway[50]. The activation of this pathway leads to the production of lipid peroxides, which in turn induce ferroptosis. Based on this, He et al.[51] conducted metabolomic assays on the HCs treated with cisplatin and found that the highest degree of change occurred in both the glutathione and arachidonic acid metabolic pathway. Their analysis identified ACSL4 as a key enzyme with substantial regulatory impact. Inhibition of ACSL4 expression enhances cellular resistance to ferroptosis, suggesting that ACSL4 could be a promising target for therapeutic interventions.

Intriguingly, the role of Hippo/YAP pathway in cisplatin sensitivity has been thoroughly investigated in cancer contexts[52,53]. Niu et al.[54] extended this research to cisplatin-induced ototoxicity, utilising *in vitro* experiments to show that YAP can also regulate this process. In the context of cisplatin exposure, the cellular viability of HEI-OC1 cells is suppressed *via* elevated levels of free Fe^{2+} and TfR1, along with the inhibition of GPX4 and SLC7A11. Concurrently, YAP is inactivated in cisplatin-induced HEI-OC1 cells. However, activation of YAP enhances HEI-OC1 cellular viability by mitigating cochlear hair cell damage through the regulation of ferritin light chain (FTL) and TfR1, which in turn inhibits ferroptosis. The findings highlight that the modulation of YAP activity could manipulate the viability of HEI-OC1 cells under the administration of cisplatin, which in turn serves as a promising therapeutic approach to ameliorate cochlear hair cell damage during chemotherapy. Thus, the elucidation of otoprotective mechanisms of this pathway suggests a potential avenue for medical intervention.

This dual modulation of ferroptosis by ACSL4 and YAP underscores the complexity of cisplatin-induced hearing loss and suggests potential therapeutic strategies. Targeting ACSL4 to inhibit ferroptosis and activating YAP to enhance cellular resilience against cisplatin ototoxicity represent promising avenues for mitigating hearing impairment in cancer patients undergoing cisplatin treatment.

Shifting focus to another critical player in this scenario, nuclear factor erythroid 2-related factor 2 (Nrf2). It emerges as a key transcription factor regulating the cellular antioxidant response and preventing ferroptosis[55]. Research has shown that the activation of Nrf2 can attenuate hearing loss induced by oxaliplatin, a platinum-based anti-cancer drug similar to cisplatin, by decreasing the expression of IRP2 and reversing the expression of GPX4[56]. However, it is interesting to notice that the expression of Nrf2 has the opposite effect in cisplatin induced hearing loss. Wang et al.[57] have reported that in Nrf2 knockout (KO) HEI-OC1 cells, the expression of TfR1 is decreased, while GPX4 is increased, which suggest that Nrf2 KO cells exhibit reduced ferroptosis. To further assess ferroptosis resistance, they treated these cells with ferroptosis inducer (RSL3 and Erastin) and measured the release of lactate dehydrogenase (LDH) as an indicator of cell death. The results revealed that the release of LDH in Nrf2 KO cells was lower than in Control cells at the same concentration of ferroptosis inducers. This strongly supported that Nrf2 KO inhibits ferroptosis in cisplatin-induced ototoxicity. Nevertheless, the reason why Nrf2 has opposite effect under various drug treatments still warrants further investigation.

Transitioning to another PCD modality, necroptosis, a caspase-independent process, has also been implicated in cisplatin-associated toxicity[58]. Similar to ferroptosis, necroptosis involves complex signalling pathways that can be activated in response to cisplatin-induced stress. Specifically, cisplatin exposure may activate receptor-interacting protein kinase-1 (RIPK1) and RIPK3, key regulators of necroptosis, leading to membrane permeabilization and cell lysis[59,60]. While the administration of nectostatin, a small molecule that inhibits the activity of RIPK1, protects HEI-OC1 cells from necroptosis under the administration of cisplatin[61]. This process further complicates the cellular demise in the cochlea, contributing to the overall hearing impairment observed in cisplatin-treated individuals. Thus, the interplay between apoptosis, ferroptosis, and necroptosis highlights the multifaceted nature of cisplatin-induced hearing loss, suggesting that targeting multiple cell death pathways may be necessary for effective therapeutic interventions.

Antibiotics

Antibiotics, particularly aminoglycosides, such as streptomycin, kanamycin, neomycin, and gentamicin, are well-known for their irreversible ototoxicity[62]. As the application of antibiotics remains the primary and effective treatment for bacterial infections, the resulting hearing loss affects millions of patients worldwide.

Since the identification of ferroptosis in 2012, researchers have been investigating its connection to antibiotic-induced hearing loss. Oxidative stress is a major factor associated with the ototoxic effects of antibiotics[63]. Overproduction of ROS disrupts intracellular redox balance, triggers mitochondrial depolarisation, activates caspase-3, and ultimately leads to HCs damage through apoptosis pathway[64]. It was well documented that apoptosis contributed to the loss of HCs under the administration of aminoglycoside[61]. The activation of caspase-9 and its downstream protein, caspase-3, plays a significant role in aminoglycoside-induced hearing loss,

which ultimately leads to HCs apoptosis[65,66]. Alongside caspase activation, Nrf2 also plays a vital role in regulating apoptosis[67,68]. It was demonstrated by Gu et al.[69] that the activation of Nrf2 by the administration of ebselen could attenuate tobramycin-induced hearing loss.

As Nrf2 has also been demonstrated to regulate ferroptosis in cisplatin-induced HCs death, it is anticipated that there might be a complicated crosstalk between apoptosis and ferroptosis in the mediation of it under the administration of aminoglycosides. However, the precise molecular mechanisms still need to be further elucidated.

In their exploration of aminoglycoside ototoxicity, Zheng et al.[70] focused on neomycin, the most ototoxic member, and its link to ferroptosis. Their research in HEI-OC1 cells revealed that neomycin pre-treatment induced mitochondrial dysfunction and heightened intracellular oxidative stress, processes associated with ferroptosis. Notably, co-treatment with liproxstatin-1 (Lip-1) significantly enhanced cell viability by alleviating ROS generation, mitigating mitochondrial dysfunction, and preserving mitochondrial morphology. The protective role of Lip-1 against neomycin-induced HCs damage hints at its therapeutic potential. Additionally, recent findings indicate that gentamicin treatment reduces the expression of ferroptosis-related proteins GPX4 and SLC7A11 while elevating iron content in HEI-OC1 cells, effects reversed by the ferroptosis inhibitor Ferrostatin-1[71]. Furthermore, p53 inhibitors reverse the expression levels of GPX4 and SLC7A11[71], suggesting that gentamicin might induce ferroptosis in HEI-OC1 cells *via* the p53 pathway, thereby implicating ferroptosis in the mechanism of aminoglycoside-induced hearing loss.

Anaesthetics

Sevoflurane, a clinically prevalent anaesthetic renowned for its rapid onset, minimal respiratory inhibition, circulatory inhibition, and quick recovery[72], has garnered attention due to its neurotoxic potential[73]. Studies have shown that sevoflurane administration in neonatal mice leads to ROS accumulation in HCs, disrupting their normal functions and ultimately causing hearing impairment in adults.[74] This ROS-induced damage to HCs may extend its impact to the regulation of cellular processes, notably those governed by microRNAs (miRNAs) that target the 3′-untranslated regions (3′-UTRs) of specific mRNAs[75], as evidenced by sevoflurane's ability to modulate the expression of specific miRNAs, thereby influencing downstream mRNA expression[76]. Jin et al.[76] have demonstrated that GPX4 is one of the targeted genes of miR-182-5p, implicating this miRNA is involved in ferroptosis related hearing loss. Application of Ferrostatin-1 shows the role of ferroptosis in sevoflurane-induced hearing loss and functional impairment of synaptic ribbons in HCs of mice. *In vitro*, exposure of HEI-OC1 cells to sevoflurane led to upregulated miR-182-5p expression, accompanied by iron overload and accumulation of intracellular lipid peroxide. This upregulation decreased GPX4 expression through binding to its 3′-UTR, thereby decreasing the intracellular antioxidant capacity. The adverse effects of sevoflurane were attenuated upon treatment with the miR-182-5p inhibitor or ferrostatin-1, which indicated that miR-182-5p/GPX4 pathway was involved in sevoflurane-induced hearing dysfunction. Thus, the inhibitor of miR-182-5p might have a therapeutic value for preventing ototoxicity associated with anaesthesia.

