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Mitochondrial Mechanisms and Research Progress in Nonsyndromic Hearing Loss: A Comprehensive Review

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ABSTRACT Mitochondrial dysfunction is a key contributor to nonsyndromic hearing loss (NSHL). This review aims to synthesise current knowledge on how mitochondrial mechanisms, including mtDNA mutations, oxidative stress, and ATP deficiency, influence auditory function. By analysing recent studies, the researchers highlight the role of genetic diagnostics (for example, next-generation sequencing) in uncovering mtDNA variants linked to NSHL and the interplay between oxidative stress and mitochondrial damage in cochlear cells. The review concludes by emphasising the need for innovative therapeutic strategies targeting mitochondrial dysfunction to mitigate NSHL.

INTRODUCTION

Nonsyndromic hearing loss (NSHL) poses a significant public health challenge, affecting millions of individuals globally without the additional clinical manifestations characteristic of syndromic forms (Chiereghin et al. 2023; Cui et al. 2020).The prevalence of hearing loss increases with age, and the condition affects 1 in 8 people in the United States age 12 and older, or about 30 million people (Pickett and Raible 2019; Velde et al. 2023). This trend highlights the growing impact of NSHL on public health, emphasising the need for effective interventions and support systems for affected individuals.

Unlike syndromic hearing loss, which presents with various phenotypic cues, NSHL is exclusively auditory, rendering its study both essential and complex (Sloan-Heggen et al. 2016). This review aims to delineate the current landscape of NSHL research, emphasising the genetic and mitochondrial mechanisms that underpin the disorder while evaluating the progression of potential therapeutic interventions (Pawlak-Osiñska et al. 2018). Approximately 50 percent of NSHL cases have a genetic basis, with mutations in the GJB2 gene being particularly prevalent across diverse populations (Koohiyan et al. 2019). This genetic variability underscores the necessity for targeted discussions on the importance of personalised genetic screening and counselling, especially in genetically distinct regions such as Saudi Arabia and Iran, where specific variants significantly contribute to the prevalence of NSHL (Ray et al. 2022). These regions offer valuable insights into the genetic architecture of NSHL, highlighting the need for tailored medical approaches.

In addition to genetic factors, the role of mitochondria in the etiology of NSHL presents a critical avenue for understanding and addressing this disease (Jackson and Theiss 2020). Mitochondria are vital for fulfilling the high energy demands of cochlear cells, and their dysfunction can trigger a cascade of cellular damage leading to hearing loss (Lu et al. 2021; Sinno et al. 2022). This review will investigate how mitochondrial dysfunction contributes to NSHL and discuss recent advances in therapeutic strategies aimed at mitigating these effects (Wilkerson et al. 2019).

Currently, the treatment landscape for NSHL predominantly involves assistive devices such as hearing aids and cochlear implants. However, these interventions have inherent limitations, emphasising the urgent need for innovative pharmacological treatments (Fletcher and Zgheib 2020). Recent investigations into compounds such as bile acids and theophylline, which have shown promise in protecting sensory hair cells

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from damage, illustrate the novel approaches being explored (Velde et al. 2023). This article will synthesise findings from recent studies, integrate them with clinical practices, and propose future research directions (Mahboubi et al. 2018). By enhancing the understanding of the genetic and molecular foundations of NSHL, particularly through mitochondrial studies, the researchers aim to improve diagnostic precision and expand therapeutic options, ultimately enhancing outcomes for individuals affected by this condition.

Objectives

The objectives of this review are to:

1. Critically synthesise recent advances (2023-2025) in mitochondrial mechanisms underlying nonsyndromic hearing loss (NSHL), emphasising mtDNA mutation profiling and oxidative stress pathways.
2. Evaluate the translational potential of emerging therapeutic strategies (for example, mitochondrial gene therapy and antioxidant therapies) by analysing their efficacy and limitations in preclinical models.
3. Identify knowledge gaps in current research to inform future directions for mitochondrial-based interventions in NSHL.

