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REVIEW

The Role and Research Progress of Mitochondria in Sensorineural Hearing Loss

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Abstract

Hearing loss is one of the most common human diseases, seriously affecting everyday lives. Mitochondria, as the energy metabolism center in cells, are also involved in regulating active oxygen metabolism and mediating the occurrence of inflammation and apoptosis. Mitochondrial defects are closely related to hearing diseases. Studies have shown that mitochondrial DNA mutations are one of the causes of hereditary hearing loss. In addition, changes in mitochondrial homeostasis are directly related to noise-induced hearing loss and presbycusis. This review mainly summarizes and discusses the effects of mitochondrial dysfunction and mitophagy on hearing loss. Subsequently, we introduce the recent research progress of targeted mitochondria therapy in the hearing system.

Keywords Mitochondrial · Inner ear · Hair cell · mtDNA · Oxidative stress · Mitophagy

Introduction

Hearing loss is thought to result from various factors, including age, oxidative damage, mitochondrial damage, and environmental factors. Mitochondria are involved in cellular energy metabolism, redox homeostasis, signal transduction, and programmed cell death. Studies have shown that there are abundant mitochondria in the outer hair cells (OHCs), supporting cells (SCs), and stria vascularis of the cochlea, which provide sufficient energy for the physiological activities of the cochlea during sound transmission [1]. When mitochondrial DNA (mtDNA) mutations or mitochondrial dysfunction occur, excessive reactive oxygen species (ROS) are produced in the cochlea, exacerbating mitochondrial damage and activating apoptosis signaling pathways, ultimately leading to inner ear cell death and hearing loss [2]. Mitochondrial dysfunction is mainly caused by mtDNA mutations and is influenced by nuclear genes, resulting in hearing loss characterized by maternal inheritance and multifactorial induction [3]. mtDNA can encode 22 tRNAs, which regulate protein synthesis. tRNA is highly conserved and may cause hearing loss when mutated, such as $tRNA^{Ser}$, $tRNA^{Thr}$, $tRNA^{Phe}$, and $tRNA^{His}$ [4]. In addition, the spatial structure of mitochondrial 12S ribosome in patients with mitochondrial 12S rRNA A1555G or C1494T mutations is more similar to the target of aminoglycosides, which is easy to combine with aminoglycosides, leading to the destruction of mitochondrial structure, and eventually causing hearing loss [5]. Hearing loss caused by mtDNA mutations often shows significant individual differences related to nuclear gene regulation and environmental factors [6]. For example, the lack of expression of Fus1 and mitochondrial DNA polymerase γ is closely related to age-related hearing loss, or presbycusis [7, 8]. Timely removal of damaged mitochondria plays an important role in maintaining the normal physiological function of cells. Mitophagy is a mechanism generated during cell evolution to selectively remove damaged mitochondria through autophagy [9]. Studies have shown that with age, the expression of most genes associated with mitophagy is downregulated, and when mitophagy is inhibited, the level of oxidative stress increases, ultimately leading to cell aging [10, 11]. Researchers have discovered that the modulation of mitophagy affects hearing levels and hair cell survival in several types of sensorineural hearing loss. For example, in presbyacusis, inhibition of mitophagy would accelerate age-related hearing loss. The induction of mitophagy in response to noise exposure could alleviate hearing loss and hair cell damage. Therefore, exploring the mechanism of hearing loss caused by mitochondrial

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dysfunction has important reference value. And mitochondrial targeted treatment for hearing loss may become a promising therapeutic.

