

Review Article

Mitochondrial Dysfunction and Sirtuins: Important Targets in Hearing Loss

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Mitochondrial dysfunction has been suggested to be a risk factor for sensorineural hearing loss (SNHL) induced by aging, noise, ototoxic drugs, and gene. Reactive oxygen species (ROS) are mainly derived from mitochondria, and oxidative stress induced by ROS contributes to cochlear damage as well as mitochondrial DNA mutations, which may enhance the sensitivity and severity of hearing loss and disrupt ion homeostasis (e.g., Ca^{2+} homeostasis). The formation and accumulation of ROS further undermine mitochondrial components and ultimately lead to apoptosis and necrosis. SIRT3–5, located in mitochondria, belong to the family of sirtuins, which are highly conserved deacetylases dependent on nicotinamide adenine dinucleotide (NAD^+). These deacetylases regulate diverse cellular biochemical activities. Recent studies have revealed that mitochondrial sirtuins, especially SIRT3, modulate ROS levels in hearing loss pathologies. Although the precise functions of SIRT4 and SIRT5 in the cochlea remain unclear, the molecular mechanisms in other tissues indicate a potential protective effect against hearing loss. In this review, we summarize the current knowledge regarding the role of mitochondrial dysfunction in hearing loss, discuss possible functional links between mitochondrial sirtuins and SNHL, and propose a perspective that SIRT3–5 have a positive effect on SNHL.

1. Introduction

Hearing loss is a common sensory disorder with high prevalence. About 500 million people in the world suffer from hearing loss [1]. It can not only cause impaired communication, but also affect the physical and mental health of individuals and social and economic development. It has been proposed that the elderly with hearing loss have higher rates of dementia, depression, and death [2]. Hearing loss is often classified as conductive, sensorineural, or mixed according to anatomical deficit [2, 3]. Sensorineural hearing loss is caused by dysfunction of cochlea or auditory nerve, which is the commonest in adult primary care [2, 3].

Many previous studies have suggested that mitochondrial dysfunction is involved in the etiology of several types of sensorineural hearing loss (SNHL), such as noise-induced hearing loss (NIHL), age-related hearing loss (ARHL), ototoxic drug-induced hearing loss (ODIHL), and inherited hearing loss. In most mammalian cells, mitochondria are

the main source of reactive oxygen species (ROS) [4, 5, 6]. Increased ROS formation results in further damage to the mitochondrial structure, including mitochondrial membranes, mitochondrial DNA (mtDNA), respiratory chain proteins, and nuclear DNA related to mitochondrial functions [7]. SNHL occurs because of the irreversible damage to hair cells (HCs) and spiral ganglion neurons (SGNs), both of which have very limited regeneration ability in adult mice cochlea [8, 9, 10, 11, 12, 13].

Sirtuins are histone deacetylases dependent on NAD^+ that remove various cellular proteins' acyl modifications [14]. They regulate metabolism, differentiation, stress responses, apoptosis, and the cell cycle [15, 16]. Seven members of the sirtuin family (named SIRT1–7) have been identified with different locations in the cell. Recent studies have revealed that mitochondrial sirtuins, especially SIRT3, modulate ROS levels in hearing loss pathologies and indicated that SIRT4 and SIRT5 may have a potential protective effect against hearing loss. In this review, we focus on

