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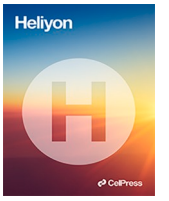

Review article

# Ferroptosis, oxidative stress and hearing loss: Mechanistic insights and therapeutic opportunities

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ABSTRACT

Hearing loss, a prevalent sensory impairment, poses significant challenges worldwide. Recent research has shed light on the intricate interplay between ferroptosis, a newly recognized form of regulated cell death characterized by iron-dependent lipid peroxidation, and oxidative stress in the pathogenesis of hearing loss. In this review, we delve into the mechanisms underlying ferroptosis and oxidative stress in various forms of hearing loss, including age-related hearing loss (ARHL), noise-induced hearing loss (NIHL) ototoxic drug-induced hearing loss and genetic hearing loss. We discuss the pivotal role of molecules such as FSP1, ACSL4, LKB1-AMPK, and Nrf2 in modulating these pathways in hearing loss. Furthermore, we explore emerging therapeutic strategies targeting the antioxidant system and ferroptosis, including iron chelators, lipid peroxide inhibitors, and antioxidants, highlighting their potential in mitigating hearing loss progression. By elucidating the molecular mechanisms underlying ferroptosis and oxidative stress, this review offers insights into novel therapeutic avenues for the treatment of hearing loss and underscores the importance of targeting these pathways to preserve auditory function.

## 1. Introduction

According to the WHO, approximately 2.5 billion individuals worldwide will struggle with various forms of hearing loss by 2050 [1]. This condition arises from a complex interplay of factors that adversely affect the cochlea. Contributing elements encompass aging, ototoxic medications, inner ear vascular disorders, and prolonged exposure to noise [2]. Apart from these acquired damage conditions, genetic abnormalities also cause hearing loss [3,4]. Sensorineural hearing loss (SNHL) stands as the most prevalent type, often stemming from degenerative changes in sensory hair cells, their synapses, and spiral ganglion neurons (SGNs) within the cochlea [5]. Because mammalian hair cells and SGNs lack regenerative capacity, their death results in irreversible damage, leading to permanent hearing loss [6]. While the precise mechanisms of hearing loss remain incompletely understood, mounting evidence underscores the pivotal role of oxidative stress in its pathogenesis [2,7]. Dysregulation of oxidative stress and excitotoxicity leads to heightened levels of reactive oxygen species (ROS), intracellular iron accumulation, and lipid peroxidation, culminating in a newly

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recognized form of regulated cell death termed "ferroptosis" [8].

Although the concept of ferroptosis as a distinct form of cell death has only recently caught researcher's attention, ferroptosis-like processes have been described for some time. Distinguishing features include mitochondrial shrinkage, altered volume, and the absence of typical mitochondrial cristae, setting it apart from classical necrosis and apoptosis. Ferroptosis plays critical role across various research domains, such as in aging and degenerative diseases. Inhibiting ferroptosis can reduce senescence-associated secretory phenotypes (SASPs), thereby alleviating senescence in vascular smooth muscle cell [9]. In recently years, ferroptosis also has gained attentions in many research fields including hearing loss [10,11].

Here, we offer a comprehensive review of current research elucidating the molecular mechanisms and potential therapeutic targets pertaining to hearing loss in the context of oxidative stress and ferroptosis. Additionally, we aim to uncover novel signaling pathways underlying cochlear damage, with the goal of advancing our understanding and devising effective treatments to safeguard hair cells through targeted interventions.

## 2. Role of oxidative stress in cochlea and central auditory system dysfunction

### *2.1. Oxidative stress induced damage to the cochlea*

Recently, the mechanisms of hearing loss have garnered significant attention, although they remain unclear. In normal auditory function, sound waves travel along the basilar membrane, which comprises three rows of outer hair cells and one row of inner hair cells sitting on top of supporting cells. Outer hair cells serve as amplifiers, while inner hair cells transmit electrical signals to the SGNs [6,12]. Furthermore, the hair cells receive innervation from the auditory nerve, responsible for conveying the electrical signals generated