mtDNA: A Cornerstone in Cellular Metabolism and Hearing Function

Mitochondria are essential not only as powerhouses of the cell but also as critical players in hearing function (Honda et al. 2017). In the cochlea, hair cells transduce sound vibrations into electrical signals, which are then relayed to the brain (Wu et al. 2010). This intricate process relies heavily on the endocochlear potential generated by the lateral wall of the cochlea, which is vital for the proper functioning of hair cells (Beurg et al. 2018). Their health is paramount, as they are particularly susceptible to damage from genetic mutations and environmental stressors (Park et al. 2018). For example, otoferlin, a protein crucial for synaptic transmission in hair cells, underscores this importance, and deficiencies in otoferlin lead to significant auditory and locomotion defects (García-Hernández et al. 2017; Ramakrishnan et al. 2014). Recent studies have emphasised the dynamics of mitochondria within the auditory system, particularly how these organelles respond to energetic stimuli, such as sound vibrations (Wu et al. 2023). Outer hair cells (OHCs) enhance hearing through a mechanism known as cochlear amplification, facilitated by their electromotility, which is influenced by the voltage-sensing protein prestin (Wu et al. 2016). This interplay between mitochondrial function and the mechanical properties of hair cells highlights the complexity of auditory transduction and the need for a well-coordinated cellular environment to maintain hearing capabilities.

Mitochondrial dysfunction can lead to the accumulation of reactive oxygen species (ROS), resulting in oxidative damage and apoptosis (Zhang et al. 2019). This phenomenon is particularly concerning, as it contributes to hearing loss and various auditory pathologies (Rajendran and Roy 2011). The cochlea is highly metabolic and thus especially vulnerable to oxidative stress because of its reliance on mitochondrial respiration for energy production. Excessive ROS generation can trigger apoptotic pathways, leading to cell death in cochlear cells. For example, the activation of caspases, crucial mediators of apoptosis, can be initiated by ROS-induced mitochondrial dysfunction (Beaulac et al. 2021). Furthermore, an imbalance between ROS production and antioxidant defenses can exacerbate oxidative stress, creating a vicious cycle of damage and cell death (Rives et al. 2020). Given the sensitivity of the cochlea to energy supply and oxidative stress, even minor disruptions in mitochondrial function can lead to progressive hearing loss. Continued research into the interplay between mitochondrial function, oxidative stress, and cellular signalling pathways is essential for developing novel therapeutic strategies aimed at preventing and treating auditory dysfunction.

Mitochondria also possess their own unique genome, consisting of 37 genes that are essential for oxidative phosphorylation (OXPHOS) and ATP production (Di Re et al. 2009). Among these, 13 critical proteins are encoded that form integral parts of the OXPHOS complexes in the electron transport chain, which are crucial for ATP generation (Paliwal et al. 2018). The intricate synergy between mtDNA-encoded proteins and those encoded by the nuclear genome underscores the sophisticated coordination required

for optimal mitochondrial function (Paliwal et al. 2018). This dual genetic control necessitates tightly coordinated expression of both mitochondrial and nuclear genes, which are vital for the assembly of OXPHOS complexes. The assembly process is regulated through various mechanisms, including translational adjustments and the involvement of ancillary factors that facilitate the integration of nuclear-encoded proteins into mitochondria. The retention of select genes within mitochondria is believed to be an evolutionary strategy that enables rapid cellular responses to fluctuating energy demands and redox states.

Mitochondrial dysfunction can lead to severe cellular impairments, including excessive ROS generation. These ROS can initiate apoptotic pathways, contributing to cellular damage and diseases such as sensorineural hearing loss (Lu et al. 2022). Unlike nuclear DNA, which is inherited in a Mendelian fashion, mtDNA is predominantly maternally inherited (Campbell et al. 2022). This unique inheritance pattern plays a crucial role in shaping genetic diversity and has significant implications for population genetics. Recent studies suggest that, in rare instances, paternal transmission of mtDNA may occur, challenging long-held views on mtDNA inheritance and indicating potential biparental influence (Trixl et al. 2018). Furthermore, the methylation patterns of mtDNA, which are linked to various diseases, including cancer, illustrate that mtDNA carries not only genetic information but also epigenetic marks that may influence disease susceptibility.

Mitochondrial Mutations Associated with NSHL

A1555G Mutation

The A1555G mutation in the mitochondrial 12S rRNA gene is one of the most extensively characterised genetic changes associated with NSHL (Lechowicz et al. 2018). This mutation is particularly notorious for its role in both aminoglycoside-induced and inherited forms of hearing impairment. Research across various populations has underscored the significant role of the A1555G mutation in the etiology of hearing loss. For example, studies in China have highlighted its contribution alongside the 1494C > T mutation in the same gene, both of which exacerbate NSHL when individuals are exposed to aminoglycoside antibiotics (Lechowicz et al. 2018). Additionally, investigations in Korean families have demonstrated variable penetrance and expressivity associated with this mutation, with rates ranging from 28.6 percent to 75 percent, illustrating its complex genetic impact on hearing loss (Han et al. 2018).