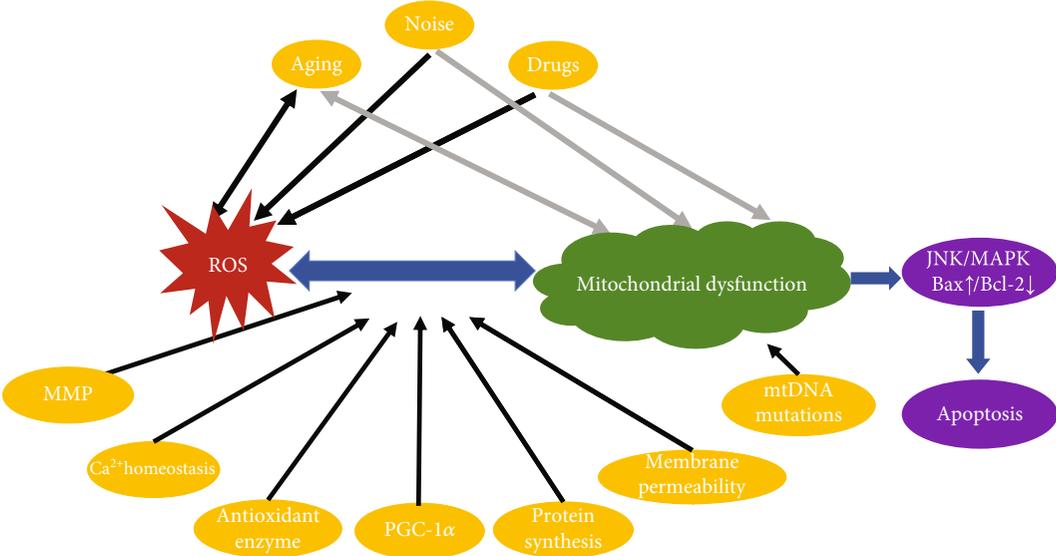


FIGURE 1: Stimulations induce ROS and mitochondrial dysfunction and finally cells’ apoptosis. Diagram showing aging, noise, and drugs could induce ROS and the probable mechanism to lead to mitochondrial dysfunction, moreover, the interaction between ROS and mitochondrial dysfunction.

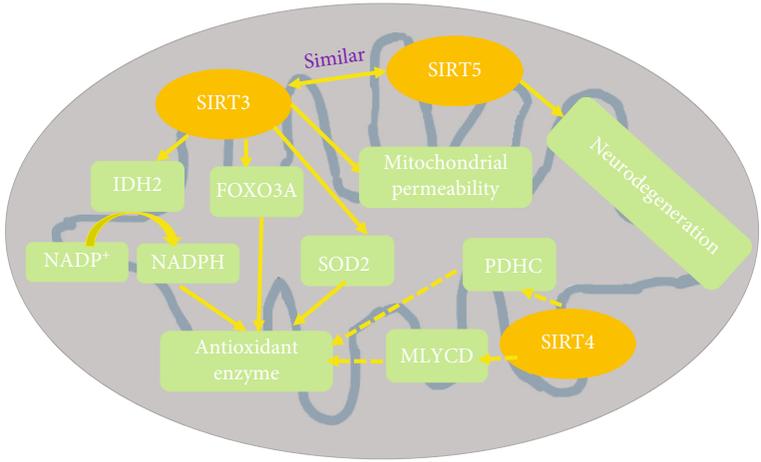


FIGURE 2: Regulation of ROS and protection of mitochondria by sirtuins. The diagram showing possible signaling ways of mitochondrial sirtuins (SIRT3~5) to reduce level of ROS and resist oxidative reaction. Solid lines represent considerable evidence for an interaction while dashed lines suggest putative interactions.

mitochondrial dysfunction and the role of mitochondrial sirtuins in SNHL, as shown in Figures 1 and 2.

2. Hearing Loss and Mitochondrial Dysfunction

2.1. Age-Related Hearing Loss (ARHL). ARHL, or presbycusis, is a progressive decline in hearing function that is the most prevalent type of SNHL in the elderly [17, 18, 19, 20]. It is characterized by higher hearing thresholds, beginning at high frequencies and spreading toward low frequencies, accompanied by the loss of HCs and SGNs from the basal to apical turn [21, 22, 23, 24, 25, 26]. The mechanism underlying ARHL is considered to be multifactorial, involving environmental and hereditary factors, but remains unclear.

Extensive evidence suggests that mitochondria make a large contribution to the pathology of ARHL.

A previous study proposed that the accumulation of mtDNA mutations could result in age-related degenerative diseases like ARHL [27]. Major mtDNA mutations arise in the genes encoding mitochondrial oxidative phosphorylation complexes, resulting in an impairment of its activity [28]. Transgenic PolgA mice with knockout of the functional nuclear gene that encodes the polymerase helping repair damaged mtDNA, POLG D257A, developed hearing loss more rapidly and earlier than their wild-type counterparts. Furthermore, 10-month old PolgA mice showed severe sensorineural degeneration in the basal turn and neural degeneration in the apical turn, including clumping of surviving neurons in the cochlea [29]. On the other hand, mtDNA

mutations affect cochlear function by leading to not only mitochondrial dysfunction but also energy metabolic disturbances and induction of apoptosis [30].