Effects of mtDNA Mutations on Hearing

mtDNA is a mitochondrial-specific genetic system with self-replication, transcription, and coding functions. mtDNA encodes two rRNAs, 22 tRNAs, and 13 protein and complex subunits in the respiratory chain [12]. mtDNA mutations play an essential role in the aging process of tissue cells, and there are three main types: deletion mutation, point mutation, and tandem repeat [13]. Researchers have found a significant correlation between the deletion of mtDNA4977 in human temporal bones and the severity of presbycusis. Compared with those who have normal hearing, individuals with presbycusis have significantly increased levels of mtDNA mutations in their cochlear tissue [14]. mtDNA mutations encoding rRNA (MTRNR1) or tRNA (MTTS1) were found to be associated with hearing loss, such as mutations in the MTRNR1 (T2095C, C1494T) and COI/MTTS1 genes (G7444A), which are associated with ototoxic hearing loss [15, 16]. The MTRNR1 gene mutations are associated with maternally inherited hearing loss [17]. In tRNA-related research, it has been found that some mutations in the MTTS1 gene are associated with sensorineural hearing loss, including A7445G, 7472insC, G8363A, T7510C, T7511C, and T7512C [18]. These mutations do not affect the integrity of tRNA structure. However, they influence the processing speed of tRNA precursors, leading to a decrease in tRNA levels and blocked tRNA metabolism, thereby affecting mitochondrial translation and respiration [17, 19]. There are several other types mtDNA mutations associated with hearing loss. For example, A3243G heterogeneous mutations are associated with maternally inherited diabetes and deafness syndrome, which will cause the inefficient aminoacylation of $tRNA^{Leu\ (UUR)}$, affect the processing of mitochondrial RNA precursors and the level of $tRNA^{Leu\ (UUR)}$, and ultimately lead to the decline of mitochondrial protein synthesis rate and respiratory defects [20–22]. A4295G mutation was detected in patients with maternally inherited hearing loss, which significantly reduced the processing efficiency of 3′-tRNAse and the functional homeostasis level of $tRNA^{Ile}$, leading to mitochondrial protein translation defects [23, 24]. T12201C heterozygous mutation was found to have a high penetrance in Chinese families with hearing impairment [25]. The T12201C mutation can lead to abnormal tRNA metabolism and a decrease in $tRNA^{His}$ steady-state level, ultimately impairing the mitochondrial translation process [26]. The homologous mutation of C3388A affects the gene encoding of the ND1 subunit and leads to a significant decrease in complex I protein levels [27]. G8078A mutation can lead to defects in respiratory chain complex IV [24].

Effect of Mitochondrial Homeostasis on Hearing

Mitochondria are highly dynamic organelles in cells that can form interconnected dynamic networks through continuous fusion, fission, and transport. Mitochondrial homeostasis is the dynamic balance between mitochondrial biogenesis and degradation, which is crucial for mitochondrial quality control and functional maintenance, as well as regulating cell morphology and function. Mitochondrial biosynthesis is the growth and division of mitochondria guided by nuclear and mtDNA, accompanied by processes related to protein synthesis, import, and assembly [28]. Mitochondrial fusion is a type of mitochondrial remodeling mediated by conserved dynamic guanosine triphosphate (GTP) enzymes located in the outer and inner membranes of mitochondria, which is crucial for maintaining cell function and adapting to environmental changes [29].

Mitochondrial homeostasis disorders have been found in aging and age-related diseases such as neurodegeneration and cardiovascular disease. In research on the auditory system, mutations in multiple important factors are associated with mitochondrial homeostasis, such as PGC-1α, TRMU, HRS2, Wars2, MRPS2, and OPA1. Peroxisome proliferator-activated receptor-γ coactivator α (PGC-1α) is one of the key regulatory factors in mitochondrial biosynthesis and plays a vital role in age-related diseases by regulating mitochondrial function [30]. In the auditory cortex of aging rats, when mtDNA common deletion (CD) mutations accumulated and cytochrome c oxidase activity (CcO) decreased, PGC-1α expression showed a compensatory increase. However, it was insufficient to compensate for the decline in CcO activity and delay the aging process [31]. In the marginal cells of aging rats, PGC-1α overexpression led to increased expression of NRF1 and TFAM and significantly reduced mtDNA CD accumulation and cell apoptosis [32]. In addition, it was found that LncRNA AW112010 can affect the mitochondrial mass and mitochondrial biosynthesis of HEI-OC1 cells by regulating the expression of the transcription factors PGC-1α and TFAM related to mitochondrial biosynthesis [33]. tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase (TRMU) is a mitochondrial protein involved in mitochondrial tRNA modification. Its mutation can decrease mitochondrial tRNA levels, resulting in mitochondrial protein translation disorders, mitochondrial dysfunction, and increased ROS levels, ultimately leading to auditory organ damage [34]. Overexpression of mitochondrial histidyl-tRNA synthase (HRS2) increased the steady-state levels of $tRNA^{His}$ and

