

VDAC1: The mitochondrial gatekeeper in the battle against hearing loss (Review)

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Abstract. The development of hearing loss is strongly associated with mitochondrial damage, particularly downstream of mitochondrial autophagy, which is a process that is coincidentally key for selectively removing damaged mitochondria. Voltage-dependent anion channel 1 (VDAC1) is an important protein in the mitochondrial outer membrane that regulates various essential biological processes, including energy metabolism, calcium ion transport and cell apoptosis. VDAC1 can bidirectionally regulate cell fate, where its oligomerization can exacerbate oxidative stress, leading to cell damage and even death. By contrast, its ubiquitination supports cell survival by regulating mitochondrial autophagy, thereby improving mitochondrial quality control. VDAC1 can significantly contribute to the prevention and management of hearing loss. The present review summarizes how the ubiquitination and oligomerization modifications of VDAC1 can balance cell survival and death, while also exploring current hypotheses on mechanisms associated with hearing loss. These findings emphasize the research prospects of VDAC1 as a novel target for hearing loss treatment.

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1. Introduction

In total, >1.5 billion individuals worldwide suffer from hearing loss, the number of which is increasing annually (1). Apart from age, noise is the second leading cause of hearing loss, with >500 million individuals suffering from noise-induced hearing loss (2). At present, it is considered that oxidative stress damage to cochlear cells, which are hair cells (HCs) and spiral neurons, is an important cause of irreversible noise-induced hearing loss. Emerging mechanisms, such as mitochondrial autophagy, are beginning to garner attention (3).

At present, the pathogenesis of various clinical diseases, such as neurodegenerative, cardiovascular, cancer and metabolic disorders, are gaining attention due to the role of mitochondria as vital energy centers in eukaryotic cells. Mitochondrial autophagy is a mechanism that maintains the stability of the internal environment of the cell by selectively degrading damaged mitochondria. Mechanisms, such as oxidative stress, inflammation, apoptosis, necrosis and energy imbalances, are closely associated with the regulation of mitochondrial autophagy (4). In the field of studying hearing loss mechanisms, oxidative stress is an important mechanism that causes damage to HCs and synaptic-related diseases in the cochlea. Mitochondrial autophagy can eliminate damaged mitochondria, prevent the production and escape of oxidative free radicals, which has important protective significance (5). These findings suggest that regulating mitochondrial autophagy is closely associated with the fate of cochlear receptor cells and therefore hearing loss. Voltage-dependent anion channel 1 (VDAC1) is a key mitochondrial outer membrane protein that is associated with the PTEN-induced putative kinase 1 (PINK1)/Parkin pathway (6). VDAC1 serves a role in maintaining the stability of the mitochondrial outer membrane (7). It is associated with the release of mitochondrial apoptosis necrosis factors [such as apoptosis-inducing factor (AIF) and cytochrome c (cyto c)], ions and mitochondrial DNA (mtDNA) (8), serving a dual role in determining cell fate within signaling pathways. It can be hypothesized that this may be a key molecule in regulating the balance between mitochondrial autophagy and cell death. The present review summarizes and examines the relevant literature on VDAC1 and its role, in addition to surmising its clinical translational significance in hearing loss research.

2. Mitophagy and oxidative stress in hearing loss

Hearing loss is a condition in which external stimuli causes damage to the sensory cells in the cochlea, resulting in impaired sound transmission. Ageing, noise, infections and ototoxic drugs can all lead to sensory cell damage. Permanent hearing loss can result from irreversible sensory cell damage, such as the destruction of cochlear hair cells due to noise-induced oxidative stress (9). However, there are cases of neurological hearing loss in clinical practice where hearing is restored through intervention measures during the early stages of injury (10), indicating the existence of mechanisms regulating the death and survival of cochlear sensory cells. Mitochondrial autophagy has been recognized to be an important endogenous mechanism for maintaining mitochondrial quality.