Extensive experimental evidence indicates that oxidative stress and ROS are closely associated with the development of ARHL. A suitable model of the senescence-accelerated mouse prone 8 (SAMP8) has been established to study the impact of the aging process on various parameters. In SAMP8 mice, oxidative stress, changes in antioxidant enzyme levels, and impairment in activities of complexes I, II, and IV were shown to be involved in premature ARHL [31]. Moreover, the level of 7,8-dihydro-8-oxoguanine, a crucial biomarker of mitochondrial and nuclear DNA damage in HCs and SGNs [32], increased with aging and mitochondrial biogenesis decreased, as assessed by the activity of citrate synthase and the ratio of mtDNA to nuclear DNA [31]. After exposure to H_2O_2 (0.1 mM) for only 1 h *in vitro*, House Ear Institute-Organ of Corti 1 auditory cells presented with premature senescence, leading to a lower mitochondrial membrane potential (MMP), breakdown of the mitochondrial fusion/fission balance, destruction of mitochondrial morphology, and collapse of the mitochondrial network [33]. Furthermore, oxidative stress and an accumulation of ROS increased expression of the mitochondrial proapoptotic gene Bcl-2-antagonist/killer 1 (Bak) to induce apoptosis. Suppression or deletion of Bak reduced apoptotic cell death of SGNs and HCs and prevented ARHL [34, 35].

As the major source of ROS, mitochondria contain a complex antioxidant system to resist the destructive effects of these species. Isocitrate dehydrogenase 2 (IDH2), which can convert $NADP^+$ to NADPH, is crucial in the mitochondrial response to oxidative stress. In male mice, IDH2 deficiency accelerated the ARHL process, along with increased oxidative DNA damage and apoptosis and a loss of SGNs and HCs [36]. Superoxide dismutase 1 (SOD1⁻) knockout mice also exhibited premature ARHL, characterized by an early loss of HCs, severe degeneration of SGNs, and leanness of the stria vascularis [37].

Glutathione peroxidase 1 (Gpx1) also has important antioxidant properties. Mice with deletion of Gpx1 showed higher hearing thresholds at high frequencies and extensive damage of HCs [34]. Ggt1^{dwg/dwg} mice, with deletion of the γ -glutamyl transferase 1 gene that encodes an antioxidant enzyme crucial for resynthesizing reduced glutathione (GSH), exhibited an extremely rare type of cochlear pathology in which the function of outer hair cells (OHCs) was unaffected while inner hair cells (IHCs) were unusually and selectively lost. Furthermore, treatment with N-acetyl-L-cysteine could completely prevent the hearing deficit and IHC loss in these mice [38]. In addition, administration of EUK-207, a synthetic SOD/catalase drug, attenuated the senescence phenotype *in vitro* and mitigated ARHL in SAMP8 mice by increasing the expression of FOXO3A and the mRNA and protein levels of manganese SOD (Mn-SOD) and catalase [39].

Peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α) could regulate mitochondrial biogenesis and upregulate the expression of oxidative stress-related genes, including Gpx1, catalase, and Mn-SOD genes [40, 41]. Over-

expression of PGC-1 α , with a consequent rise in nuclear respiratory factor 1 and mitochondrial transcription factor A, resulted in reduced damage to mtDNA and decreased apoptosis in the strial marginal cell aging model harboring mtDNA4834 deletion [34, 42, 43].

2.2. Noise-Induced Hearing Loss (NIHL). Excessive exposure to noise from recreation, the environment, and various occupations can lead to hearing loss, known as NIHL, which is one of the most prevalent types of SNHL. Its typical characteristics are an increased hearing threshold, tinnitus, decreased speech discrimination score, and auditory processing disorders [44]. Higher frequencies are preferentially affected, creating a V-shaped dip or notch, around 4 or 6 kHz [45]. The cochlear injury following noise exposure is mainly caused by mechanical damage and biochemical pathways. Generally, OHCs are more sensitive to noise exposure than IHCs [28].