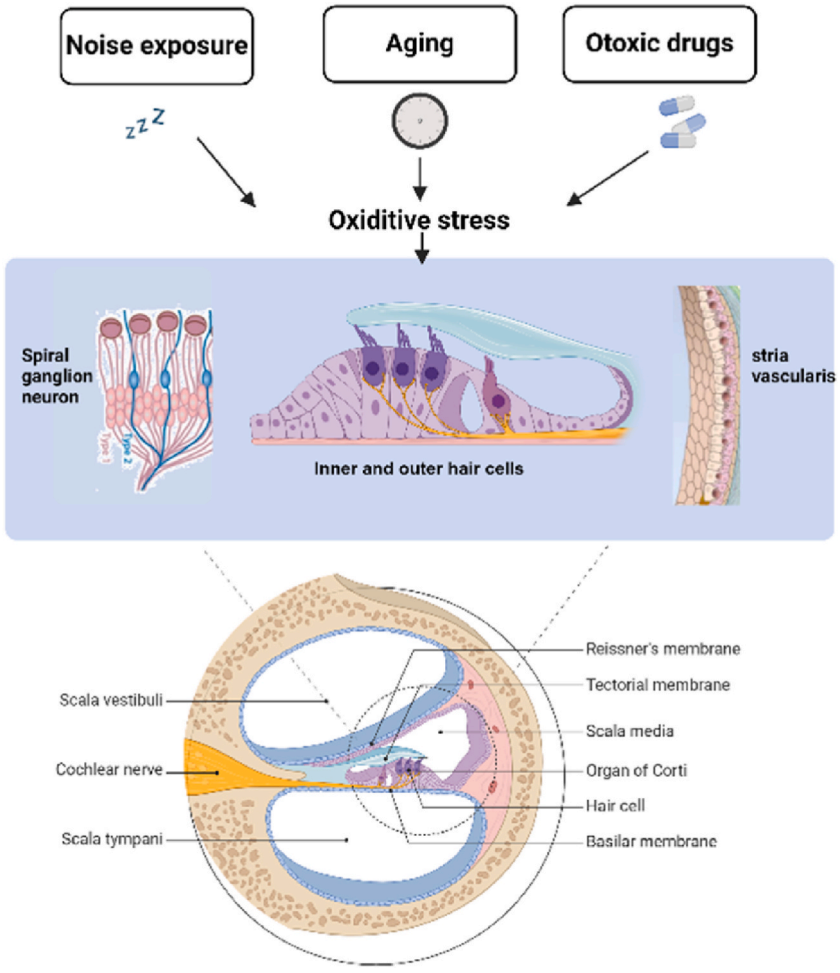


**Fig. 1. Potential mechanisms linking of Pathological changes of the cochlea.** Hearing loss is a complex outcome influenced by various factors such as aging, ototoxic drugs, and noise exposure. These factors collectively contribute to pathophysiological changes within the inner ear, including stria vascularis aging, basement membrane thickening, calcification, hyalinization, hair cell atrophy, reduced supporting cells, and spiral ganglion cell degeneration.

by hair cells to the brain for further processing and interpretation. Consequently, the cochlea experiences heightened metabolic demands and is particularly vulnerable to the deleterious effects of ROS. Various damaging conditions, such as aging, ototoxic drugs, and prolonged exposure to noise, result in the overproduction of ROS, exerting a significant influence on the progression of hearing loss (Fig. 1).

ROS, derivatives of molecular oxygen, are normal byproducts of aerobic cellular respiration (oxidative phosphorylation), regulating various biological processes such as cell proliferation, gene expression, and cell survival [13,14]. Under physiological conditions, cellular ROS levels are regulated by a range of endogenous antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), to maintain cellular homeostasis. However, an imbalance between ROS production and clearance by the cellular antioxidant defense system leads to oxidative stress. Oxidative stress adversely affects macromolecules such as DNA, proteins, and lipids, impairing their physiological functions and potentially resulting in cell death including the activation of apoptosis, autophagy and ferroptosis. The three primary vulnerable regions to ROS damage in cochlea are the organ of Corti, SGNs, and the stria vascularis [6]. Excessive ROS levels can cause various alterations, including a reduced number of inner and outer hair cells, atrophy of the stria vascularis, and degeneration of spiral ganglion cells [6,15].Outer hair cells, being energetically demanding, are particularly susceptible to ROS damage, especially those located in the basal turn [12]. The base turn of hair cells primarily processes high-frequency sounds, resulting in very high metabolic activity. However, due to its relatively low blood supply, weaker antioxidant defenses, and structural sensitivity, it is more susceptible to damage from ROS [3,16,17]. Inner hair cells play a crucial role in auditory signal transduction. Excessive ROS production leads to calcium influx, resulting in glutamate neurotoxicity at ribbon synapses, thereby damaging synaptic structures and diminishing connectivity between inner hair cells and SGNs [3,6]. Moreover, certain ototoxic drugs can induce damage to hair cells and SGNs due to ROS overproduction, disrupting their permeability and mitochondrial structure, ultimately leading to hair cells apoptosis [6,18] (Fig. 1).