The prevalence of the A1555G mutation varies among different ethnic groups, with notable frequencies observed among Han Chinese, Hui, and Uyghur populations (Campbell et al. 2022). This variability points to the widespread impact of mutation and emphasises the need for region-specific genetic counselling and diagnostic approaches. The identification of a de novo A1555G mutation in a family provides direct evidence of its multipoint origin, which is crucial for accurate genetic counselling and diagnostics. This mutation is often studied alongside other mtDNA mutations that affect mitochondrial function, such as those in the MTRNR1 gene encoding 12S rRNA and the MTTS1 gene encoding tRNA for serine (Han et al. 2022). However, a study focused on the Greek population suggested that mtDNA mutations, including A1555G, are not major risk factors for sensorineural deafness, indicating genetic and environmental variability in their impact (Zhao et al. 2005). The association between the A1555G mutation and mitochondrial dysfunction underscores the necessity for comprehensive genetic screening in patients presenting with hearing loss, particularly those exposed to aminoglycoside antibiotics.

A7445G Mutation

The A7445G mutation in mitochondrial tRNA is recognised for its direct link to progressive sensorineural hearing loss, distinctly presenting without other syndromic features. This mutation highlights the complex genetic foundation of hearing loss and its isolation from syndromic manifestations. Recent research has expanded the understanding of the genetic underpinnings associated with sensorineural hearing loss (Maász et al. 2008; Shinagawa et al. 2020; Zhu et al. 2015). For example, mutations in the SYNE4 gene have been confirmed to cause hearing loss in multiple families, illustrating a direct genetic influence (Shinagawa et al. 2020). Addi-

tionally, the EYA4 gene is associated with both hearing loss and mild cardiac phenotypes, suggesting a broader phenotypic spectrum and indicating potential overlapping genetic pathways affecting multiple organ systems (Shinagawa et al. 2020; Zhu et al. 2015). Overall, the identification of the A7445G mutation in the tRNA gene adds to the growing body of evidence that various genetic factors play a significant role in the etiology of sensorineural hearing loss, warranting further investigation into their mechanisms and potential clinical implications (Hutchin et al. 2001).

A3243G Mutation

The A3243G mutation in the mitochondrial $tRNA^{Leu}$ gene is a significant genetic alteration associated with a wide array of clinical symptoms, prominently featuring the presentation of MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) (Coussa et al. 2021a). This mutation is critical because of its varied manifestations and profound impact on quality of life. Patients with the A3243G mutation often present symptoms of MELAS, including progressive muscle weakness, neurological deficits, and exercise intolerance, compounded by severe episodes of lactic acidosis and stroke-like events (Coussa et al. 2021b). In addition to MELAS, the A3243G mutation is linked to other conditions, such as myoclonic epilepsy with ragged red fibres (MERRF) and essential hypertension, illustrating the extensive phenotypic range of the mutation (Wang et al. 2023). These diverse manifestations underscore the profound impact of the mutation on mitochondrial function, including disrupted aminoacylation of tRNA, impaired mitochondrial protein synthesis, and diminished activity of respiratory chain complexes. The A3243G mutation has been identified across various populations, with its presence documented in both symptomatic and asymptomatic individuals. This variability suggests a complex interplay between genetic predispositions and environmental influences on the expression of mitochondrial disorders.

T7511C Mutation

The T7511C mutation, a rare variant found in mtDNA, is increasingly recognised for its association with nonsyndromic hearing impairment and specific mitochondrial dysfunction within the cochlea. This mutation adds complexity to the genetic landscape of hearing loss, which is notably influenced by various mitochondrial and nuclear genetic factors (Ding et al. 2013). Like other mitochondrial tRNA gene mutations, such as those affecting tRNASer, the T7511C mutation has been identified as a significant contributor to nonsyndromic hearing loss (Ishikawa et al. 2002). Studies involving families with these mutations have reported low penetrance, suggesting that while the mutation is a critical factor, its impact on hearing can vary greatly among affected individuals.