ROS production was observed as an early event in cochlear damage after noise exposure [46]. As the major source of ROS, mitochondria are assumed to be damaged and, in turn, increase the accumulation of ROS. It has also been reported that mitochondrial ROS provide feedback regulation after metabolic excess, autophagy, and the inflammatory response [44]. ROS generate lipid peroxidation products, such as 8-iso-prostaglandin F 2α , that reduce blood flow in the cochlea [47], finally resulting in apoptosis [44]. Ischemia may lead to cochlear hypoxia and lower adenosine triphosphate (ATP) levels and further increase the generation of ROS. On the other hand, mitochondria possess a potent antioxidant enzyme system to scavenge ROS, relying on the NADPH pool. Mn-SOD heterozygous knockout mice had worse hearing thresholds, particularly at 4 kHz, and greater damage of OHCs in all cochlear turns after noise exposure and exacerbation of NIHL [14]. In another study, Gpx1-knockout mice exhibited greater HC and nerve fiber loss with higher auditory brainstem response thresholds [48].

Calcium homeostasis is also a significant factor in the occurrence and development of NIHL. After noise exposure, the level of free Ca^{2+} increased immediately in HCs [43, 49]; the probable ion channels allowing entry are L-type Ca^{2+} and P2X2 ATP-gated channels [50]. Mitochondria modulate cellular calcium homeostasis through selective calcium entry channels, the mitochondrial calcium uniporter (MCU), and the sodium-calcium exchanger with the function of extruding calcium from mitochondria [51]. Inhibiting the MCU in CBA/J mice attenuated the loss of sensory HCs, synaptic ribbons, and the NIHL process. Furthermore, MCU-knockout mice showed resistance to noise-induced seizures and recovery of IHC synaptic connections, the auditory brainstem response, and wave I amplitude after noise exposure [51]. Mitochondrial Ca^{2+} overload not only results in a decline in the MMP and overproduction of ROS but also triggers ROS-independent apoptotic and necrotic cell death pathways [50, 52, 53].

Before there is a permanent threshold shift caused by noise exposure, the level of 5'-AMP-activated protein kinase (AMPK) is elevated in the spiral ligament of cochlea, in addition to an increased level of phospho-c-Jun N-terminal

kinase, and this mediates the activation of apoptosis [54, 28]. Apoptosis occurs through both extrinsic and intrinsic pathways; the latter is activated by the change of mitochondrial membrane permeability. In addition to ROS, cytochrome C and caspase-independent apoptosis-inducing factor increase membrane permeability [28, 50, 55].

2.3. Ototoxic Drug-Induced Hearing Loss (ODIHL). Platinum-based anticancer drugs, such as cisplatin, and aminoglycoside antibiotics are clinically common ototoxic drugs [56, 57, 58]. Platinum-based anticancer drugs are widely adopted to treat different kinds of cancer, and aminoglycosides are broad-spectrum antibiotics used to treat many life-threatening bacterial infections. Both can lead to hearing loss at high frequencies and preferential damage to OHCs at the cochlea basal turn [43, 59, 60–62, 63, 64].

The ototoxicity of both cisplatin and aminoglycoside antibiotics is modulated by genetic factors, and mitochondrial mutations are well-defined risk factors. Individuals bearing the mtDNA mutation A1555G in the 12S ribosomal RNA gene suffer more profound hearing loss [56, 65, 66]. C1494T is the second most common mutation identified, especially in Chinese populations [67, 68, 69]. Mutations in thiopurine S-methyltransferase (TMPT) and catechol O-methyltransferase (COMT) are related to earlier onset and greater severity of hearing loss induced by cisplatin in children [70]. However, a more recent study revealed that variations in the TMPT or COMT genes may not correspond to cisplatin ototoxicity and did not affect hearing damage induced by cisplatin in mice. Thus, the precise role of these genes in cisplatin ototoxicity remains unclear [71].