### *2.2. Oxidative stress in drug-induced hearing loss*

In addition to aging and noise exposure, SNHL can also result from two classes of drugs that are widely used in clinical practice [19]. These ototoxic drugs include aminoglycoside antibiotics, such as amikacin, neomycin, kanamycin, gentamicin, streptomycin, and vancomycin, as well as platinum-based chemotherapeutic agents like cisplatin. These drugs are known to cause high-frequency hearing loss and significant damage to hair cells in the basal turn of the cochlea. Research suggests that systemically administered ototoxic drugs typically cross the blood-labyrinth barrier (BLB) to reach the stria vascularis of the cochlea, and then enter the hair cells through the endolymph, leading to ototoxicity [20]. Consequently, these drugs may cause vestibular dysfunction and even central nervous system impairment. After accumulating in outer hair cells, ototoxic drugs lead to excessive production of ROS within mitochondria, thereby activating the mitochondrial apoptosis pathway. Cisplatin, in particular, excessively activates NADPH oxidase such as NOX3, causing a rise in ROS levels and depleting the capacity of the endogenous antioxidant system, which exacerbates oxidative damage and triggers cell apoptosis [21]. Additionally, the depletion and inactivation of GSH result in iron accumulation and lipid peroxidation, ultimately leading to ferroptosis. These mechanisms collectively contribute to sensorineural hearing loss.

### *2.3. Oxidative stress induced damage to the central auditory system*

In addition to cochlear damage, hearing loss can also stem from deficiencies in auditory information processing. The central auditory system comprises a series of structures responsible for the transmission and processing of auditory information from the inner ear to the central nervous system. These structures perform hierarchical and regional processing of auditory signals and regulate inner ear function through feedback mechanisms, such as modulating the activity of hair cells. Individuals with hearing loss frequently experience atrophy in the temporal lobe (auditory cortex), and proliferation of brain gliosis [22,23]. Some endogenous metabolites, such as elevated bilirubin levels, and extrinsic ones, such as noise exposure can impact both the peripheral and central auditory systems [23,24]. The main mechanism is oxidative stress. Oxidative stress arises from a shift in tissue redox balance towards oxidation, resulting in the unregulated production of oxygen free radicals and an inability to counteract them with endogenous antioxidant substances such as glutathione [25,26]. These factors individually impair auditory cortex function, rendering it more vulnerable to oxidative stress damage, ultimately leading to elevated levels of malondialdehyde (MDA), a recognized marker of lipid peroxidation. Throughout the aging process, oxidative stress also affects central auditory pathways and nuclei, resulting in cellular atrophy, reduced cell numbers, and diminished nuclear volume. In summary, oxidative stress in cochlea and central nervous system contributes to various types of hearing impairment.

## 3. Ferroptosis in hearing loss: Iron metabolism and ferritinophagy

Ferroptosis, characterized by disruptions in iron metabolism, free radical accumulation, and lipid peroxidation, holds significant implications for cellular health [10,27]. Iron, a vital component in numerous physiological processes, plays a pivotal role at both systemic and cellular levels [28]. Its transportation involves uptake, utilization, and efflux mechanisms. Transferrin (Tf) primarily binds iron, facilitating its entry into cells via the Fe-Tf-TfR1 complex mediated by transferrin receptor 1 (TfR-1). Following metabolism, iron can be directed to mitochondria or extracellular spaces through ferritin-bound ferroprotein channels. The labile iron pool, in turn, can catalyze the peroxidation of polyunsaturated fatty acids (PUFAs), leading to lipid peroxides formation, plasma membrane rupture, and eventual cell death-manifestations characteristic of ferroptosis. Autophagy also associated with accumulation of $Fe2+$ and lipid peroxidation, eventually leading to ferroptosis. Another mode of ferritin metabolism is ferritinophagy, which refers to the

process of degrading intracellular ferritin through autophagy, leading to the release of $Fe^{2+}$ and thus impacting cellular iron homeostasis [29]. Ferritin is enclosed within an autophagosome and subsequently fuses with a lysosome to form an autolysosome. During this process, ferritin is degraded, releasing $Fe^{2+}$. The increase in $Fe^{2+}$ can promote lipid peroxidation, thereby inducing ferroptosis [30]. Ferritinophagy plays a critical role in maintaining cellular iron homeostasis, regulating oxidative stress responses, and influencing ferroptosis.

In the auditory cortex, observations by Chen et al. revealed a notable increase in iron content with aging, and additionally, elevated levels of ferroprotein and TfR-1 were noted in simulated aging mice groups [31]. Similarly, the significance of iron metabolism extends to hair cell injury contexts. Experimental findings demonstrate that Neomycin-induced damage in the HEI-OC1 cell line and active ferroptosis, marked by heightened $Fe^{2+}$ levels [32]. Notably, chronic iron accumulation amplifies oxidative stress and disrupts normal cellular function. Cisplatin-induced ferroptosis in HEI-OC1 cells manifests as increased lipid peroxidation, iron accumulation, and decreased mitochondrial membrane potential (MMP) [33]. Consequently, aging or exposure to ototoxic drugs can lead to iron accumulation in both the auditory cortex and hair cells, exacerbating oxidative stress and cellular demise, ultimately culminating in hearing impairment.