noncognate tRNAs. It improved the efficiency of mitochondrial translation, the activity of oxidative phosphorylation complexes, and respiratory capacity. In addition, overexpression of HRS2 significantly increased mitochondrial ATP levels and membrane potential, reduced ROS production, and corrected mitochondrial dysfunction caused by $tRNA^{His}$ mutation [35]. Mitochondrial protein synthesis and transport dysfunction are important factors leading to sensorineural hearing loss (SNHL), such as tryptophanyl-tRNA synthetase 2 (Wars2) [36], mitochondrial ribosomal proteins S2 (MRPS2) [37], GFER [38], and DDP [39]. During noise exposure, cellular calcium influx will causing mitochondrial calcium overload and initiates cell death pathways, resulting hearing system damage. Using calcium uniporter inhibitor or siRNA pretreatment will alleviate noise induced hearing loss [40, 41]. In summary, mitochondrial homeostasis disorder is an important cause of auditory neuropathy and mitochondrial biological dysfunction.

As an important structure in the cochlea, lateral wall (LW) plays an important role in maintaining the homeostasis of lymph in the inner ear microenvironment. In order to maintain the stability of the endolymphatic fluid, the LW is the highly oxygen-consuming part of the cochlea, which is also relatively rich in mitochondria and endoplasmic reticulum. The mitochondrial toxin 3-nitropropionic acid (3-NP) will induction of the CHOP signal activation and causing type II and type IV fibrocytes apoptosis in LW [42]. 3-NP can also induction inflammatory cytokines increase, like interleukin and CC-type chemokine, which will induce LW inflammatory responses and acute mitochondrial dysfunction [43]. During the mouse cochlear development process, the stability mitochondrial function in the LW is very important to hearing developing. In connexin $30^{-/-}$ mice, ROS activity and oxidative stress level increased early at stria vascularis (SV) compare with WT group. The overload ROS level will damage SV function and lead to the EP produce failure, which may the primary reason for the connexin $30^{-/-}$ mice showing earlier hearing loss [44]. In Slc4a10 knockout mouse model, both Slc4a10 and Slc4a7 expression is lost in inner ear fibrocyte. Furthermore, Slc4a10 knockout will reducing inner ear EP reducing and causing hearing develop damage [45]. Mitochondrial dysfunction is closely related with presbycusis. Cdk5rap1 deficiency will inducing mitochondrial protein translation defective. Cdk5rap1-knockout mice showed a characterization of accelerated aging hearing level. The KO mice exhibit mitochondrial dysfunction and causing LW SLi fibrocyte degeneration. Finally, the local endolymph abnormalities lead to LW dysfunction and aging-related hearing loss [46]. Type 1 diabetic Akita mice showed accelerating hearing loss than WT mice, and the histology data turns out that mitochondria-mediated apoptosis pathway plays an important role in type 1 diabetic-related LW degeneration [47].

The Relationship Between Mitochondrial Oxidative Stress and Hearing Loss

ROS are indispensable regulatory factors for regular cell activity, including intercellular communication, proliferation, differentiation, and apoptosis. However, excessive ROS accumulation may lead to oxidative damage, cell death, cancer, and neurodegeneration [48]. Much research has shown that oxidative damage in the cochlea is caused by age-related decline in antioxidant capacity and increase in ROS levels, playing a crucial role in the development of age-related hearing loss (ARHL) [49]. In ARHL-related research, excessive free radicals were found in the sensory epithelium, spiral ganglion neuron (SGN), and stria vascularis cells of the cochlea; mitochondrial DNA oxidative damage and structural damage were also observed [50]. Mitochondrial-related antioxidant enzyme activity can also affect the progression of ARHL. For example, compared to young mice, SGNs in SAMP8 mice exhibit mitochondrial structural disorder with missing cristae, and a decrease in antioxidant enzyme activity at 12 months [51]. Inhibiting the expression of antioxidant enzyme superoxide dismutase (SOD) increases the sensitivity of the cochlea to oxidative stress during normal metabolic processes and promotes the progression of ARHL [52]. In addition, overexpression of catalase can inhibit the progression of ARHL [53]. NADPH is an important antioxidant cofactor in cells, produced by the housekeeper enzyme glucose-6-phosphate dehydrogenase (G6PD). Overexpression of G6PD can inhibit oxidative damage in the cochlea, promote the survival of HCs and SGNs, and delay the progression of ARHL [54]. Glutathione (GSH) and glutathione-related antioxidant enzymes (GST) are suggested to play important roles in the metabolism and inactivation of ototoxic compounds, and their reduced activity levels cause increased susceptibility of cells to damage [55]. Population-based studies have found that mutations in GSTM1 and GSTT1 are closely related to ARHL [56]. Mitochondrial NADP + -dependent isocitrate dehydrogenase 2 (IDH2) is essential for maintaining the redox balance. Loss of IDH2 activity can lead to decreased NADPH and glutathione levels, resulting in abnormal accumulation of ROS and oxidative damage, and eventually aging damage of hair cells [57]. Ye-Ri Kim et al. found that MitoQ treatment can inhibit the increase of ROS and hair cell damage caused by IDH2 deficiency [58]. The primary function of mitochondrial uncoupling protein 2 (UCP2) is to regulate the ROS produced by mitochondria. In a study of the Japanese population, UCP2 Ala55Val polymorphism was found to be significantly correlated with ARHL [59]. Tan et al.