Ferroptosis in age-related hearing loss

This section summarised the current studies which linked age-related hearing loss and ferroptosis and its mechanisms of onset, as ageing is an inevitable process that affects all individuals.

Age-related hearing loss (ARHL) is characterised by progressive bilateral decline in hearing[6]. Despite the pressing need for medical interventions, the precise molecular mechanisms underlying ARHL remain largely unclear. While degeneration of auditory cortex and related peripheral auditory structures are well-recognised causes, apoptosis has been the primary focus of investigation[8,77,78]. However, recent studies have revealed that ferroptosis may also play a significant role in ARHL. Chen et al.[79] revealed that relieving ferroptosis could partially reverse neurodegeneration in the auditory cortex. Using D-galactose to create ageing models, they observed that the ultrastructural features of ferroptosis appeared in the auditory cortex with ageing, including upregulation of IRP2 and TfR1, which led to increased iron influx and ferroptosis. Application of DFO and knockdown of IRP2 mitigated ferroptosis and provided partial protection against ageing. This study offers new insights into potential strategies for alleviating ARHL.

In addition to the appearance of pro-ferroptotic features in auditory cortex, genetic factors have also been demonstrated to contribute to ARHL. KCNMA-1, a gene that encodes the α-subunit of the large conductance calcium-activated potassium channel (BK channel), has been associated with ARHL[80–82]. Tang et al.[83] underscores the significance of KCNMA-1 in the context of ARHL and provides novel insights. By demonstrating that downregulation of KCNMA-1 in HEI-OC1 cells leads to enhanced ferroptosis and accelerated cellular ageing, they have highlighted a potential regulatory role for this gene in maintaining cochlear health. The observation of mitochondrial ultrastructural damage, including cristae loss and membrane disruption, further supports the notion that KCNMA-1 is intricately linked to mitochondrial function and stability. Given its role in regulating ferroptosis and mitigating ageing processes, KCNMA-1 emerges as a promising therapeutic target for interventions aimed at preserving auditory function in ageing individuals. However, a notable limitation of this study is the lack of specific elucidation on the precise molecular mechanisms through which KCNMA-1 influences ferroptosis and senescence. Therefore, it is imperative for future research to meticulously investigate these mechanisms as well as exploring potential pharmacological strategies to modulate its activity.

Oxidative stress is a prominent feature in senescence-accelerated mouse prone 8 (SAMP8) models, extending beyond gene expression alterations[84]. This stress appears to be intricately linked to the ferroptosis pathway, which plays a pivotal role in the pathogenesis of neurodegenerative diseases. Characterised by GSH depletion, lipoxygenase activation, ROS accumulation, and calcium dysregulation due to cGMP-gated channel activation[85–87], ferroptosis has been hypothesised to be implicated in ARHL as well.

Transitioning to the cellular consequences of oxidative stress in ageing, particularly in auditory tissues. Hallmarks of ferroptosis, such as GSH depletion and lipid peroxidation, are evident in the auditory cortex[79] and cochlea[88]. Recent studies in ageing rats have demonstrated that ferroptosis contributes to neurodegeneration in the auditory cortex, a process that can be alleviated by iron chelators, such as DFO or through IRP2 knockdown[79]. Building on these findings, cutting-edge research employing bioinformatics has now pointed lactotransferrin (LTF) as a pivotal gene in the ageing cochlea. This finding has been validated *in vivo* and *in vitro* models of senescence, where a significant reduction in LTF expression accompanies the occurrence of ferroptosis. Furthermore, they have confirmed that CEBPA functions as a transcription factor (TF) and miR-130b as an miRNA, both regulating LTF expression in mice and humans, as it exhibits a high homology between these two species. This suggests the existence of a potential regulatory network, CEBPA-miRNA-130b-LTF (TF-miRNA-mRNA), modulates

cochlear ferroptosis[88]. Despite the current absence of gene data from cochlear tissue of ARHL patients, the regulatory network identified in this study holds considerable potential for application in both mice and humans. Targeting these molecular mechanisms could potentially mitigate or even reverse the progression of hearing decline associated with ageing.

In addition, excitingly pharmacological interventions aimed at reducing lipid peroxidation have also shown promise in preserving auditory function. CMS121, a neuroprotective drug with good oral bioavailability, inhibits fatty acid synthase (FASN) to reduce the lipid peroxidation[89]. Pham et al.[90] demonstrated that SAMP8 mice fed a CMS121-containing diet from 4 weeks of age showed improved auditory brainstem response (ABR) thresholds at 13 weeks compared to those fed a vehicle diet. This study highlights the potential of fatty acid synthase antagonists in alleviating ARHL.

Ferroptosis in noise-induced hearing loss

This section reviews the current studies on the mechanisms of ferroptosis-mediated noise-induced hearing loss (NIHL), particularly important in today's highly urbanised society where noise is difficult to avoid.

NIHL stands as one of the most prevalent forms of sensorineural hearing loss, second only to ARHL. Intense noise exposure, the primary initiating factor, disrupts the perilymphatic and endolymphatic fluids, compromising HCs, ribbon synapses, and neural conduction, ultimately culminating in NIHL[91]. Extensive research into the causes of NIHL has revealed multiple factors, with mechanical damage, inflammatory cascades, and oxidative stress being the most prominent. Following noise exposure, cochlear tissues rapidly accumulate ROS, persisting for 7–10 days, marking early HCs damage[92]. Concurrently, inner ear immune response disrupts cellular energy metabolism, leading to increased ROS[93]. ROS induces lipid peroxidation, generating vasoactive products that reduce cochlear blood flow. Noise-induced ischaemia and subsequent reperfusion could further promote ROS generation in a positive feedback loop, further compromising cochlear cell health[92]. Since ROS can induce ferroptosis, researchers are exploring that whether inhibiting ferroptosis might mitigate NIHL.

Research on the role of ferroptosis in NIHL has been advancing rapidly. Studies have shown that ferroptosis inhibitors, such as ferrostatin-1, can protect cochlear HCs from oxidative damage both *in vivo* and *in vitro*[14]. For instance, CBA/J mice models of NIHL treated with ferrostatin-1 demonstrated reduced hearing threshold shifts and cochlear damage, ribbon synapse disruption, and auditory nerve fibre damage compared to untreated controls. This was accompanied by downregulation of FSP1, p53, and TfR1. These findings suggest that targeting ferroptosis may offer a novel therapeutic strategy for NIHL.

To further explore the potential of ferroptosis inhibitor in NIHL treatment, researchers are developing novel drug delivery systems, such as thermosensitive nanodelivery system loaded with ferrostatin-1, for intratympanic injection[94]. This approach aims to enhance drug delivery to the inner ear while minimising systemic side effects. Preliminary studies have shown promising results, indicating that this targeted therapy may effectively protect against noise-induced hearing loss and cochlear structural damage.