Mitochondrial dysfunction and ROS are the main initiators of ODIHL. Aminoglycoside antibiotics, such as gentamicin, tend to accumulate in the mitochondria of HCs through nonselective mechano-electrical transducer cation channels expressed on the stereociliary membranes of HCs [72–74, 75, 76]. Administration of gentamicin can directly inhibit mitochondrial protein synthesis [28], trigger opening of the mitochondrial permeability transition pore, and lower the MMP [77]. Aminoglycosides can induce the release of arachidonic acid, leading to lipid peroxidation and generation of ROS [78, 79, 80, 81]. The ototoxic effect of aminoglycosides has been proposed to be linked to the formation of iron-aminoglycoside complexes that promote the formation of ROS [82]. Downregulation of tRNA^{Ser}-methylaminomethyl-2-thiouridylate methyltransferase, a mitochondrial protein, significantly made HEI-OC1 auditory cells more sensitive to damage induced by neomycin [80]. Aminoglycosides also dysregulate calcium homeostasis, facilitating the transfer of Ca²⁺ into mitochondria [83]. Elevation of mitochondrial Ca²⁺ levels promotes both mitochondrial oxidation and cytoplasmic ROS prior to cell death [84]. In an *in vitro* study, mitochondria-specific ROS formation was evaluated in cochlear explants after exposure to gentamicin, which was accompanied by a reduction of NAD(P)H and the MMP [85]. ROS formation in HCs in response to cisplatin leads to depletion of NADPH and binding to the sulfhydryl groups of enzymes [28, 86]. Cisplatin could stimulate the activity of NADPH oxidase 3, a relevant source of ROS, to

elevate ROS levels [87]. Oxidative stress induced by cisplatin could lead to GSH depletion, increased lipid peroxidation, and an imbalance of the oxidant/antioxidant systems [43].

Mitochondrial apoptotic pathways are activated following both cisplatin and aminoglycoside cochlear injury through the Bcl-2 family of proteins. After cisplatin treatment, the level of Bax was increased and the level of Bcl-2 was decreased in HCs, spiral ganglia, and the lateral wall [88]. Pretreatment with an adenovector expressing human Bcl-2 (Ad.11D.Bcl-2) could protect HCs and preserve hearing in mice treated with gentamicin [89].

2.4. Inherited Hearing Loss. Sensorineural hearing loss which mainly causes by mutation of genes, known as inherited hearing loss, has been identified more common due to the development of science and technology [90, 91, 92]. Its clinical and genetical characteristics are very heterogeneous [93]. Though the mechanism of many cases remains unclear, large evidence has proved that it has much to do with the mitochondrial function.

13 crucial polypeptides of oxidative phosphorylation were encoded by mitochondrial genome [94]. Mutation in the mitochondria DNA has been proved to be related to the maternally inherited susceptibility in both syndromic and nonsyndromic hearing loss [93]. Mitochondrial disorders including Kearns-Sayre syndrome, MELAS syndrome, and MERRF syndrome are always accompanied by syndromic hearing loss [94]. In view of nonsyndromic hearing loss, extensive research has been carried out to identify the role of A1555G and C1494T mutations in 12S rRNA and emphasize the high susceptibility to hearing loss induced by drugs such as cisplatin and aminoglycoside [95, 65, 66, 96]. Mutation of 7505A>G in the tRNA^{Ser(UCN)} would lead to mitochondrial dysfunction by lowering the activity of cellular respiratory chain and the level of ATP, MMP, and over produce ROS [97], finally induce cell apoptosis [98]. Other variants in the tRNA^{Ser(UCN)} including A7445G, T7505C, T7510C, and T7511C alter mitochondrial translation and function, involving in SNHL [95, 99, 100, 101].