## 4. Antioxidant enzymes in ferroptosis and hearing loss

Ferroptosis entails the depletion of crucial antioxidant enzymes, notably GSH, and subsequent inactivation of glutathione peroxidase 4 (GPX4). Within the cochlear endogenous antioxidant system, GSH is predominantly found in basal and intermediate cells of the stria vascularis, as well as in spiral ligament fibrocytes in guinea pig cochlea. GSH plays a vital role in cellular antioxidant defense by catalyzing the reduction of toxic lipid peroxides to non-toxic fatty alcohols under GPX4's catalysis [34]. GPX4 serves as a central regulator and lethal signal of ferroptotic cell death. Its inactivation or absence results in lipid peroxide accumulation, disrupting redox homeostasis and culminating in ferroptotic cell death. Under normal circumstances, the cochlear antioxidant defense system, including GSH and enzymes responsible for its synthesis and regeneration, effectively neutralizes ROS [35]. Studies have shown that cisplatin inhibits the biosynthesis of GPX4 and GSH [35]. Additionally, Hu et al. observed inhibited GPX4 expression due to

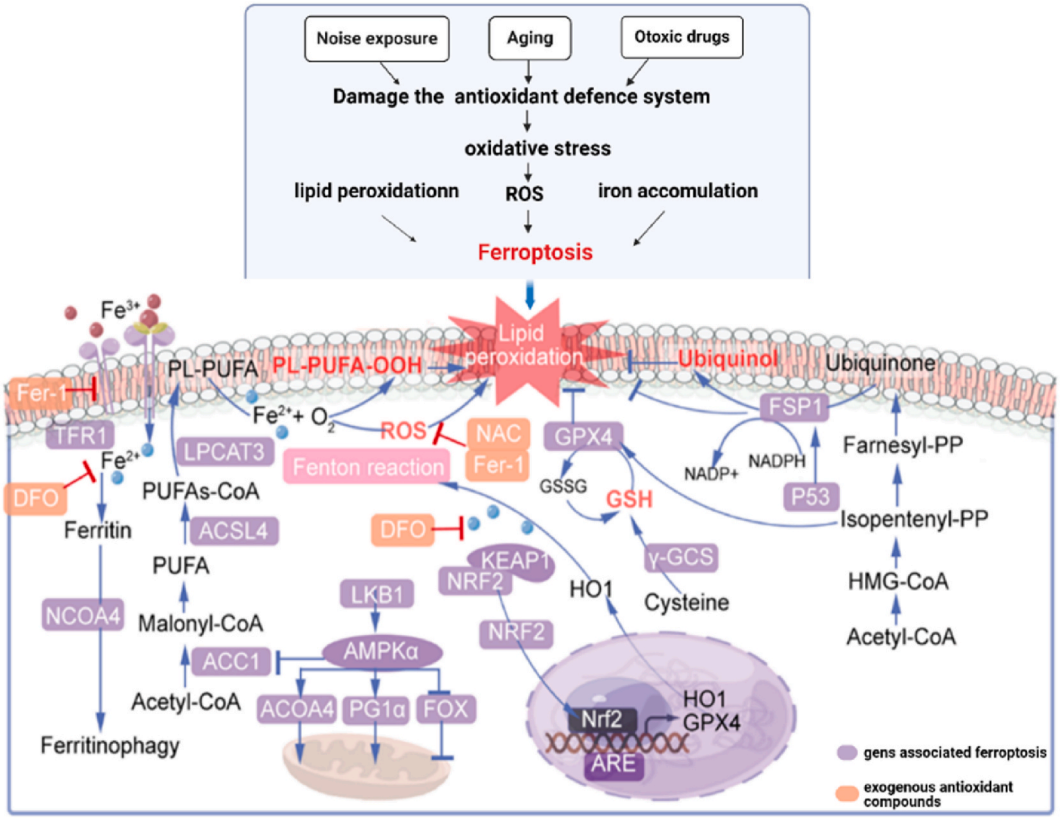


**Fig. 2. Overview of the common signaling pathways of oxidative and ferroptosis in hearing loss**. Ferroptosis encompasses three main components: iron metabolism, free radicals, and lipid peroxidation. This process involves a dynamic interplay between oxidative stress and antioxidant defense systems. The molecular machinery and signaling pathways of ferroptosis. Iron accumulation, ROS and lipid metabolism disorder are three main characteristics of ferroptosis. Ferroptosis involves a progress between oxidative stress and antioxidant defense systems, this progress may damage hair cells. Accumulation of ROS, iron and lipid metabolism disorder trigger change of FSP1-CoQ10-NAD(P)H, PUFA-ACSL4, AMPK and Nrf2. we speculate that if expression of these signaling pathways altered, they would cause hearing loss.