In addition, apoptosis, a well-recognised PCD, occurs in response to stressors like noise exposure. In NIHL, intense noise activated caspase-3 in cochlear hair cell, leading to cellular breakdown and apoptotic body release[95]. In contrast, necrosis, resulting from severe physical or chemical injury, occurs under extreme noise conditions, characterised by cellular swelling, organelle disruption, and release of cellular contents, triggering inflammation and tissue damage[96]. Research showed noise exposure elicited apoptotic and necrotic features in cochlear hair cells. Caspase inhibitors reduced apoptosis but increased necrosis, whereas necrostatin-1 decreased necrosis but elevated apoptosis[97]. These findings suggest that noise-induced hair cell death involves a balance among multiple cell death modalities, including apoptosis, necrosis, and ferroptosis. Further investigation into the underlying mechanisms is required.

Ferroptosis in otitis-media-induced hearing loss

Otitis media (OM) is characterised by conductive hearing loss, mastoiditis, and tympanic membrane perforation, and it often results in hearing disability in children[98,99]. In this section, the mechanisms of hearing dysfunction caused by OM through ferroptosis were summarised based on existing studies.

Recent studies have highlighted a correlation between iron homeostasis and inflammatory diseases, suggesting that excessive intracellular iron may trigger inflammatory response[100]. Consequently, some scientists hypothesise a close relationship between ferroptosis and OM, given that both conditions involve inflammation.

Yan et al.[101] confirmed the involvement of ferroptosis in OM. They successfully created OM models in C57BL/6 mice using PGPS and examined ferroptosis related genes, such as ACSL4, GPX4, and COX2, as well as lipid peroxidation markers including 4-HNE and MDA. Cochlear histological changes were assessed using H&E staining. The results indicated that ACSL4 and COX2 were upregulated in the PGPS-induced OM group, while GPX4 was downregulated, confirming the occurrence of ferroptosis in OM. Moreover, levels of 4-HNE and MDA were also elevated, accompanied by excessive immune cell infiltration, as observed in H&E staining. Treatment with ferroptosis inhibitors, such as DFO, ferrostatin-1, and Lip-1, restored the expression levels of ACSL4, GPX4, and COX2, and reversed the histological changes induced by PGPS, thereby efficiently inhibiting the onset of OM. Additionally, the expression of TNF-α, an inflammatory factor, was reduced. These findings demonstrated that ferroptosis contributed to the pathogenesis of OM and that inhibiting ferroptosis might alleviate PGPS-induced OM. The findings point to ferroptosis as a potential therapeutic target for future treatment strategies.

Potential therapeutic targets for preventing ferroptosis in hearing loss

As hearing loss can be caused by a variety of causes, seeking for methods to protect or alleviate this problem becomes more and more imminent. In this section, we reviewed the current existing studies of the drugs or strategies which exerted the otoprotective effect by targeting ferroptosis and their mechanisms.

The exploration of Chinese medicine therapy

Preventing ferroptosis in hearing loss represents a promising therapeutic approach, with various potential therapeutic targets emerging from both traditional and modern medicinal research. Chinese medicinal herbs, such as tangerine peel and lotus leaves, have shown potential in mitigating cisplatin-induced ototoxicity. Tangerine peel contains nobiletin[102], a compound that mimics the

effects of ferrostatin-1 by inhibiting ferroptosis linked to decreased GPX4 levels and alleviating cisplatin-induced damage by promoting Nrf2 transcription[103]. Similarly, nuciferine, derived from lotus leaves[104,105], can inhibit cisplatin-induced ferroptosis by blocking ferritinophagy, albeit with a need for careful dose management due to potential cytotoxicity at higher concentrations[106]. Building on this foundation, Chinese medicine, with its rich tradition and complex formulations, offers a promising avenue by potentially modulating the pathways involved in ferroptosis through its bioactive compounds. Future research could explore deeper into the specific active compounds and their modes of action, paving the way for the development of novel therapeutic agents derived from traditional Chinese medicine.

The exploration of gene therapy

Gene therapy has emerged as a transformative treatment for hearing loss, offering global hope. A recent Lancet article (2024) on "AAV1-hOTOF Gene Therapy for Autosomal Recessive Deafness 9: A Single-Arm Trial"[107] reports preliminary clinical success, marking a pivotal milestone. This study fosters optimism for future gene therapies targeting diverse hearing loss conditions. Furthermore, gene therapy's potential extends beyond treating inherited deafness, as it also presents viable strategies for targeting ferroptosis, a critical mechanism implicated in hearing loss[108]. Specific miRNAs, such as miR-182-5p, which regulates GPX4 expression, show potential in modulating iron overload and lipid peroxidation[76]. Building on this, gene therapy strategies, like overexpressing GPX4, have demonstrated reversal of cochlear HCs damage in mouse models[109]. Additionally, the role of Nrf2 and other genes like KCNMA-1 and Niemann-Pick type C1 (NPC1) in ferroptosis suggests that targeting these pathways could offer innovative solutions for ARHL and chemotherapy-induced hearing impairment[83,110]. Given the significant role of LTF in this CEBPA-miR-130b-LTF network and its homology in mice and humans, therapeutic strategies focusing on LTF holds considerable potential for addressing ARHL in humans. Therapeutic strategies focused on LTF have considerable potential to treat ARHL in humans, potentially by modulating its expression level or activity. To mitigate ARHL, specific therapeutic strategies involve inhibiting miR-130b to upregulate LTF expression, modulating CEBPA to indirectly affect LTF levels, and utilising gene therapy for LTF overexpression. Additionally, combining these approaches with iron chelators could provide synergistic benefits in reducing cochlear ferroptosis.

Gene therapy, on one hand, holds the promise of directly correcting genetic defects or modulating gene expression to restore balance in iron metabolism and antioxidant defences. Future studies could explore the use of RNA interference or CRISPR-Cas technologies to precisely manipulate gene expression networks, offering personalised therapeutic approaches tailored to individual genetic profiles through localised cochlear targeting methods.

On the other hand, gene therapy, specifically localised gene therapy targeting the cochlea, stands as a frontier in treating ferroptosis-induced hearing loss. By directly delivering therapeutic genes to the site of action, high concentrations can be achieved with minimal systemic exposure, enhancing both efficacy and safety. This precision in delivery is crucial for effectively modulating gene expression and restoring the delicate balance of iron metabolism and antioxidant defences. Thus, the unique features of the cochlea pose not only challenges but also present opportunities for innovative therapeutic strategies to address hearing impairments associated with ferroptosis. Future research could focus on optimising gene delivery vectors, enhancing gene expression stability, and exploring combination therapies that synergize the effects of gene therapy with other treatment modalities.

The exploration of innovative therapeutic agents

Other strategies involve the use of small molecules and nanomaterials. 4-Octyl itaconate (4-OI) activates the NRF2/HO-1 signalling pathway to inhibit cisplatin-induced HCs ferroptosis[111], while DFO exhibits otoprotective effects by inhibiting both apoptosis and ferroptosis, albeit with potential ototoxicity at high doses[79]. Nanozymes, with antioxidant activities akin to natural enzymes, such as a palladium single-atom nanozyme, convert ROS to oxygen and water, exerting an otoprotective effect against neomycin-induced ototoxicity[112].

The exploration of preclinical trials and dietary modifications

In recent preclinical trials, anti-ferroptotic compounds, such as vitamin E, particularly its alpha-tocopherol form, have emerged as promising agents for hearing health[113–115]. Elevated serum levels of vitamin E have been inversely associated with the risk of sudden SNHL[116], and dietary intake has shown protective effects against various hearing impairments, including cisplatin-induced ototoxicity[117] and noise-induced hearing loss[118–120]. Similarly, N-acetylcysteine (NAC), a glutathione precursor with potent antioxidant properties[121], has demonstrated clinical benefit in hearing loss[122–125], particularly when used synergistically with corticosteroids[126–129], hinting at its potential as a ferroptosis-targeted therapy. However, despite these promising findings, direct experimental validation of the NAC-ferroptosis link in hearing loss remains an area of ongoing research, underscoring the potential and progress yet to be made in this field.