found that the decreased expression of mitochondrial protein Fus1 would lead to mitochondrial damage, increased ROS production, and decreased mitochondrial membrane potential, thus causing cochlear tissue damage and hearing loss [7]. Sirt3 is a major deacetylase that plays a vital role in cell metabolism, apoptosis, and signal transduction during aging. Downregulation of Sirt3 expression can lead to oxidative damage, mitochondrial dysfunction, and abnormal expression of various signal pathways related to ARHL [60].

In addition to aging factors, cochlea-related oxidative stress caused by noise and ototoxic drugs is also considered an important factor in hearing loss. As an inflammatory mediator, the upregulated expression of high-mobility group box 1 (HMGB1) protein is related to increased ROS/RNS (reactive nitrogen species) production after noise exposure. Inhibiting the expression of HMGB1 can reduce the production of ROS/RNS and inflammatory response in the cochlea, thus reducing noise-induced hearing loss [61]. The accumulation of ROS is often considered to be caused by ototoxic drug damage (e.g., by aminoglycoside antibiotics and cisplatin). The overproduction of ROS disrupts the redox balance, triggering mitochondrial depolarization and the release of cytochrome c, which then activates caspase-3 and eventually leads to hair cell apoptosis [62]. He et al. found that inhibiting the expression of the protein arginine methyltransferase (PRMT6) could significantly reduce the damage of ototoxic drugs, and it could reduce the ROS level and the release of cytochrome c, and inhibit the level of caspase-3, thus reducing the number of hair cell losses [63].

The Role of Mitochondrial Apoptosis Pathway and Mitophagy in Inner Ear Cells

Apoptosis pathways can be divided into intrinsic or extrinsic pathways. Intrinsic pathways, also known as mitochondrial pathways, are initiated by the loss of integrity in the mitochondrial outer membrane [64]. Due to aminoglycosides accumulating in the mitochondria of hair cells, the mitochondrial apoptosis pathway plays a key role in aminoglycoside-induced apoptosis [65]. Recent studies have shown that hair cells with more cumulative changes in mitochondrial activity are more susceptible to aminoglycosides-induced damage [66]. The endogenous apoptotic pathway caused by the loss of mitochondrial membrane potential is necessary for the progression of ARHL, and it has been demonstrated in multiple ARHL models that apoptosis occurs through a caspase-dependent pathway and involves Bcl-2 family proteins [67, 68]. Age-related apoptosis of spiral ganglion neurons and hair cells in the cochlea was reduced in C57BL/6 J mice with the mitochondrial pro-apoptotic gene Bak deleted [53]. In a study of noise-induced hearing loss, exogenous and endogenous apoptotic pathways were found to activate caspase-8 and caspase-9 after noise exposure, and both apoptotic markers were associated with the signaling pathway leading to the activation of caspase 3 [67]. Vicente-Torres et al. found that calcium-dependent phosphatase is activated in OHC after noise exposure, triggering mitochondria-mediated apoptosis pathways by activating Bcl-2-associated death promoters (BAD) [69].

Autophagy is a process in which cells selectively remove organelles to regulate their number and maintain quality control, while mitophagy is a particular form of autophagy that achieves quality control by removing damaged mitochondria [70]. When mitophagy is inhibited, dysfunctional mitochondria accumulate gradually, resulting in cell and tissue damage [71]. Mitophagy plays an important role in the process of age-related hearing loss. Mitophagy in the cochlea of mice gradually decreases with age, resulting in aggravated hearing loss [72]. Impaired mitophagy is associated with aging of the mouse auditory central system (auditory cortex and inferior colliculus), and PINK1/Parkin pathway-dependent mitophagy is impaired with age [73]. Xiong et al. found that overexpression of SIRT1 increased the levels of PINK1 and Parkin in cochlear hair cells of aged mice and reduced age-related cochlear hair cell loss and hearing loss [74]. The dynamin-related protein 1 (DRP-1) activates mitophagy, thereby eliminating dysfunctional mitochondria and preventing oxidative stress-induced aging. When DRP-1 expression is inhibited, cochlear hair cell aging and ARHL are aggravated [75].