cisplatin, leading to ROS accumulation in HEI-OC1 cells [11]. Notably, neomycin significantly reduces GPX4 expression in cochlear hair cells [32]. Moreover, genetic factors can influence susceptibility to oxidative stress. Some genetic mutations associated with hearing loss affect pathways involved in antioxidant defense and cellular metabolism, potentially impacting susceptibility to oxidative damage and ferroptosis. For instance, mutations in genes encoding antioxidant enzymes such as SOD or iron homeostasis genes could disrupt the cellular antioxidant defense system, leading to increased oxidative stress and potentially exacerbating susceptibility to hearing loss [36,37]. Moreover the SOD1 knockout mice had higher ROS levels and experience premature age-related hearing loss due to hair cell loss [38].

ROS generated from lipid peroxidation also promotes ferroptosis. During lipid peroxidation, PUFAs generate highly reactive lipid peroxides such as MDA, severely damaging the plasma membrane and leading to cell death. Conditions such as cisplatin exposure and noise-induced trauma increase lipid peroxidation [37,39], and ferroptosis inhibitors can mitigate this process. Glutathione S-transferase alpha 4 (GSTA4) reduces cisplatin ototoxicity by detoxifying the toxic byproduct 4-HNE in the cochlea of female mice [37]. Moreover, metabolomic assays reveal significant alterations in the glutathione and arachidonic acid metabolic pathways in cisplatin-induced mice, suggesting that excessive ROS production leads to decreased levels of antioxidant enzymes, rendering cells insufficient to counteract ferroptosis [35]. Hence, antioxidant enzymes like GSH and anti-lipid peroxidation play a crucial role in the cochlear endogenous antioxidant system.

## 5. Signaling pathways in hearing loss associated with oxidative stress and ferroptosis

Molecules such as ferroptosis suppressor protein 1 (FSP1), ACSL4, LKB1-AMPK and Nrf2 play pivotal roles in modulating oxidative Stress and ferroptosis pathways. A comprehensive understanding of these signaling pathways is essential for elucidating the pathogenic mechanisms of hearing loss and developing relevant therapeutic strategies.

### *5.1. FSP1-CoQ10-NAD(P)H*

FSP1, also known as apoptosis-inducing factor mitochondria-associated 2 (AIFM2), has emerged as a key protective factor against ferroptosis induced by GPX4 deletion [40]. FSP1 exerts its inhibitory effect on ferroptosis through the involvement of ubiquinone, also known as Coenzyme Q10 (CoQ10), which plays a critical role in the mitochondrial electron transport chain [26]. In its reduced form, ubiquinol, CoQ10 can bind to lipid peroxyl radicals and mediate lipid peroxidation. FSP1 catalyzes the regeneration of CoQ10 through the utilization of NAD(P)H, a vital redox coenzyme in cellular processes [41]. By regulating CoQ10 regeneration elicited by GPX4 deletion, FSP1 confers significant protection against ferroptosis [40,41](Fig. 2).

Researchers have observed a notable upregulation in FSP1 expression in hair cells and the cochlea following increased expression of the upstream protein P53 [40]. This upregulation occurs in response to excessive accumulation of ROS and lipid peroxidation, both known to induce apoptosis and ferroptosis. However, FSP1 activates protective mechanisms against ferroptosis. Supplementation of CoQ10 in mice has successfully delayed age-related high-frequency hearing loss [42,43]. Clinical investigations have further demonstrated substantial improvement in pure tone audiometric thresholds at various frequencies with CoQ10 administration in patients with age-related hearing loss [44]. Moreover, CoQ10 has shown efficacy in ameliorating aging-induced memory deficits through modulation of apoptosis, oxidative stress, and mitophagy in aged rats [43]. Thus, NAD(P)H overproduction from an early stage serves as an efficient mechanism to maintain the balance between ROS production and cellular detoxification power during aging, thereby preventing hearing loss progression [45,46].

In summary, these studies suggest that reduced expression of FSP1 in the inner ear with aging may lead to decreased expression of its target CoQ10 and affect downstream NAD(P)H levels. This reduction in NAD(P)H expression may result in ROS overload, impairing mitochondrial function and leading to neuronal degeneration and cell apoptosis, ultimately contributing to hearing loss. FSP1-CoQ10-NAD(P)H may represent a potential drug target for preventing hearing loss; however, further investigation into the role of FSP1 in hearing loss is warranted (Fig. 2).