These findings highlight a diverse range of potential therapeutic targets and therapeutic strategies for suppressing ferroptosis in

Table 1. Summary of these potential therapeutic compounds and their mechanisms of action.

Potential therapeutic compounds	Mechanisms of action	Models	References
Ferrostatin-1	Antioxidant Inhibit p53/SLC7A11/GPX4 pathway Inhibit TfR1, ACSL4	HEI-OC1 cells Rats	14,51,76,101
Chloroquine	Autophagy and Toll-like receptor (TLR) inhibitor	HEI-OC1 cells	21
Rosiglitazone	ACSL4 inhibitor	HEI-OC1 cells	51
Liproxstatin-1	Antioxidant Increase GPX4, inhibit ACSL4	HEI-OC1 cells	70
miR-182-5p inhibitor	Inhibit the downregulation of GPX4	HEI-OC1 cells	76
Deferoxamine	Iron chelator Increase GPX4, inhibit ACSL4	HEI-OC1 cells	26,79
CMS121	Fatty acid synthase antagonist	SAMP8 mice	90
alpha-tocopherol (Vitamin E)	Antioxidant Anti-ferroptosis (not known)	Human	117–119
N-acetylcysteine (NAC)	Antioxidant Anti-ferroptosis (not known)	Human	123–125
Nobiletin	Antioxidant	HEI-OC1 cells	103
Nuciferine	Inhibit NCOA4-mediated autophagy	HEI-OC1 cells	106
4-Octyl itaconate	Anti-inflammatory Antioxidant	HEI-OC1 cells	111
Pd SAN	ROS scavenger	HEI-OC1 cells Zebrafish	112

hearing loss, offering new avenues for future research and clinical applications.

In addition to these therapeutic strategies mentioned earlier, dietary modifications to augment antioxidant intake, particularly vitamin E, a potent lipid-soluble antioxidant that scavenges ROS and mitigates oxidative damage to cellular membranes pivotal in ferroptosis pathogenesis, represent a promising adjunctive therapy for ferroptosis-induced hearing loss. Incorporating foods rich in vitamin E, such as nuts, seeds, leafy greens, and oils, significantly elevates serum levels of this nutrient. Additionally, a holistic antioxidant screening approach should encompass glutathione, vitamin C, and polyphenols from fruits and vegetables, which also maintain redox balance and protect auditory cells. Evaluating dietary intake and serum concentrations of these antioxidants, with targeted supplementation as needed, could further enhance protection against ferroptosis-related hearing decline.

These potential therapeutic compounds which exhibit the ability to protect hearing loss were summarised in Table 1[130].

Conclusion and expectation

In conclusion, this review offers a concise overview of ferroptosis, highlighting its emerging role as a critical factor in the pathogenesis of various forms of hearing loss. By examining the links between ferroptosis and hearing loss, including its involvement in drug-induced, age-related, noise-induced, and otitis media-induced hearing impairments, we have demonstrated the widespread and profound impact of this novel cell death mechanism. The intricate interplay between ferroptosis and hearing loss pathways has been elucidated, revealing potential therapeutic targets for mitigating hearing damage.

In particular, the exploration of therapeutic strategies to prevent ferroptosis in hearing loss has been a focal point of this review. The potential of Chinese medicine therapy, gene therapy, and innovative therapeutic agents in targeting ferroptosis has been discussed, showing the diverse approaches being pursued to address this complex issue. Furthermore, the importance of preclinical trials and dietary modifications in assessing the efficacy and safety of these therapies has been emphasised. However, it is important to note that therapeutic interventions targeting ferroptosis-related pathways have thus far been primarily exploratory and preclinical. There is an urgent need for clinical trials to validate the efficacy and safety of these novel therapeutic approaches, ultimately paving the way for the translation of ferroptosis-targeted therapies into clinical practice for the management of hearing loss.

Our analysis revealed substantial potential for ferroptosis inhibitors in treating hearing loss. By targeting key factors in the ferroptosis pathway, such as GPX4 and ACSLs, these inhibitors hold promise for mitigating oxidative stress-related hearing damage and cellular injury. In animal models, these inhibitors have demonstrated positive outcomes by improving auditory function and protecting cochlear hair cells. Given these findings, we firmly believe that this therapeutic approach merits further exploration. Accumulating evidence links ferroptosis to hearing loss, and encouraging preclinical results with ferroptosis inhibitors provide a robust rationale for human clinical trials. Future efforts must prioritise clinical trials to validate the efficacy and safety of these novel therapies, facilitating the translation of ferroptosis-targeted treatments into clinical practice for hearing loss. However, we acknowledge the multifaceted challenges involved in transitioning preclinical successes to clinical applications, including identifying efficacious and safe inhibitors, optimising dosing and administration protocols, and developing reliable biomarkers and diagnostic tools to assess cochlear ferroptosis levels and monitor therapeutic responses. These are pivotal areas of ongoing research.

Moreover, early detection and intervention are crucial in managing hearing loss associated with ferroptosis. Serial assessments of serum levels of total antioxidant capacity (TAC) and specific antioxidants are indispensable for understanding physiological processes predisposing individuals to ferroptosis-induced hearing impairment. Specifically, elevated ferrous iron and depleted antioxidants reserve augment oxidative stress, a key driver of ferroptosis, thereby highlighting those at heightened risk. Additionally, genetic screening for mutations related to iron metabolism disorders or oxidative stress susceptibility further refines risk assessment and enables the tailoring of personalised intervention strategies.

In future, we anticipate rapid advancements in the field of ferroptosis-targeted therapies for hearing loss. As our understanding of the molecular mechanisms underlying ferroptosis and hearing loss deepens, and novel therapeutic agents are developed, we are optimistic that effective and safe treatments for hearing loss will become a reality in the near future.

In summary, ferroptosis inhibitors offer a promising therapeutic strategy for treating hearing loss. Despite the numerous challenges that remain, the potential benefits of these inhibitors in preserving auditory function and improving the quality of life for patients with hearing impairments cannot be overlooked. We eagerly await the outcomes of future research and clinical trials, which will further elucidate the role of ferroptosis in hearing loss and validate the effectiveness of ferroptosis inhibitors as therapeutic interventions.

Author contributions

Conceptualisation, X.L., M.W., and L.L.; writing—original draft preparation, X.L.; writing—review and editing, M.W. and L.L.; visualisation, C.Y., X.Li., Y.L., Y.Y., T.J., Z.C., and J.J.; funding acquisition, M.W. and L.L. All authors have read and agreed to the published version of the manuscript.

Disclosure statement

The authors report no conflicts of interest.

Funding

This research was funded by National Natural Science Foundation of China (81960188), Exploration Project of Natural Science Foundation of Zhejiang Province (LMS25H130002), Scientific Research Fund of Zhejiang Provincial Education Department (Y202454380), Starlit South Lake Leading Elite Program (2022A100001), and Scientific Research and Training Program of Jiaxing University (8517231303).

Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

References

1. Michels TC, Duffy MT, Rogers DJ. Hearing loss in adults: differential diagnosis and treatment. Am Fam Physician. 2019;100(2):98–108.
2. Nieman CL, Oh ES. Hearing loss. Ann Intern Med. 2020;173(11):ltc81–itc96.
3. Ding T, Yan A, Liu K. What is noise-induced hearing loss? Br J Hosp Med. 2019;80(9):525–529.
4. Tan WJT, Song L. Role of mitochondrial dysfunction and oxidative stress in sensorineural hearing loss. Hear Res. 2023;434:108783.
5. Teraoka M, Hato N, Inufusa H, You F. Role of oxidative stress in sensorineural hearing loss. Int J Mol Sci. 2024;25(8):4146.
6. Bowl MR, Dawson SJ. Age-related hearing loss. Cold Spring Harb Perspect Med. 2019;9(8):a033217.
7. Chen H, Tang J. The role of mitochondria in age-related hearing loss. Biogerontology. 2014;15(1):13–19.
8. Keithley EM. Pathology and mechanisms of cochlear aging. J Neurosci Res. 2020;98(9):1674–1684.
9. Oza AM, DiStefano MT, Hemphill SE, Cushman BJ, Grant AR, Siegert RK, Shen J, Chapin A, Boczek NJ, Schimmenti LA, et al. Expert specification of the ACMG/AMP variant interpretation guidelines for genetic hearing loss. Hum Mutat. 2018;39(11):1593–1613.
10. Sloan-Heggen CM, Bierer AO, Shearer AE, Kolbe DL, Nishimura CJ, Frees KL, Ephraim SS, Shibata SB, Booth KT, Campbell CA, et al. Comprehensive genetic testing in the clinical evaluation of 1119 patients with hearing loss. Hum Genet. 2016;135(4):441–450.
11. Kros CJ, Steyger PS. Aminoglycoside- and cisplatin-induced ototoxicity: mechanisms and otoprotective strategies. Cold Spring Harb Perspect Med. 2019;9(11):a033548.
12. Wu J, Ye J, Kong W, Zhang S, Zheng Y. Programmed cell death pathways in hearing loss: a review of apoptosis, autophagy and programmed necrosis. Cell Prolif. 2020;53(11):e12915.
13. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;149(5):1060–1072.
14. Ma PW, Wang WL, Chen JW, Yuan H, Lu PH, Gao W, Ding XR, Lun YQ, Liang R, He ZH, et al. Treatment with the ferroptosis inhibitor ferrostatin-1 attenuates noise-induced hearing loss by suppressing ferroptosis and apoptosis. Oxid Med Cell Longev. 2022;2022:3373828.
15. Mou Y, Wang J, Wu J, He D, Zhang C, Duan C, Li B. Ferroptosis, a new form of cell death: opportunities and challenges in cancer. J Hematol Oncol. 2019;12(1):34.
16. Reichert CO, de Freitas FA, Sampaio-Silva J, Rokita-Rosa L, Barros PL, Levy D, Bydlowski SP. Ferroptosis mechanisms involved in neurodegenerative diseases. Int J Mol Sci. 2020;21(22):8765.
17. Tuo QZ, Liu Y, Xiang Z, Yan HF, Zou T, Shu Y, Ding XL, Zou JJ, Xu S, Tang F, et al. Thrombin induces ACSL4-dependent ferroptosis during cerebral ischemia/reperfusion. Signal Transduct Target Ther. 2022;7(1):59.
18. Shah R, Shchepinov MS, Pratt DA. Resolving the role of lipoxygenases in the initiation and execution of ferroptosis. ACS Cent Sci. 2018;4(3):387–396.
19. Park E, Chung SW. ROS-mediated autophagy increases intracellular iron levels and ferroptosis by ferritin and transferrin receptor regulation. Cell Death Dis. 2019;10(11):822.
20. Rui T, Wang H, Li Q, Cheng Y, Gao Y, Fang X, Ma X, Chen G, Gao C, Gu Z, et al. Deletion of ferritin H in neurons counteracts the protective effect of melatonin against traumatic brain injury-induced ferroptosis. J Pineal Res. 2021;70:e12704.
21. Jian B, Pang J, Xiong H, Zhang W, Zhan T, Su Z, Lin H, Zhang H, He W, Zheng Y. Autophagy-dependent ferroptosis contributes to cisplatin-induced hearing loss. Toxicol Lett. 2021;350:249–260.
22. Zhou L, Jiang J, Huang Z, Jin P, Peng L, Luo M, Zhang Z, Chen Y, Xie N, Gao W, et al. Hypoxia-induced lncRNA STEAP3-AS1 activates Wnt/β-catenin signaling to promote colorectal cancer progression by preventing m(6)A-mediated degradation of STEAP3 mRNA. Mol Cancer. 2022;21(1):168.
23. Hwang J, Park A, Kim C, Kim CG, Kwak J, Kim B, Shin H, Ku M, Yang J, Baek A, et al. Inhibition of IRP2-dependent reprogramming of iron metabolism suppresses tumor growth in colorectal cancer. Cell Commun Signal. 2024;22(1):412.
24. Singh A, Kaur N, Kosman DJ. The metalloreductase Fre6p in Fe-efflux from the yeast vacuole. J Biol Chem. 2007;282(39):28619–28626.
25. Schilstra MJ, Veldink GA, Vliegenthart JF. The dioxygenation rate in lipoxygenase catalysis is determined by the amount of iron (III) lipoxygenase in solution. Biochemistry. 1994;33(13):3974–3979.
26. Lu PH, Ma PW, Wang WL, Gao W, Chen JW, Yuan H, Ding XR, Lun YQ, Liang R, Li SY, et al. Deferoxamine protects cochlear hair cells and hair cell-like HEI-OC1 cells against tert-butyl hydroperoxide-induced ototoxicity. Biochim Biophys Acta Mol Basis Dis. 2024;1870(3):167024.
27. Cui J, Wang Y, Tian X, Miao Y, Ma L, Zhang C, Xu X, Wang J, Fang W, Zhang X. LPCAT3 is transcriptionally regulated by YAP/ZEB/EP300 and collaborates with ACSL4 and YAP to determine ferroptosis sensitivity. Antioxid Redox Signal. 2023;39(7–9):491–511.
28. Xue Q, Kang R, Klionsky DJ, Tang D, Liu J, Chen X. Copper metabolism in cell death and autophagy. Autophagy. 2023;19(8):2175–2195.
29. Doll S, Proneth B, Tyurina YY, Panzilius E, Kobayashi S, Ingold I, Irmler M, Beckers J, Aichler M, Walch A, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat Chem Biol. 2017;13(1):91–98.
30. Xu C, Sun S, Johnson T, Qi R, Zhang S, Zhang J, Yang K. The glutathione peroxidase Gpx4 prevents lipid peroxidation and ferroptosis to sustain Treg cell activation and suppression of antitumor immunity. Cell Rep. 2021;35(11):109235.
31. Ursini F, Maiorino M. Lipid peroxidation and ferroptosis: the role of GSH and GPx4. Free Radic Biol Med. 2020;152:175–185.
32. Imai H, Matsuoka M, Kumagai T, Sakamoto T, Koumura T. Lipid peroxidation-dependent cell death regulated by GPx4 and ferroptosis. Curr Top Microbiol Immunol. 2017;403:143–170.
33. Yang WS, Stockwell BR. Ferroptosis: death by lipid peroxidation. Trends Cell Biol. 2016;26(3):165–176.
34. Yagoda N, von Rechenberg M, Zaganjor E, Bauer AJ, Yang WS, Fridman DJ, Wolpaw AJ, Smukste I, Peltier JM, Boniface JJ, et al. RAS-RAF-MEK-dependent oxidative cell death involving voltage-dependent anion channels. Nature. 2007;447(7146):864–868.
35. Wang L, Liu Y, Du T, Yang H, Lei L, Guo M, Ding HF, Zhang J, Wang H, Chen X, et al. ATF3 promotes erastin-induced ferroptosis by suppressing system Xc. Cell Death Differ. 2020;27(2):662–675.