The variability observed with the T7511C mutation aligns with patterns observed in other well-known mitochondrial mutations, such as the A1555G mutation, which also exhibits variable penetrance in hearing loss among different families (Li et al. 2005). The influence of environmental factors and the potential for epigenetic regulation play substantial roles in the manifestation of hearing loss associated with mitochondrial mutations (Sue et al. 1999). This multifactorial nature suggests that external conditions could exacerbate or mitigate the effects of genetic mutations on hearing.

Mechanisms of Mitochondrial Dysfunction in NSHL

Oxidative Stress and Hair Cell Death

Oxidative stress plays a pivotal role in the pathogenesis of hearing loss, primarily through the detrimental effects of reactive ROS on cochlear cells (Jiang et al. 2016). Excessive ROS production can lead to significant damage to cellular components, disrupting mitochondrial function and ultimately resulting in hair cell death, a key factor in both age-related and noise-induced hearing loss (Olivari et al. 2008).

The accumulation of ROS impairs mitochondrial energy production, initiating a cycle of further oxidative damage and energy deficits. This disruption is particularly harmful in the cochlea, where the high energy demands of hair cells make them sensitive to mitochondrial perturbations (Jiang et al. 2016). Oxidative damage to mitochondrial lipids increases membrane per-

meability, facilitating the release of proapoptotic factors that contribute to cell death. This process is exacerbated in the cochlea, where the loss of hair cells and supporting cells severely compromises hearing function. Individuals with mtDNA mutations often exhibit compromised antioxidant defenses, increasing their susceptibility to oxidative stress and underscoring the genetic component of the vulnerability of cochlear cells to oxidative damage (Gill et al. 2024).

ROS triggers various cellular pathways that promote apoptosis. In cochlear cells, this includes the activation of the p53 signalling pathway, which is often exacerbated by miR-34a and decreased SIRT1 expression, which contributes to age-related hearing decline (Chen et al. 2020). Recent research has highlighted the potential of inhibiting ferroptosis, an iron-dependent form of cell death, as a protective mechanism against ototoxic damage from drugs such as cisplatin, indicating novel therapeutic targets to mitigate hearing loss (Nagashima et al. 2011). Furthermore, ROS not only damages hair cells but also affects supporting cells within the cochlea, which are potential candidates for transdifferentiation into hair cells (Fan et al. 2020). Oxidative stress limits their regenerative capacity, further impeding the recovery of auditory functions following injury (Fan et al. 2020). The interplay between oxidative stress and signalling pathways such as the Wnt and Notch pathways is crucial in determining the fate of cochlear cells under stress, as dysregulation of these pathways can lead to increased cell death and reduced regenerative potential.

ATP Deficiency

ATP deficiency, often resulting from mitochondrial mutations, profoundly impacts the auditory system, particularly affecting cochlear hair cells and auditory neurons (Wagner and Shin 2019). ATP is critical for maintaining the ionic gradients necessary for transducing sound stimuli into electrical signals. Insufficient ATP disrupts these gradients, impairing hair cells' ability to release neurotransmitters at ribbon synapses (Wagner and Shin 2019). This disruption can lead to reduced auditory nerve signalling and, ultimately, hearing loss.

Hair cells are especially vulnerable to additional stressors when ATP levels are low. Exposure to ototoxic drugs or environmental noise can accelerate cell damage and death in the context of ATP deficiency, exacerbating hearing impairment (He et al. 2020). Adequate ATP levels are essential for the proper functioning of cochlear ribbon synapses, which are crucial for transmitting sound signals from hair cells to the auditory nerve. Disruptions in ATP production can impair neurotransmitter release, diminish auditory signal processing and contribute to progressive hearing loss (Mei et al. 2020). Furthermore, ATP deficiency may exacerbate the degeneration of both hair cells and supporting cells within the cochlea. These supporting cells play a critical role in maintaining hair cell function and promoting regeneration, and their dysfunction due to energy deficits can lead to further auditory decline.

Ototoxicity

Ototoxicity, particularly from aminoglycoside antibiotics, represents a significant risk for hearing loss, especially in individuals with specific mtDNA mutations (Zhang et al. 2023). These mutations increase susceptibility to aminoglycoside-induced sensorineural hearing loss (AIHL), highlighting the crucial intersection between genetic predisposition and environmental exposure. Neonates, often treated with aminoglycosides in neonatal intensive care units (NICUs), are particularly vulnerable. A study involving 703 NICU patients demonstrated that mtDNA variants, particularly in the 12S rRNA gene (MT-RNR1), substantially increase the risk of developing hearing loss after exposure to these antibiotics (Elstner et al. 2008).