Mitochondrial autophagy is a vital intrinsic protective mechanism that enables cells to respond to stimuli and damage, significantly contributing to the process of hearing loss. Oxidative stress leads to mitochondrial dysfunction, triggering autophagy reactions to clear damaged mitochondria and excess reactive oxygen species (ROS) (11). ROS are mainly derived from mitochondria (12). Superoxide dismutase (SOD)2 in the mitochondrial matrix and SOD1 in the intermembrane space catalyze the conversion of O_2^- to H_2O_2 , which subsequently transforms into superoxide (13). The destructive effects of ROS have been extensively studied. Morioka *et al* (9) previously found that excessive ROS can damage inner ear hair cells, resulting in hearing loss. Oxidative stress is a key pathogenic factor in the noise-induced hearing loss (NIHL) model. Liang *et al* (14) reported that ROS accumulation in the inner ear is significantly associated with cell death following noise exposure. However, ROS can also induce autophagy (15). A previous study revealed that the activation of autophagy in outer hair cells (OHCs) can exert a protective effect against NIHL by reducing oxidative stress (16). During noise-induced temporary threshold shift, oxidative stress can elevate microtubule-associated protein 1 light chain 3B (LC3B) levels in OHCs, while sirolimus treatment can mitigate 4-hydroxynonenal and 3-nitrotyrosine (3-NT) levels to reduce OHC damage. Similarly, the use of 3-methyladenine or LC3B small interfering RNA leads to an increase in 3-NT levels and cell death in OHCs (17).

Therefore, cell fate following damage caused by ROS to the cochlear sensory cells depends on the balance achieved by mitochondrial autophagy and apoptosis signalling pathways. The apoptosis-related pathways guided by mitochondria, such as caspase pathway and AIF pathway, involve the release of apoptosis factors from mitochondria, such as the TNF receptor (18). In addition, mitochondrial autophagy, as a cellular protective pathway, can also promote the clearance of damaged mitochondria and maintain mitochondrial function through PINK/Parkin-mediated ubiquitination (19). However, during the temporary threshold shift, the increased expression of mitophagy-related protein LC3B, activated by oxidative stress, indicates that oxidative stress also promotes mitochondrial autophagy, as previously reported (19). Overall, mitochondrial autophagy and apoptosis may function as balanced regulators of cell fate, however there is no literature that provides a detailed explanation on how the balance

between autophagy and apoptosis is regulated. A study of mitochondrial autophagy previously revealed that VDAC1 is involved in cell damage and can mediate a dual regulatory effect. It primarily serves a role in regulating the mitochondrial permeability transition pore (20), facilitating the movement of apoptotic factors (such as AIF) from the mitochondria to the cytoplasm, thereby contributing to cell apoptosis (21). It also functions as a regulator of mitochondrial autophagy by recruiting the autophagy receptor protein sequestosome 1 (SQSTM1/p62), thereby mediating mitochondrial autophagy to maintain mitochondrial quality control and cell survival balance (22). Huang *et al* (23) demonstrated the interaction between VDAC1 and myeloid cell leukemia 1 as being crucial for mitochondrial function and ROS regulation, offering insights into hearing loss pathogenesis. In another study, Kurabi *et al* (5) highlighted the association between cell apoptosis and inner ear damage following noise exposure, noting the involvement of VDAC1 underlying this apoptotic process. The interplay between autophagy and oxidative stress is likely important in hearing loss, with the bidirectional functionality of VDAC1 being potentially pivotal.

3. Molecular characteristics and dual regulatory mechanism of VDAC1

Structural features and basic functions. VDAC1 is a key protein on the mitochondrial outer membrane that serves to regulate substance and ion exchange between mitochondria and the cytoplasm upstream of cellular energy metabolism. It participates in various functions, such as energy generation, calcium ion transport and the regulation of cell apoptosis (24). Research has indicated that VDAC1 expression can vary in neurodegenerative diseases (such as Alzheimer's disease), in addition to interacting with disease-related molecules and contributing to disease progression (25). VDAC was initially purified from *paramecium* mitochondria in 1976 (25). At present, three subtypes of VDAC family proteins have been identified in mammals, namely VDAC1, VDAC2 and VDAC3. VDAC1 is extensively expressed and exhibits notable bidirectional functionality (24,26). VDAC2 has been reported to interact with proteins containing Bcl-2 homology 3 (BH3) death domains, including truncated BH3-interacting domain death agonist, Bcl-2-like protein 11 and Bcl-2-associated agonist of cell death, to facilitate Bcl-2 homologous antagonist/killer oligomerization, create apoptotic channels and trigger cell apoptosis (27). VDAC3, which is particularly rich in cysteine residues, is important for mitochondrial protection (28). VDAC subtypes have a tissue-specific expression pattern, where VDAC1 is highly expressed in general, especially in the cochlea. VDAC1 is the most highly expressed among the three subtypes in most organs, such as the heart, liver, brain tissue, including cochlear tissue and other mitochondrial-rich tissues. VDAC1 is considered the gatekeeper of mitochondrial and cytoplasmic material transport, and is therefore widely expressed in mitochondrial-rich tissues (29). In the cochlea (30), hair cells and spiral neurons are the concentrated areas of mitochondrial distribution, therefore, VDAC1 exhibits expression distribution in this region. In addition, in the latest research on the mechanism of hearing loss (31), it was found that VDAC1 is widely expressed in cochlear cells and increases after noise exposure.