The phenotypic expression of variants in mitochondrial DNA could be modulated by nuclear modifier genes, which may also play an important role in inherited hearing loss. Fan et al. had found that the interaction between p.191Gly>Val mutation in mitochondrial tyrosyl-tRNA synthetase 2 (YARS2) and the 7511A>G mutation in tRNA^{Ser(UCN)} caused hearing loss [102]. Moreover, in the study of Chinese families, people who suffer both mutations present much higher penetrance of hearing loss than those who carry only one [102]. Mtu1 is a tRNA-modifying enzyme and mtu1 knockout zebrafish exhibited a smaller number of hair cells and reductions in the hair bundle densities in the auditory and vestibular organs [103]. Deletion of Gtppb3 also resulted in impairment of mitochondria function in zebrafish, which provided novel opportunities for studying pathophysiology of mitochondrial disorders [104].

Much more mitochondrial gene loci associated with hearing loss have been discovered due to advanced technology. Mitochondrial dysfunction caused by mtDNA mutations are one of the major molecular mechanisms

responsible for deafness. However, many cases remained unclear. We hope more research will be carried out in the future.

3. Sirtuins and Function

Sirtuins were originally described in yeast and named Sir2, with seven Sir2 homologs (SIRT1-7) discovered. Sirtuins consume NAD⁺ to deacetylate lysine residues and generate nicotinamide and 2'-O-acetyl-ADP-ribose [105]. The crucial function of sirtuins is to sense and regulate cellular metabolic responses [106, 107]. They display diverse subcellular localizations in the cell. In the nucleus, there are mainly SIRT1, SIRT6, and SIRT7, whereas in the cytoplasm, SIRT2 is located. SIRT3, SIRT4, and SIRT5 are predominantly located in the mitochondria [16] and are the main focus of this review. SIRT3 is the principal mitochondrial deacetylase, whereas SIRT4 and SIRT5 only have weak deacetylase functions [108]. However, SIRT5 has robust demalonylase, desuccinylase, and deglutarylase activities [109], and SIRT4 can regulate lipamidation [110].

3.1. SIRT3. SIRT3 is the main deacetylase in mitochondria, and its expression is the highest in tissues with vigorous metabolism such as the liver, kidney, and heart [111]. SIRT3 level increases under calorie restriction, fasting, and exercise training in different tissues [112, 113]. Acetyl-CoA synthetase 2 was the first reported target of SIRT3 [114]. However, further research revealed that SIRT3 also affected a diverse range of target proteins and participated in all major biochemical reactions and metabolic activities of mitochondria, including the respiratory chain, antioxidant defenses, and apoptosis [15, 16].

SIRT3 is an important factor involved in resisting various mitochondrial stresses, especially by utilizing cellular antioxidant systems to combat oxidative stress. SOD2, which reduces ROS levels and protects against oxidative stress, is activated by SIRT3-mediated deacetylation [115]. SIRT3 deacetylates and activates IDH2, the major source of NADPH in mitochondria, which helps maintain GSH levels [16, 15, 116]. Deacetylation of FOXO3A, a forkhead transcription factor, by SIRT3 activates the transcription of SOD2, catalase, and other crucial antioxidant genes and protects mitochondria from further oxidative stress [117, 118]. Another key stress-sensitive pathway in mitochondria affected by SIRT3 is the mitochondrial permeability transition pore. SIRT3 deacetylates cyclophilin D [119] and mitochondrial fusion protein optic atrophy protein 1. These proteins affect mitochondrial dynamics and the MMP [120].

SIRT3 plays important roles in a wide range of diseases, including hearing loss. As mentioned above, ROS and mitochondrial dysfunction have much to do with the etiology of SNHL. SIRT3 deacetylates and activates the antioxidant system in mitochondria to reduce the level of ROS induced by noise, aging, or drugs and maintain mitochondrial permeability through deacetylation of proteins. Under caloric restriction, deacetylation and activation of IDH2 by SIRT3 increased the levels of NADPH and GSH in mitochondria, thus preventing ARHL in wild-type, but not SIRT3-

knockout mice [112]. Similarly, overexpression of SIRT3 in mice aided in preventing NIHL. Administration of the NAD⁺ precursor nicotinamide riboside to mice prevented the degeneration of spiral ganglia neurites and NIHL by activating the NAD⁺-SIRT3 pathway, and these protective effects were abrogated with SIRT3 deletion [121]. Adjudin, a lonidamine analog, could protect cochlear HCs from gentamicin-induced damage mediated by the SIRT3-ROS axis [122].