### *5.2. PUFA-ACSL4*

ACSL4 plays a crucial role in the biosynthesis of PUFAs [33]. This enzyme, an isozyme of the long-chain fatty-acid-coenzyme A ligase family, converts free long-chain fatty acids into fatty acyl-CoA esters, thereby regulating lipid biosynthesis and fatty acid degradation [33]. ACSL4 is involved in fatty acid synthesis by upregulating sterol regulatory element-binding protein 1 (SREBP1) in hepatocytes, leading to intracellular accumulation of triglycerides, cholesterol, and lipid droplets [47]. Thus, the ACSL4-PUFA axis plays a pivotal role in lipid metabolism regulation.

ACSL4 predominantly utilizes arachidonate as a substrate, making it a key enzyme in arachidonic acid-induced ferroptosis. Metabolomic assays have revealed a significant upregulation of the arachidonic acid metabolic pathway in hair cells exposed to cisplatin treatment [48]. Targeted inhibition of ACSL4 expression has resulted in notable reductions in lipid peroxide levels, providing significant protection for hair cells [36]. In aged rat models, ACSL4 expression levels are upregulated in the auditory cortex [31]. Treatment with deferoxamine, a potent ferroptosis inhibitor that removes excess iron from cells, significantly suppresses ferroptosis occurrence, postponing cellular senescence [31]. Consequently, ACSL4 emerges as a promising therapeutic target for addressing hearing loss and plays a significant role in hair cell susceptibility to cisplatin-induced damage [49].These findings underscore the potential interplay between ACSL4 and the generation of lipid products in hearing loss. Understanding the molecular mechanisms underlying these alterations provides valuable insights into the complex pathophysiology of hearing loss and paves the way for the

development of targeted therapeutic interventions aimed at delaying hearing loss (Fig. 2).

### 5.3. LKB1-AMPK

The LKB1 gene, located on chromosome 19p13, encodes the serine/threonine kinase LKB1, which acts as an upstream regulator of AMP-activated protein kinase (AMPK) [50]. Under normal conditions, LKB1 primarily localizes within the nucleus and requires the formation of a ternary complex with STRAD and Mo25 for activation. AMPK, a downstream kinase of LKB1, plays a pivotal role in cellular survival, metabolism, and response to metabolic stresses [51]. Activation of AMPK helps maintain cellular energy balance, particularly during hypoxia and stress, by enhancing fatty acid uptake into mitochondria and promoting ATP synthesis. Recent studies have also linked AMPK to ferroptosis [52].

In inner ear research, the LKB1/AMPK axis is intricately involved in critical cellular processes such as cell polarity, energy metabolism, embryonic growth, development, and cell differentiation. LKB1-deficient mice exhibit impaired hearing and malformations of hair bundles in cochlear hair cells. AMPK phosphorylates and activates the SIRT1/PGC-1α pathway, important for mitochondrial function and inhibition of hair cell apoptosis [53,54]. Moreover, AMPK activation during ischemia or stroke helps maintain energy balance by increasing glucose transporter 3 (GLUT3) trafficking, thus exerting a neuroprotective effect [55]. The LKB1-AMPK axis also influences ferroptosis by modulating the activity of acetyl coenzyme A carboxylase 1 (ACC1), a key enzyme in lipid peroxidation during PUFAs synthesis. Regulating ACC1 activity affects PUFAs substrate availability and impacts ferroptosis susceptibility. A comprehensive understanding of the LKB1-AMPK regulator is crucial for elucidating the role of ferroptosis in age-related hearing loss. Unraveling the mechanisms of AMPK and its associated pathways holds promise for developing innovative treatments for neurodegenerative diseases and hearing loss (Fig. 2).

### 5.4. Nrf2-HO1

The nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor activated in response to oxidative stress. Upon activation, Nrf2 proteins translocate to the nucleus and stimulate the expression of various genes containing antioxidant response elements (AREs), such as the heme oxygenase-1 (HO-1) gene [56]. Normally, Nrf2 is bound to Keap1 and undergoes ubiquitination and degradation in the proteasome under normal oxygen conditions [57]. However, during oxidative stress or exposure to electrophiles or cytotoxic factors, Nrf2 is released from Keap1, allowing it to enter the nucleus and interact with AREs to activate the transcriptional pathway, thus maintaining cellular redox homeostasis.