VDAC1 consists of 19 transmembrane β chains forming a β pore, which contains a 25-residue fragment in the N-terminal domain. N-terminal domain migration serves a role in channel gating and VDAC1 dimer formation. An α -helix is located at the midpoint of the barrel hole and is horizontal, where it regulates the transport of metabolites by reducing the pore size (32). VDAC1 facilitates the transfer of a number of metabolites, such as pyruvate, succinate, malonate, nucleotides and NADH, into the mitochondria, enabling subsequent metabolism (33). In addition, VDAC1 is involved in cholesterol transport, lipid metabolism, Ca^{2+} signaling between mitochondria and the endoplasmic reticulum and redox status regulation (34). VDAC1 is also essential for mitochondria-mediated cell apoptosis. Drug-induced cell apoptosis can promote overexpression and oligomerization of VDAC1, leading to the formation of large pores on the surface of mitochondria, and promoting the transfer of AIF, cyto c and apoptotic protease-activating factor 1 (Apaf-1) to the cytoplasm, thereby activating apoptotic pathways (35-37). For example, AIF can transfer out of mitochondria and enter the nucleus to promote DNA condensation and cleavage, and promote cell apoptosis. Similarly, cyto c and Apaf-1 are also involved in related apoptotic mechanisms. Therefore, VDAC1 is considered a 'mitochondrial gatekeeper'.

Ubiquitination modification and mitophagy regulation. VDAC1 regulates cell fate determination through the dynamic balance of the ubiquitination/oligomerization switch. Through the classical pathway, VDAC1 serves as a substrate for the E3 ligase Parkin (38). During autophagy induction, VDAC1 can be ubiquitinated to form adapter proteins with ubiquitin-binding motifs and LC3B-binding motifs, recruiting p62/SQSTM1 or LC3B to promote autophagosome formation and induce lysosomal binding to these labelled mitochondria for selective degradation. In the traditional PINK1/Parkin mitochondrial autophagy pathway, PINK1 phosphorylates Parkin on S65 within the ubiquitin-like domain, thereby activating its E3 ubiquitin ligase activity. Notable Parkin substrates include the mitochondrial outer membrane-associated proteins mitofusin (MFN)1, MFN2, outer membrane transposase 20, mitochondrial Rho GTPase 1 and VDAC1, which clear damaged mitochondria and maintain their stability through the ubiquitination autophagy mechanism (39). In addition, the ubiquitination sites of VDAC1 include β -chain K53, K274, K12, K20, K53, K109 and K110. In a previous study on liver fibrosis, ubiquitination at the K53 site of VDAC1 was found to negatively regulate VDAC1 oligomerization and mtDNA release (40). Apart from Parkin, other E3 ubiquitin ligases, such as neural precursor cell expression and developmental downregulation 4, can connect with the ubiquitylated protein through the K48 site to negatively regulate acetaminophen-induced mitochondrial damage in liver cells (41). In Parkinson's disease, tripartite motif-containing protein 31, a triple motif protein, can promote the degradation of VDAC1 by catalyzing ubiquitination at the K48 site of VDAC1, a process which helps stabilize dopaminergic neurons (42). Therefore, investigating the ubiquitination sites and specific signaling pathways of VDAC1 in cochlear receptor cells offers a novel perspective for studying hearing loss mechanisms.