36. Zhao Y, Li Y, Zhang R, Wang F, Wang T, Jiao Y. The role of erastin in ferroptosis and its prospects in cancer therapy. Onco Targets Ther. 2020;13:5429–5441.
37. Cui Y, Zhang Z, Zhou X, Zhao Z, Zhao R, Xu X, Kong X, Ren J, Yao X, Wen Q, et al. Microglia and macrophage exhibit attenuated inflammatory response and ferroptosis resistance after RSL3 stimulation via increasing Nrf2 expression. J Neuroinflammation. 2021;18(1):249.
38. Li S, He Y, Chen K, Sun J, Zhang L, He Y, Yu H, Li Q. RSL3 drives ferroptosis through NF-κB pathway activation and GPX4 depletion in glioblastoma. Oxid Med Cell Longev. 2021;2021(1):2915019.
39. Liu P, Feng Y, Li H, Chen X, Wang G, Xu S, Li Y, Zhao L. Ferrostatin-1 alleviates lipopolysaccharide-induced acute lung injury via inhibiting ferroptosis. Cell Mol Biol Lett. 2020;25(1):10.
40. Bersuker K, Hendricks JM, Li Z, Magtanong L, Ford B, Tang PH, Roberts MA, Tong B, Maimone TJ, Zoncu R, et al. The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. Nature. 2019;575(7784):688–692.
41. Kraft VAN, Bezjian CT, Pfeiffer S, Ringelstetter L, Müller C, Zandkarimi F, Merl-Pham J, Bao X, Anastasov N, Kössl J, et al. GTP cyclohydrolase 1/tetrahydrobiopterin counteract ferroptosis through lipid remodeling. ACS Cent Sci. 2020;6(1):41–53.
42. Courtois S, Angelini C, C MD, Dias Amoedo N, Courreges A, Dumon E, Le Quang M, Goizet C, Martin-Negrier ML, Rossignol R, et al. Mutation on MT-CO_2 gene induces mitochondrial disease associated with neurodegeneration and intracerebral iron accumulation (NBIA). Biochim Biophys Acta Mol Basis Dis. 2024;1870(1):166856.
43. Liu J, Bai Y, Feng Y, Liu X, Pang B, Zhang S, Jiang M, Chen A, Huang H, Chen Y, et al. ABCC1 deficiency potentiated noise-induced hearing loss in mice by impairing cochlear antioxidant capacity. Redox Biol. 2024;74:103218.
44. Castiglione A, Ciorba A, Aimoni C, Orioli E, Zeri G, Vigliano M, Gemmati D. Sudden sensorineural hearing loss and polymorphisms in iron homeostasis genes: new insights from a case-control study. Biomed Res Int. 2015;2015:834736.
45. Dasari S, Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol. 2014;740:364–378.
46. Qi L, Luo Q, Zhang Y, Jia F, Zhao Y, Wang F. Advances in toxicological research of the anticancer drug cisplatin. Chem Res Toxicol. 2019;32(8):1469–1486.
47. Ramkumar V, Mukherjea D, Dhukhwa A, Rybak LP. Oxidative stress and inflammation caused by cisplatin ototoxicity. Antioxidants. 2021;10(12):1919.
48. Mancias JD, Wang X, Gygi SP, Harper JW, Kimmelman AC. Quantitative proteomics identifies NCOA4 as the cargo receptor mediating ferritinophagy. Nature. 2014;509(7498):105–109.
49. Santana-Codina N, Gikandi A, Mancias JD. The role of NCOA4-mediated ferritinophagy in ferroptosis. Adv Exp Med Biol. 2021;1301:41–57.
50. Ji Q, Fu S, Zuo H, Huang Y, Chu L, Zhu Y, Hu J, Wu Y, Chen S, Wang Y, et al. ACSL4 is essential for radiation-induced intestinal injury by initiating ferroptosis. Cell Death Discov. 2022;8(1):332.
51. He F, Huang X, Wei G, Lin X, Zhang W, Zhuang W, He W, Zhan T, Hu H, Yang H. Regulation of ACSL4-catalyzed lipid peroxidation process resists cisplatin ototoxicity. Oxid Med Cell Longev. 2022;2022:3080263.
52. Gao R, Kalathur RKR, Coto-Llerena M, Ercan C, Buechel D, Shuang S, Piscuoglio S, Dill MT, Camargo FD, Christofori G, et al. YAP/TAZ and ATF4 drive resistance to Sorafenib in hepatocellular carcinoma by preventing ferroptosis. EMBO Mol Med. 2021;13(12):e14351.
53. Yang WH, Huang Z, Wu J, Ding CC, Murphy SK, Chi JT. A TAZ-ANGPTL4-NOX2 axis regulates ferroptotic cell death and chemoresistance in epithelial ovarian cancer. Mol Cancer Res. 2020;18(1):79–90.
54. Niu X, Han P, Liu J, Chen Z, Ma X, Zhang T, Li B, Ma X. Regulation of Hippo/YAP signaling pathway ameliorates cochlear hair cell injury by regulating ferroptosis. Tissue Cell. 2023;82:102051.
55. Dodson M, Castro-Portuguez R, Zhang DD. NRF2 plays a critical role in mitigating lipid peroxidation and ferroptosis. Redox Biol. 2019;23:101107.
56. Xu K, Chang X, Bai X, Liu HB, Chen XB, Chen HP, Liu YH. Activation of Nrf2 inhibits ferroptosis and protects against oxaliplatin-induced ototoxicity. Biomed Pharmacother. 2023;165:115248.
57. Wang W, Ma P, Gao W, Lu P, Ding X, Chen J, Yuan H, Lu L. Nrf2 knockout affected the ferroptosis signaling pathway against cisplatin-induced hair cell-like HEI-OC1 cell death. Oxid Med Cell Longev. 2022;2022:2210733.
58. Frank D, Vince JE. Pyroptosis versus necroptosis: similarities, differences, and crosstalk. Cell Death Differ. 2019;26(1):99–114.
59. Wegner KW, Saleh D, Degterev A. Complex pathologic roles of RIPK1 and RIPK3: moving beyond necroptosis. Trends Pharmacol Sci. 2017;38(3):202–225.
60. Choi MJ, Kang H, Lee YY, Choo OS, Jang JH, Park SH, Moon JS, Choi SJ, Choung YH. Cisplatin-induced ototoxicity in rats is driven by RIP3-dependent necroptosis. Cells. 2019;8(5):409.
61. Ruhl D, Du TT, Wagner EL, Choi JH, Li S, Reed R, Kim K, Freeman M, Hashisaki G, Lukens JR, et al. Necroptosis and apoptosis contribute to cisplatin and aminoglycoside ototoxicity. J Neurosci. 2019;39(15):2951–2964.
62. Selimoglu E. Aminoglycoside-induced ototoxicity. Curr Pharm Des. 2007;13(1):119–126.
63. Huang T, Cheng AG, Stupak H, Liu W, Kim A, Staecker H, Lefebvre PP, Malgrange B, Kopke R, Moonen G, et al. Oxidative stress-induced apoptosis of cochlear sensory cells: otoprotective strategies. Int J Dev Neurosci. 2000;18(2–3):259–270.
64. Warchol ME. Cellular mechanisms of aminoglycoside ototoxicity. Curr Opin Otolaryngol Head Neck Surg. 2010;18(5):454–458.
65. Ding D, Jiang H, Salvi RJ. Mechanisms of rapid sensory hair-cell death following co-administration of gentamicin and ethacrynic acid. Hear Res. 2010;259(1–2):16–23.
66. Kaiser CL, Chapman BJ, Guidi JL, Terry CE, Mangiardi DA, Cotanche DA. Comparison of activated caspase detection methods in the gentamicin-treated chick cochlea. Hear Res. 2008;240(1–2):1–11.
67. Li N, Yan X, Huang W, Chu M, Dong Y, Song H, Peng Y, Shi J, Liu Q. Curcumin protects against the age-related hearing loss by attenuating apoptosis and senescence via activating Nrf2 signaling in cochlear hair cells. Biochem Pharmacol. 2023;212:115575.
68. Lou J, Wu F, He W, Hu R, Cai Z, Chen G, Zhao W, Zhang Z, Si Y. Hesperidin activates Nrf2 to protect cochlear hair cells from cisplatin-induced damage. Redox Rep. 2024;29(1):2341470.