Apoptotic pathways in cochlear ototoxicity refer to the mechanisms through which cells in the cochlea undergo programmed cell death in response to ototoxic agents. Ototoxicity refers to the harmful effects on the ear, particularly the cochlea and auditory nerve, caused by certain drugs, chemicals, or environmental factors [76, 77]. Apoptosis of sensory hair cells in the cochlea is a hallmark of cochlear ototoxicity and is a significant contributor to hearing loss associated with ototoxic damage. Many ototoxic agents induce mitochondrial dysfunction in cochlear cells. Mitochondria play a crucial role in energy production and cell survival. Mitochondrial dysfunction and free radical accumulation are presumed to be the principal cellular mechanism underlying cisplatin-induced HC apoptosis. Overproduction of ROS by cisplatin could overwhelm the redox balance, increase lipid peroxidation and inhibit the synthesis of endogenous antioxidants, promote mitochondrial cytochrome c release, and trigger the mitochondrial apoptosis pathway in HC, stria vascularis, marginal cell, and spiral ganglion neuron apoptosis. Thus, maintaining mitochondrial function and preventing ROS-accumulation-activated caspase-mediated programmed cell death has been proposed as important strategies to avoid ototoxicity [78, 79]. Furthermore,

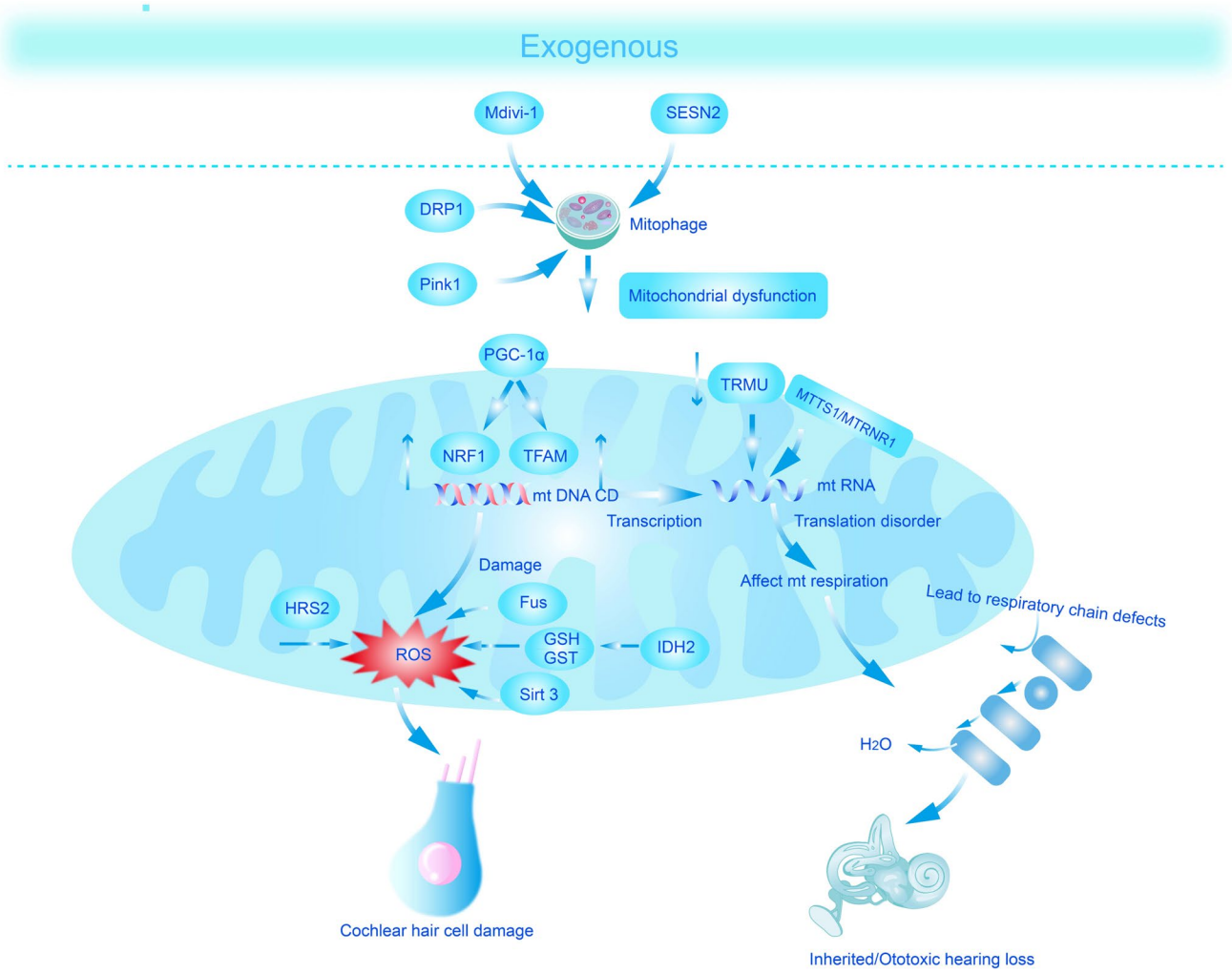

Fig. 1 Mechanisms of mitochondria-related signaling pathways in hearing loss

inflammatory cytokines, COX-2, IL-1β, TNF-α in concert with NF-κB, released in response to ototoxic insult can induce apoptosis in cochlear cells. This inflammatory response can amplify cellular damage and apoptosis [80]. Autophagy, a process by which cells degrade and recycle cellular components, can either promote cell survival or lead to cell death depending on the context. Dysregulation of autophagy can contribute to apoptosis in cochlear cells exposed to ototoxic agents [81]. Understanding these apoptotic pathways is critical for developing strategies to protect cochlear cells from ototoxic damage and to preserve hearing function. Therapeutic approaches aimed at mitigating oxidative stress, inhibiting caspase activation, reducing inflammation, modulating the level of autophagy was or promoting cell survival pathways could potentially help prevent or reduce hearing loss associated with ototoxicity.

The Research Progress on Targeted Mitochondrial Therapy for Hearing Loss