Nrf2 regulates numerous ferroptosis-related genes, including those involved in GSH regulation, NAD(P)H regeneration, and iron regulation, which includes iron output and storage, as well as heme synthesis and catabolism [58]. Activation of the p62-Keap1-Nrf2 signaling pathway promotes System Xc- (a dedicated cystine transporter)expression, accelerating cystine/glutamate transport and facilitating the clearance of accumulated lipid peroxides [59,60].As a major regulator of antioxidant capacity, Nrf2 plays a critical role in reducing oxidative stress injury in hair cells and is implicated in various chronic and age-related diseases associated with oxidative stress. In humans, Nrf2 is present in the cytoplasm and nuclei of the Corti organ and contributes to immunoreactivity [61]. Upon exposure to oxidative stress, antioxidant drugs, or aging, Nrf2 translocates from the cytoplasm to the nucleus and binds to AREs. This results in increased expression of downstream antioxidant factors such as HO-1 in hair cells and ganglion cells, accompanied by elevated levels of GSH and SODs [62]. By enhancing HO-1 and SOD expression in cochlear hair cells and spiral ganglion neurons, the Nrf2-ARE signaling pathway mitigates hearing loss and protects hair cells [63,64]. Targeting Nrf2 to regulate ferroptosis presents a promising direction for the prevention and treatment of hearing loss (Fig. 2).

## 6. Potential treatment strategies: targeting the antioxidant system and ferroptosis

Current interventions for hearing loss primarily involve medical devices such as hearing aids and cochlear implants, yet their effectiveness is limited by ongoing cochlear damage. Therefore, promising therapeutic approaches focused on hearing protection and antioxidant strategies are currently undergoing experimental development. We have summarized several pharmacological treatments targeting pathways involved in ferroptosis aim to mitigate cellular iron-mediated death by either reducing intracellular free iron levels or enhancing cellular antioxidative capacity. These treatments encompass iron chelators, lipid peroxidation inhibitors, GSH system inhibitors, antioxidants, and other compounds. Targeting ferroptosis and reducing cellular ROS sources in the cochlea may present a promising therapeutic strategy for attenuating hearing loss [6].

### 6.1. Iron chelators

Various interventions targeting ferroptosis have shown promise in preventing the progression of hearing loss. Studies conducted on the auditory cortex of ARHL have demonstrated that treatment with the iron chelating agent, deferoxamine (DFO), significantly alleviates iron-induced ferroptosis during the aging process [31]. Additionally, pre-treatment with DFO has been shown to enhance the homing ability of mesenchymal stem cells (MSCs) to the injured ear in a noise-induced hearing loss rat model, leading to a notable reduction in hearing loss [65]. Another iron chelator, Deferiprone, approved by the FDA, exhibits neuroprotective, anti-inflammatory, antioxidant, and anti-aging properties [66]. Deferiprone has been found to enhance the survival rate of aging fibroblasts and reduce lactate dehydrogenase (LDH) levels [67], suggesting its potential as a promising drug candidate for hearing loss in the future(Table 1).

### 6.2. Lipid peroxide inhibitors or activators of the glutathione transport system

Ferrostatin-1 (Fer-1) and Liproxstatin-1 are potent ferroptosis inhibitors that demonstrate significant protective effects against cisplatin-induced damage to hair cells. Fer-1 inhibits noise-induced hair cell apoptosis, regulates iron homeostasis, and suppresses apoptotic signaling pathways [68]. Similarly, Liproxstatin-1 protects HEI-OC1 cells and cochlear hair cells against neomycin ototoxicity by targeting ferroptosis [32]. CMS121, a fatty acid synthase inhibitor, exhibits efficacy in attenuating age-related hearing impairment in animal models [69,70]. These lipid peroxide inhibitors or activators of the glutathione transport system hold promise as targeted drugs for the treatment of hearing decline (Table 1).

### 6.3. Anti ROS antioxidants

N-acetyl-L-cysteine (NAC) have shown potential in reducing cochlear hair cell death, thereby preventing or delaying the onset of ARHL. Alpha-lipoic acid (ALA), a dithiol compound, acts as a natural coenzyme and an iron-chelating agent, blocking iron overload and inflammation associated with cell death [71,72].NAC exhibits strong antioxidant capabilities, effectively clearing reactive oxygen species and upregulating glutathione levels. These antioxidant drugs targeting oxidative stress may offer new therapeutic avenues for delaying age-related hearing loss [73]. Additionally, some drugs capable of generating NAD + can prevent degenerative hearing loss by reducing ROS and exhibiting antioxidant properties [74]. Overall, research into the mechanisms of ferroptosis holds promise for developing therapeutic approaches to treat hearing loss (Table 1).