69. Gu R, Longenecker RJ, Homan J, Kil J. Ebselen attenuates tobramycin-induced ototoxicity in mice. J Cyst Fibros. 2021;20(2):271–277.
70. Zheng Z, Tang D, Zhao L, Li W, Han J, Hu B, Nie G, He Y. Liproxstatin-1 protects hair cell-like HEI-OC1 cells and cochlear hair cells against neomycin ototoxicity. Oxid Med Cell Longev. 2021;2021:9873282.
71. Li Y, Xu H, Shi J, Li C, Li M, Zhang X, Xue Q, Qiu J, Cui L, Sun Y, et al. Regulation of the p53/SLC7A11/GPX4 pathway by gentamicin induces ferroptosis in HEI-OC1 cells. Otol Neurotol. 2024;45(8):947–953.
72. Sun LS, Li G, Dimaggio C, Byrne M, Rauh V, Brooks-Gunn J, Kakavouli A, Wood A, Coinvestigators of the Pediatric Anesthesia Neurodevelopment Assessment (PANDA) Research Network. Anesthesia and neurodevelopment in children: time for an answer? Anesthesiology. 2008;109(5):757–761.
73. Ward CG, Loepke AW. Anesthetics and sedatives: toxic or protective for the developing brain? Pharmacol Res. 2012;65(3):271–274.
74. Li Y, Yu H, Zhou X, Jin L, Li W, Li GL, Shen X. Multiple sevoflurane exposures during the neonatal period cause hearing impairment and loss of hair cell ribbon synapses in adult mice. Front Neurosci. 2022;16:945277.
75. Shang R, Lee S, Senavirathne G, Lai EC. microRNAs in action: biogenesis, function and regulation. Nat Rev Genet. 2023;24(12):816–833.
76. Jin L, Yu X, Zhou X, Li G, Li W, He Y, Li H, Shen X. The miR-182-5p/GPX4 pathway contributes to sevoflurane-induced ototoxicity via ferroptosis. Int J Mol Sci. 2024;25(12):6774.
77. Sun G, Zheng Y, Fu X, Zhang W, Ren J, Ma S, Sun S, He X, Wang Q, Ji Z, et al. Single-cell transcriptomic atlas of mouse cochlear aging. Protein Cell. 2023;14(3):180–201.
78. Luo X, Hu Y, Zhou X, Zhang C, Feng M, Yang T, Yuan W. Potential roles for lncRNA Mirg/Foxp1 in an ARHL model created using C57BL/6J mice. Hear Res. 2023;438:108859.
79. Chen X, Li D, Sun HY, Wang WW, Wu H, Kong W, Kong WJ. Relieving ferroptosis may partially reverse neurodegeneration of the auditory cortex. FEBS J. 2020;287(21):4747–4766.
80. Bailey CS, Moldenhauer HJ, Park SM, Keros S, Meredith AL. KCNMA1-linked channelopathy. J Gen Physiol. 2019;151(10):1173–1189.
81. Dworetzky SI, Trojnacki JT, Gribkoff VK. Cloning and expression of a human large-conductance calcium-activated potassium channel. Brain Res Mol Brain Res. 1994;27(1):189–193.
82. Rüttiger L, Sausbier M, Zimmermann U, Winter H, Braig C, Engel J, Knirsch M, Arntz C, Langer P, Hirt B, et al. Deletion of the Ca^{2+}-activated potassium (BK) alpha-subunit but not the BKbeta1-subunit leads to progressive hearing loss. Proc Natl Acad Sci USA. 2004;101(35):12922–12927.
83. Tang X, Zhong H, Xu C, Sun Y, Lou Y, Zhao Y, Liang Y, Guo X, Pan C, Sun J, et al. Downregulation of KCNMA1 in mice accelerates auditory hair cells senescence via ferroptosis. Neurobiol Aging. 2024;134:115–125.
84. Benkafadar N, François F, Affortit C, Casas F, Ceccato JC, Menardo J, Venail F, Malfroy-Camine B, Puel JL, Wang J. ROS-induced activation of DNA damage responses drives senescence-like state in postmitotic cochlear cells: implication for hearing preservation. Mol Neurobiol. 2019;56(8):5950–5969.
85. Lewerenz J, Ates G, Methner A, Conrad M, Maher P. Oxytosis/ferroptosis-(re-) emerging roles for oxidative stress-dependent non-apoptotic cell death in diseases of the central nervous system. Front Neurosci. 2018;12:214.
86. Maher P, Currais A, Schubert D. Using the oxytosis/ferroptosis pathway to understand and treat age-associated neurodegenerative diseases. Cell Chem Biol. 2020;27(12):1456–1471.
87. Tan S, Schubert D, Maher P. Oxytosis: a novel form of programmed cell death. Curr Top Med Chem. 2001;1(6):497–506.
88. Zeng C, Gu X, Chen Y, Lin Y, Chen J, Chen Z, Chen C, Yao G, Lin C. Identification and experimental validation of ferroptosis-related gene lactotransferrin in age-related hearing loss. Front Aging Neurosci. 2024;16:1309115.
89. Chiruta C, Schubert D, Dargusch R, Maher P. Chemical modification of the multitarget neuroprotective compound fisetin. J Med Chem. 2012;55(1):378–389.
90. Pham TB, Boussaty EC, Currais A, Maher P, Schubert DR, Manor U, Friedman RA. Attenuation of age-related hearing impairment in senescence-accelerated mouse prone 8 (SAMP8) mice treated with fatty acid synthase inhibitor CMS121. J Mol Neurosci. 2023;73(4–5):307–315.
91. Kujawa SG, Liberman MC. Synaptopathy in the noise-exposed and aging cochlea: primary neural degeneration in acquired sensorineural hearing loss. Hear Res. 2015;330(Pt B):191–199.
92. Kurabi A, Keithley EM, Housley GD, Ryan AF, Wong AC. Cellular mechanisms of noise-induced hearing loss. Hear Res. 2017;349:129–137.
93. Keithley EM. Inner ear immunity. Hear Res. 2022;419:108518.
94. Ma P-W, Lu P-H, Yuan H, Chen J-W, Gao W, Lun Y-Q, Guo J-N, Ding X-R, Liang R, Li S-Y, et al. Ferrostatin-1-loaded thermosensitive nanodelivery system for noise-induced hearing loss treatment. Chem Eng J. 2023;476:146584.
95. Wang X, Zeng C, Lai Y, Su B, Chen F, Zhong J, Chu H, Bing D. NRF2/HO-1 pathway activation by ATF3 in a noise-induced hearing loss murine model. Arch Biochem Biophys. 2022;721:109190.
96. Wang W, Yu L, Li S, Han L, Zheng H. NFAT3-FasL axis synchronously regulates apoptosis and necroptosis in murine cochlear outer hair cells after noise trauma. Front Mol Neurosci. 2024;17:1422646.
97. Zheng HW, Chen J, Sha SH. Receptor-interacting protein kinases modulate noise-induced sensory hair cell death. Cell Death Dis. 2014;5(5):e1262.
98. Bardou MLD, Pontarolli D, Grumach AS. Otitis media and inborn errors of immunity. Curr Allergy Asthma Rep. 2020;20(10):59.
99. Harmes KM, Blackwood RA, Burrows HL, Cooke JM, Harrison RV, Passamani PP. Otitis media: diagnosis and treatment. Am Fam Physician. 2013;88(7):435–440.
100. Lönnerdal B. Excess iron intake as a factor in growth, infections, and development of infants and young children. Am J Clin Nutr. 2017;106(Suppl 6):1681S–1687S.
101. Yan B, Xie D, Wu Y, Wang S, Zhang X, Zhao T, Liu L, Ma P, Li G, Yang Y, et al. Ferroptosis is involved in PGPS-induced otitis media in C57BL/6 mice. Cell Death Discov. 2022;8(1):217.
102. Wang HH, Sun YN, Qu TQ, Sang XQ, Zhou LM, Li YX, Ren FZ. Nobiletin prevents D-galactose-induced C2C12 cell aging by improving mitochondrial function. Int J Mol Sci. 2022;23(19):11963.
103. Song W, Zhang L, Cui X, Wang R, Ma J, Xu Y, Jin Y, Wang D, Lu Z. Nobiletin alleviates cisplatin-induced ototoxicity via activating autophagy and inhibiting NRF2/GPX4-mediated ferroptosis. Sci Rep. 2024;14(1):7889.
104. Li D, Liu B, Fan Y, Liu M, Han B, Meng Y, Xu X, Song Z, Liu X, Hao Q, et al. Nuciferine protects against folic acid-induced acute kidney injury by inhibiting ferroptosis. Br J Pharmacol. 2021;178(5):1182–1199.