Oligomerization modification and activation of cell apoptosis. There are multiple post-translational modification modes of VDAC1, including phosphorylation, acetylation, tyrosine nitration, ubiquitination and oligomerization, but their consequences remain poorly elucidated. VDAC1 is known for its oligomerization, because it is associated with cell death. VDAC1 can form pore-like channels in the outer membrane of mitochondria, regulating the entry and exit of Ca^{2+} to maintain the balance of the outer membrane. However, under stimulation, VDAC1 will self-aggregate to form dimeric, trimeric or even oligomeric forms, expanding the pore size and disrupting the balance on the outer membrane of mitochondria. During cell apoptosis, it interacts with the apoptotic protein Bax to form an oligomeric structure that increases the central pore size of VDAC1, allowing the release of cyto c, Apaf-1, deoxyadenosine triphosphate (dATP) and AIF to promote apoptosis (35). VDAC1 oligomerization pores also facilitate mtDNA release from mitochondria into the cytoplasm, disrupting mitochondrial homeostasis and aggravating lupus erythematosus (43). In addition, VDAC1 is associated with the uptake and release of mitochondrial Ca^{2+} . It can interact with the endoplasmic reticulum and become an important part of the mitochondrial Ca^{2+} connection. Excessive Ca^{2+} transport can also stimulate the regulatory effect of VDAC1 (44). A previous study reported that upregulation of the mitochondrial calcium uniporter protein in a cadmium toxicity model of liver cells can trigger the oligomerization and ubiquitination of VDAC1 (45,46), where the balance between oligomerization and ubiquitination can determine the fate of cells.

VDAC1 plays a significant role in ubiquitination. Mitochondrial autophagy involves a critical step known as ubiquitination, which functions analogously to tagging substrates for subsequent lysosomal degradation. While ubiquitination marks cellular components for phagocytosis by lysosomes, the detailed mechanisms of lysosomal engulfment and degradation fall beyond the scope of this discussion (42). Previous research has elucidated the role of VDAC1 in mitochondrial ubiquitination, such as its potential as a substrate for E3 ubiquitin ligase (47). It can also regulate classic mitochondrial autophagy pathways such as the PINK1/Parkin pathway. However, the role of VDAC1 in autophagy remains only partially understood, including its inhibition of the PINK1/Parkin pathway to mitigate noise-induced hearing loss (31). In addition, increased expression of VDAC1 may serve as an additional anchor site for polyubiquitination recruitment, triggering mitochondrial autophagy (48). Thus, VDAC1 has been revealed to be associated with autophagy, but further research is still required.

4. Possible mechanism of VDAC1 in hearing loss

At present, research on the mechanism of hearing loss injury caused by VDAC1 remains insufficient and is limited mainly to its regulatory effect on Ca^{2+} . El-Emam *et al* (49) found that the inositol trisphosphate receptor/glucose-regulated protein 75/VDAC1 complex in cochlear sensory cell mitochondria can facilitate the transfer of Ca^{2+} from the endoplasmic reticulum into the mitochondria. In another study, Zhao *et al* (50) reported that endoplasmic reticulum Ca^{2+} can transfer to