## 7. Conclusion

Understanding oxidative stress and ferroptosis—an iron-dependent form of programmed cell death driven by $Fe^{2+}$ accumulation, ROS, and lipid peroxidation—has opened up new therapeutic possibilities for treating hearing loss. Aging, genetic mutations, noise exposure, ototoxic drugs, and other damaging conditions contribute to the progression of hearing impairment by inducing oxidative stress and triggering ferroptosis in cochlear cells. These damaging factors lead to intracellular injury and alter various molecular mechanisms, such as the depletion of endogenous antioxidant systems, DNA damage, increased production of ROS, and mitochondrial dysfunction, which together contribute to inner ear dysfunction and ultimately lead to hearing loss. Up to date, many potential therapeutic drugs have been proposed, with most focusing on the development of antioxidant treatments, such as ALA and NAC reduce oxidative stress and preserve cochlear function. Additionally, lipid peroxidation inhibitors, such as Lip-1 and other related compounds, have been extensively studied for their roles in blocking iron-induced lipid peroxidation and their effects in animal models of ARHL and drug-induced hearing impairment. These findings highlight the significance of ferroptosis in the pathogenesis of hearing loss and underscore the potential of ferroptosis-targeted interventions as novel treatment strategies. Further research into the mechanisms underlying ferroptosis and its regulation holds promise for the development of effective therapies to prevent or delay hearing impairment.

Since the repair process is speculated to involve multiple cell types, including hair cells, supporting cells, fibrocytes in the lateral wall, and migrated macrophages, precise targeted drug delivery remains a significant challenge. Actively administering antioxidants to the inner ear, enhancing the antioxidant system, and reducing lipid peroxide accumulation in the early stages of cochlear injury are essential. However, due to the complex structure and location of the inner ear, clinical methods for delivering drugs directly to this area

**Table 1**
Summary of potential interventions targeting ferroptosis and oxidative stress mechanisms in hearing loss.

| Regulatory Mechanism | Intervention | Targeted Action | Development Stage | Reference |
|---|---|---|---|---|
| Iron Chelators | DFO | Reacts with $Fe^{3+}$, induces GPX4, system $xc^-$, and glutathione expression. | Preclinical stage: Effect on improving ARHL in rats | [31] |
| | Deferiprone | Lowering iron levels, improving mitochondrial function, and reducing ROS levels. | Preclinical Stage: Protecting HEI-OC1 cells against neomycin-induced ototoxicity | [67,75] |
| Lipid Peroxidation Inhibitors or Glutathione Transport System Activators | Lip-1 | Inhibits mitochondrial lipid peroxidation, restores GSH, GPX4, and FSP1 expression. | Preclinical Stage: Demonstrating protection of HEI-OC1 cells from neomycin-induced ototoxicity. | [76,77] |
| | Fer-1 | Induces GPX4 protein expression, reduces lipid ROS. | Preclinical Stage: Attenuation of NIHL by suppressing ferroptosis. | [68,78] |
| | CMS-121 | Inhibit ACC1 to alleviate inflammation and lipid peroxidation reactions. | Preclinical Stage: Attenuation of ARHL in SAMP8. | [69,70] |
| Antioxidants | NAC | Upregulates the levels of GSH and glutathione peroxidase, preventing lipid peroxidation and inhibiting ROS generation. | Preclinical Stage：Prevention of severe NIHL and drug-induced ototoxicity. | [73] |
| | ALA | Blocking iron overload, lipid peroxidation, and inflammation associated with iron-dependent cell death. | Preclinical Stage: Prevention of Cisplatin-Induced Ototoxicity. | [71] |
| | NRH | Increasing NAD + levels and decreasing ROS levels. | Preclinical Stage: prevention of aminoglycoside-induced ototoxicity | [74] |

Abbreviations: DFO: Deferoxamine; Lip-1: Liproxstatin-1; Fer-1: Ferrostatin-1; NAC: N-acetylcysteine; ALA: Alpha-lipoic acid; NRH: A reduced form of nicotinamide riboside; NIHL: Noise-induced hearing loss; SAMP8: Senescence-Accelerated Mouse; GSH: Glutathione.

are often limited. Therefore, improving delivery systems, such as utilizing nanomaterials to achieve higher and more stable concentrations of antioxidant drugs within the inner ear, remains a significant challenge. These approaches represent significant opportunities and challenges for the future treatment of hearing loss.

## Data availability

No data was used for the research described in the article.

## CRediT authorship contribution statement

**Chenyang Yuan:** Writing – original draft, Conceptualization. **Tianyu Ma:** Visualization. **Mengting Liu:** Visualization, Supervision. **Xiaoyun Zeng:** Supervision, Methodology. **Gongrui Tang:** Visualization, Supervision. **Yazhi Xing:** Writing – original draft, Visualization, Supervision. **Tianhong Zhang:** Writing – review & editing, Validation, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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