3.2. SIRT4. SIRT4 is widely expressed and abundant in pancreatic β -cells, kidney, heart, brain, and liver [123, 110]. It has been reported that SIRT4 has no detectable NAD⁺-dependent deacetylase activity and function through NAD⁺-dependent ADP-ribosylation [16, 123]. Few studies have been carried out in other tissues, except pancreatic β -cells, and the precise enzymatic functions of SIRT4 remain unclear. ATP is indispensable for insulin secretion by pancreatic β -cells, and SIRT4 inhibits the activity of glutamate dehydrogenase (GDH) to reduce the amount of ATP produced by the catabolism of glutamate and glutamine [124, 16]. Mice deficient in SIRT4 or subjected to calorie restriction exhibited upregulation of amino acid-stimulated insulin secretion [123]. It is interesting that SIRT3 deacetylates and activates GDH, indicating that this enzyme may be regulated by both SIRT3 and SIRT4 [124, 125]. SIRT4 knockdown also caused increased fatty acid oxidation dependent on SIRT1, respiration, and AMPK phosphorylation [126].

Compared with those on SIRT3, there have been fewer studies on the regulation of SIRT4. Recent research suggests that SIRT4 may be involved in ROS homeostasis by the pyruvate dehydrogenase complex and GDH and fatty acid oxidation through malonyl-CoA decarboxylase [110, 127], ultimately reducing ROS production, that is, may have potentially optimistic effect in preservation of hearing function. However, there are studies showing that increased activity of SIRT4 may raise ROS levels in murine cardiomyocytes [128, 129]. Nevertheless, the precise mechanism of SIRT4 enzymatic activity is unknown, though it may play a role in hearing loss. Further studies are needed to identify the mechanism underlying SIRT4 function.

3.3. SIRT5. Unlike other sirtuins, SIRT5 primarily originated from prokaryotes [130], with high expression in various tissues such as the heart, brain, and liver. [131]. The function of SIRT5 has generally become an important research topic.

SIRT5-deficient mice show no detectable alterations in the whole acetylation state of mitochondria, indicating there is a specific acetyl substrate for SIRT5 or alternative functions [132]. And global protein hypermalonylation and hypersuccinylation are observed, indicating that SIRT5 catalyzes lysine demalonylation and desuccinylation reactions in mammals [133]. One target of SIRT5 is carbamoyl phosphate synthetase 1 (CPS1). This enzyme has been identified as the key rate-determining step of the urea cycle for detoxification and removal of ammonia. SIRT5 upregulates CPS1 activity through deacetylation and desuccinylation, and this function is absent in SIRT5-deficient mice [124, 134, 15]. In mice overexpressing SIRT5, the CPS1 protein was more deacetylated and activated in the liver than in wild-type mice [135].

In terms of occurrence and development of SNHL, SIRT5 has been demonstrated to contribute to ROS homeostasis and attenuate oxidative stress. It may reduce ROS levels and oxidative stress through a mechanism similar to that of SIRT3, by deacetylation of FOXO3A and desuccinylation of IDH2, so that it may have optimistic effect on preserve hearing function [136, 137]. Another study showed that SIRT5 enhanced SOD1-mediated ROS reduction by desuccinylation [138]. Recent evidence suggests that SIRT5 plays a potential protective role against neurodegeneration, which is a common phenomenon in SNHL. Although the mechanism remains undetermined, SIRT5 may protect neurons by limiting overproduction of ROS directly and controlling systemic ammonia levels indirectly [139].

4. Conclusion

Although extensive research is required to probe the pathology of hearing loss, a causative role for mitochondrial dysfunction remains one of the most solid theories. Mitochondrial sirtuins (SIRT3-5) are intimately linked to responses to stress, such as oxidative stress, metabolic regulation, and apoptosis, all of which are related to the occurrence and development of hearing loss. Moreover, we have reasons to believe SIRT3-5 have positive effect on SNHL. Moving forward, it is important to determine the precise activities of mitochondrial sirtuins as crucial targets to help prevent and cure hearing loss.

Data Availability

The data that support the findings of this study are openly available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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