105. Zhao T, Zhu Y, Zhao R, Xiong S, Sun J, Zhang J, Fan D, Deng J, Yang H. Structure-activity relationship, bioactivities, molecular mechanisms, and clinical application of nuciferine on inflammation-related diseases. Pharmacol Res. 2023;193:106820.
106. Gao X, Mao H, Zhao L, Li X, Liao Y, Li W, Li H, Chen Y. Nuciferine protects cochlear hair cells from ferroptosis through inhibiting NCOA4-mediated ferritinophagy. Antioxidants. 2024;13(6):714.
107. Lv J, Wang H, Cheng X, Chen Y, Wang D, Zhang L, Cao Q, Tang H, Hu S, Gao K, et al. AAV1-hOTOF gene therapy for autosomal recessive deafness 9: a single-arm trial. Lancet. 2024;403(10441):2317–2325.
108. Adams BD, Parsons C, Walker L, Zhang WC, Slack FJ. Targeting noncoding RNAs in disease. J Clin Invest. 2017;127(3):761–771.
109. Liu Z, Zhang H, Hong G, Bi X, Hu J, Zhang T, An Y, Guo N, Dong F, Xiao Y, et al. Inhibition of Gpx4-mediated ferroptosis alleviates cisplatin-induced hearing loss in C57BL/6 mice. Mol Ther. 2024;32(5):1387–1406.
110. Liang L, Wang H, Yao J, Wei Q, Lu Y, Wang T, Cao X. NPC1 deficiency contributes to autophagy-dependent ferritinophagy in HEI-OC1 auditory cells. Front Mol Biosci. 2022;9:952608.
111. Zhang L, Song W, Li H, Cui X, Ma J, Wang R, Xu Y, Li M, Bai X, Wang D, et al. 4-octyl itaconate alleviates cisplatin-induced ferroptosis possibly via activating the NRF2/HO-1 signalling pathway. J Cell Mol Med. 2024;28(7):e18207.
112. Huo Q, Chen C, Liao J, Zeng Q, Nie G, Zhang B. Application of self-assembly palladium single-atom nanozyme over polyoxometalates in protection against neomycin-induced hearing loss by inhibiting ferroptosis. Biomaterials. 2024;311:122665.
113. Browne D, McGuinness B, Woodside JV, McKay GJ. Vitamin E and Alzheimer's disease: what do we know so far? Clin Interv Aging. 2019;14:1303–1317.
114. Ogawa S, Iuchi K. α-Tocopherol: new perspectives and challenges for achieving the sustainable development goals (SDG) target. J Oleo Sci. 2024;73(4):519–538.
115. Zhu R, Kang Y, Li Q, Peng K, Shi X, Yin Z, Xuan Y. Alpha-tocopherol inhibits ferroptosis and promotes neural function recovery in rats with spinal cord injury via down-regulating Alox15. Biomed Pharmacother. 2024;175:116734.
116. Gonçalves LF, Mary de Paiva K, Machado MJ, Samelli AG, Haas P. Effectiveness in preventing hearing loss: meta-analysis of dietary consumption studies. Am J Lifestyle Med. 2024;15598276241231941.
117. Villani V, Zucchella C, Cristalli G, Galiè E, Bianco F, Giannarelli D, Carpano S, Spriano G, Pace A. Vitamin E neuroprotection against cisplatin ototoxicity: preliminary results from a randomized, placebo-controlled trial. Head Neck. 2016;38 Suppl 1:E2118–E2121.
118. Hatano M, Uramoto N, Okabe Y, Furukawa M, Ito M. Vitamin E and vitamin C in the treatment of idiopathic sudden sensorineural hearing loss. Acta Otolaryngol. 2008;128(2):116–121.
119. Kapoor N, Mani KV, Shyam R, Sharma RK, Singh AP, Selvamurthy W. Effect of vitamin E supplementation on carbogen-induced amelioration of noise induced hearing loss in man. Noise Health. 2011;13(55):452–458.
120. Kaya H, Koç AK, Sayın İ, Güneş S, Altıntaş A, Yeğin Y, Kayhan FT. Vitamins A, C, and E and selenium in the treatment of idiopathic sudden sensorineural hearing loss. Eur Arch Otorhinolaryngol. 2015;272(5):1119–1125.
121. Gillissen A, Jaworska M, Orth M, Coffiner M, Maes P, App EM, Cantin AM, Schultze-Werninghaus G. Nacystelyn, a novel lysine salt of N-acetylcysteine, to augment cellular antioxidant defence *in vitro*. Respir Med. 1997;91(3):159–168.
122. Chen CH, Young YH. N-acetylcysteine as a single therapy for sudden deafness. Acta Otolaryngol. 2017;137(1):58–62.
123. Kopke R, Slade MD, Jackson R, Hammill T, Fausti S, Lonsbury-Martin B, Sanderson A, Dreisbach L, Rabinowitz P, Torre PIII, et al. Efficacy and safety of N-acetylcysteine in prevention of noise induced hearing loss: a randomized clinical trial. Hear Res. 2015;323:40–50.
124. Orgel E, Knight KR, Chi YY, Malvar J, Rushing T, Mena V, Eisenberg LS, Rassekh SR, Ross CJD, Scott EN, et al. Intravenous N-acetylcysteine to prevent cisplatin-induced hearing loss in children: a nonrandomized controlled phase I trial. Clin Cancer Res. 2023;29(13):2410–2418.
125. Rosenhall U, Skoog B, Muhr P. Treatment of military acoustic accidents with N-Acetyl-L-cysteine (NAC). Int J Audiol. 2019;58(3):151–157.
126. Bai X, Chen S, Xu K, Jin Y, Niu X, Xie L, Qiu Y, Liu XZ, Sun Y. N-acetylcysteine combined with dexamethasone treatment improves sudden sensorineural hearing loss and attenuates hair cell death caused by ROS stress. Front Cell Dev Biol. 2021;9:659486.
127. Chen SL, Ho CY, Chin SC. Effects of oral N-acetylcysteine combined with oral prednisolone on idiopathic sudden sensorineural hearing loss. Medicine. 2022;101(26):e29792.
128. Kouka M, Bevern N, Bitter J, Guntinas-Lichius O. N-acetylcysteine combined with prednisolone treatment shows better hearing outcome than treatment with prednisolone alone for patients with idiopathic sudden sensorineural hearing loss: a retrospective observational study. Eur Arch Otorhinolaryngol. 2024;281(1):107–116.
129. Rewerska A, Pawelczyk M, Rajkowska E, Politanski P, Sliwinska-Kowalska M. Evaluating D-methionine dose to attenuate oxidative stress-mediated hearing loss following overexposure to noise. Eur Arch Otorhinolaryngol. 2013;270(4):1513–1520.
130. Yuan C, Ma T, Liu M, Zeng X, Tang G, Xing Y, Zhang T. Ferroptosis, oxidative stress and hearing loss: mechanistic insights and therapeutic opportunities. Heliyon. 2024;10(20):e38553.