With increasing research into the mechanisms between mitochondrial dysfunction and hearing loss, targeted mitochondrial therapy has received more attention. Antioxidants may inhibit SNHL by eliminating excess ROS products. MitoQ, a derivative of CoQ10/ubiquinone and an antioxidant that targets mitochondria, mitigates aminoglycoside (AG)-induced hearing loss [82]. Recently work found that AG aberrantly activate the autophagy/mitophagy pathway and causing permanent hair cell death. The hair cells will resistant to AG ototoxicity by reducing the expression of PINK1 or PRKN/parkin, two mitophagy proteins [83]. However, another research report that hyperactive PINK1-PRKN pathway could rescue mitophagy to against neomycin-induced hair cell damage, and the administration of deferiprone or kinetin to restored motophagy could alleviate neomycin-induced hearing loss

in vivo [84]. Mitochondria-targeted antioxidant SkQR1 treatment can effectively reduce gentamicin-induced hearing loss [85]. Mitochondria-targeted apoptosis inhibitors also inhibit the progression of SNHL, such as the calpain inhibitor PD150606, which can inhibit the apoptosis of SGNs through calpain activity and AIF nucleus release [86]. The SESN2 protein could activation mitophagy and serve as therapeutic target for hearing protection during noise-induced hearing loss [87]. In aged mice, blocked mitophagy by Mdivi-1 administration could exacerbated hearing loss and overexpression Dynamin-related Protein-1 may provide a potential therapeutic target for presbycusis by initiating mitophagy [75]. Therefore, the mechanisms of mitophagy in drug-induced hearing loss should be further studied and the intervention target of mitophagy should be found for clinical treatment.

Conclusion

Mitochondria are the critical organs for energy supply, biosynthesis, and apoptosis of inner ear cells. The severity of hearing loss is related to cochlear cell damage, and mitochondria-related pathophysiological mechanisms may play an important role in the process of cochlear injury, such as the accumulation of mtDNA damage, the production of ROS, the reduction of antioxidant function, and homeostasis imbalance (Fig. 1). In conclusion, the current treatment for hearing loss caused by mitochondria dysfunction is still limited, and more exploration of the molecular mechanisms related to mitochondria is needed.

Author Contributions Shan Xu and Ning Yang wrote the main manuscript text. All authors reviewed the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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