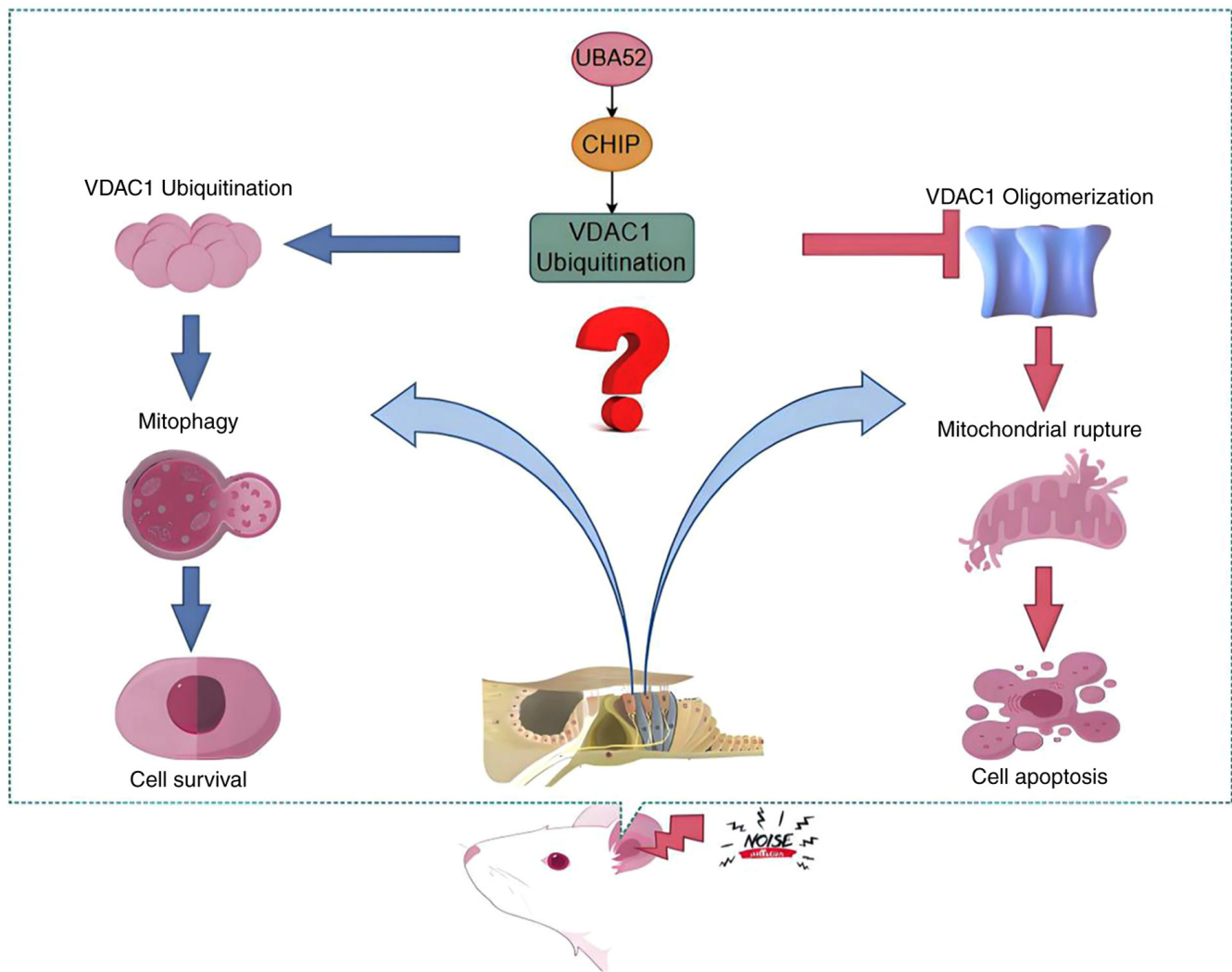


Figure 1. Hypothetical diagram illustrating the effect of VDAC1 on the fate of cochlear cells under noise stimulation. The regulation of VDAC1 ubiquitination by the E3 ubiquitin ligase CHIP may lead to different fates of cochlear sensory cells. First, increased VDAC1 ubiquitination leads to mitochondrial autophagy, and mitochondrial quality control mediates the clearance of damage factors and cell survival. Second, decreased VDAC1 ubiquitination mediates VDAC1 oligomerization in the outer mitochondrial membrane, leading to abnormal opening of the mitochondrial permeability transition pore, the release of apoptotic factors, mitochondrial rupture, and cell apoptosis. The figure was created using Figdraw 2.0 Online Drawing Platform; <https://www.figdraw.com/#/>. VDAC1, voltage-dependent anion channel 1; CHIP, carboxy terminus of HSP-70-interacting protein; UBA52, ubiquitin A-52 residue ribosomal protein fusion product 1.

the mitochondria through the VDAC1 pathway, triggering autophagy in HEI-OC1 cells in response to cisplatin (50). Li *et al* (51) proposed that the decline in mitochondrial function associated with noise-induced hearing loss is associated with oxidative stress and nucleotide-binding oligomerization domain-, leucine-rich repeat-, and pyrin domain-containing protein 3 inflammasome activation, with VDAC1 involved in mitochondrial regulation (51). Wang *et al* (52) previously found that VDAC1 expression is significantly increased in a noise-induced hearing loss model, which was associated with mitochondrial dysfunction (52). Le *et al* (53) emphasized the impact of noise-induced hearing loss on cochlear cells, highlighting the importance of mitochondrial membrane stability (53). A previous study demonstrated that inhibition of VDAC1 can enhance mitochondrial autophagy in cochlear hair cells within cochlear explants and HEI-OC1 cells, thereby serving a key role in mitigating oxidative stress and inflammation (50). Downregulation of VDAC1 has been found to reduce hair cell damage and apoptosis by activating the PINK1/Parkin

pathway, thereby contributing to the preservation of hearing function (31). However, the multiphase protein modification and regulatory mechanisms of VDAC1 in sensory cell damage in individuals with hearing loss has not been fully elucidated. According to a previous study, after 7 days of noise exposure, the expression of AIF decreased in cochlear sensory cells suggesting a potential protective response to mitochondrial dysfunction (54). Ma *et al* (47) reported that the decrease in AIF expression during hypoxia is due to the ubiquitination and clearance of ubiquitin A-52 residue ribosomal protein fusion product 1 (UBA52) by ubiquitination. Tiwari *et al* (55) reported that UBA52 can also ubiquitinate VDAC1 through the E3 ligase carboxyl terminus of Hsc70-interacting protein, thereby activating mitochondrial autophagy. These findings establish a link between VDAC1 ubiquitination and AIF ubiquitination clearance. In addition, Chen *et al* (38) reported that VDAC1 expression was reduced to activate autophagy and alleviate cell apoptosis in leafhoppers infected with arboviruses, thereby protecting the cells. These findings indicate that

VDAC1 ubiquitination can reduce cell apoptosis and regulate autophagy (38). In addition, the aforementioned findings offer insights into the study of noise-induced hearing loss and its prevention (Fig. 1). Further elucidation of the role of VDAC1 in the regulation of cell survival and death is key to identifying novel targets for cochlear sensory cell protection.

Prospects and clinical translation of VDAC1 in hearing loss. Given the potential role of VDAC1 in cochlear sensory cell stress, modulating VDAC1 function can enhance cochlear cell environments, mitigate oxidative stress and bolster resistance, thereby reducing cochlear cell damage. Livingston *et al* (56) previously showed that ischemic pretreatment of renal tubular cells activated autophagy, which prevented mitochondrial depolarization, enhanced ATP production and regulated cell apoptosis and autophagy, thereby protecting these cells from ischemic damage and offering novel insights for hearing loss treatment. It is surmised that reducing the expression of VDAC1, regulating VDAC1 ubiquitination, enhancing mitochondrial autophagy, reducing cell damage and protecting hearing are effective strategies in protecting from hearing loss. The VDAC1 oligomerization inhibitor, VBIT-4, has been previously applied to reduce mtDNA release by inhibiting VDAC1 oligomerization, which had protective significance in lupus-like diseases (57). VBIT-4 has also been reported to alleviate the neuropathological features of Alzheimer's disease mouse models by targeting VDAC1 (58). In addition, VDAC1 inhibition has been achieved using CRISPR/Cas9 gene editing technology to alter its active site (59). However, this approach is currently limited to scientific research, where owing to the biological homology of VDAC1, knockout has not achieved protective results. In addition, the clinical use of the antidepressant sertraline (Sert) has been reported to act as an autophagy inducer, targeting and antagonizing VDAC1 expression and enhancing autophagy (60). Exploring the application of Sert as a protective measure against noise-induced hearing loss presents a potential intervention strategy. Consequently, targeting VDAC1 may offer a novel approach for future hearing loss treatments. It is necessary to further explore the mechanism of VDAC1 protein modification in different types of sensory cells involved in hearing loss, such as hair cells and spiral neurons, to integrate the protein modification strategies of VDAC1 and provide theoretical evidence for research on hearing protection.

In summary, there is a possible association between VDAC1 and hearing loss through mitochondrial autophagy, but there are unsolved research gaps. Further exploration and research are needed to determine which sensory cells are regulated by VDAC1 under conditions of hearing loss injury and whether this regulation can induce mitochondrial autophagy or cell death. Furthermore, little is known regarding the specific regulatory mechanism of targets in the ubiquitination process of VDAC1. The advancement in VDAC1 inhibitors for Alzheimer's and type 2 diabetes, along with the significance of ubiquitination regulation in drug development, offers a novel approach for future hearing loss treatment and prevention.

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Authors' contributions

ZJD contributed to the conception, formal analysis, and supervision of the study. Additionally, ZJD played a key role in writing the original draft and participated in the review and editing process. YW contributed to the writing, reviewing and editing of the manuscript, as well as providing consultation. Both authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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