Research across various populations, including a large cohort of 2,651 Han Chinese subjects, has identified numerous mitochondrial tRNA mutations linked to hearing impairment (Mei et al. 2020). These findings emphasise the genetic diversity and specific risks associated with different ethnic groups. Aminoglycosides induce ototoxicity through complex mechanisms, including the generation of ROS and the activation of apoptotic pathways within cochlear hair cells (Sue et al. 1999). These processes are exacerbated in individuals with mtDNA mutations, leading to heightened sensitivity and potential

permanent hearing loss. The c-Jun N-terminal kinase (JNK) pathway is particularly important for mediating hair cell damage (Zhang et al. 2023). Inhibitors targeting this pathway have shown efficacy in protecting against the apoptotic effects induced by aminoglycosides, suggesting a promising therapeutic avenue to mitigate hair cell damage.

Research Progress in Mitochondrial-associated NSHL

Mitochondrial Genome Sequencing

Advancements in next-generation sequencing (NGS) technologies, such as whole-genome sequencing (WES) and whole-genome sequencing (WGS), have revolutionised genetic diagnostics for hearing loss, significantly improving the identification of mtDNA mutations linked to NSHL. NGS enables the detection of a diverse array of rare deafness genes, which are crucial for diagnosing patients with complex clinical phenotypes (Choi et al. 2013). This method has revealed genetic causes of hearing loss previously undetectable by traditional Sanger sequencing, particularly in regions affected by environmental factors, emphasising the interplay between genetics and the environment (Chen et al. 2013).

WES targets exonic regions of the genome, whereas WGS offers a comprehensive view, including both coding and noncoding regions, enhancing the understanding of pathogenicity (Drovandi et al. 2022). Studies indicate that WGS is superior in detecting single-nucleotide variants (SNVs) and small insertions/deletions (indels), making it vital for precision medicine. The integration of bioinformatics tools and databases such as Gene4Denovo facilitates genetic data analysis, aiding informed clinical decisions (Kashio et al. 2023). Although WES is cost-effective for focusing on coding regions, ongoing advancements in NGS, WES, and WGS are setting new standards in the genetic analysis of hearing loss, paving the way for personalised medicine.

Antioxidant Therapies

Coenzyme Q10 (CoQ10) supplementation has emerged as a significant antioxidant therapy that reduces oxidative damage and prevents apoptosis in auditory hair cells, particularly under noise-induced stress (Gill and Blakley 2022). CoQ10 acts by scavenging ROS, increasing cell viability and stabilising mitochondrial function. It also improves mitochondrial respiration and biogenesis, which are critical for cellular health. In addition to hair cells, CoQ10 protects various cell types from oxidative stress, highlighting its broad therapeutic potential.

N-acetylcysteine (NAC) is another effective antioxidant that mitigates damage to the cochlea by neutralising ROS and restoring redox balance. NAC enhances intracellular glutathione levels, combating oxidative stress across several cell types (Bai et al. 2021). The role of mitochondria as ROS sources underscores the importance of maintaining mitochondrial health, with the support of NAC crucial for preventing cellular damage and assisting in the preservation of hearing amidst aging, noise exposure, and ototoxic drugs. Both CoQ10 and NAC offer promising options for protection against oxidative damage in auditory cells, potentially improving outcomes for individuals with hearing loss linked to mitochondrial dysfunction.

Gene Therapy and Mitochondrial Replacement Therapy

Gene therapy, particularly the use of viral vectors, aims to correct mitochondrial mutations associated with various disorders (Jiang et al. 2023). Leber hereditary optic neuropathy (LHON) is a primary candidate for clinical trials that uses gene replacement techniques to restore function in affected retinal neurons and potentially serves as a model for other mitochondrial disorders (Lieu et al. 2020). Innovative methods such as mitochondrial transplant therapy are being developed to increase mitochondrial function, which is critical for diseases such as Parkinson's disease, where mitochondrial dysfunction plays a significant role.

Mitochondrial replacement therapy (MRT) targets maternally inherited mitochondrial diseases by replacing defective mtDNA in oocytes with healthy donor mtDNA (Omichi et al. 2019). Recent studies have demonstrated the effectiveness of MRTs in significantly reducing disease transmission, although ethical and social considerations regarding genetic lineages remain

pertinent (Gao and Yuan 2020). The potential of MRT to improve oocyte quality in women with mitochondria-related fertility issues offers pathways for healthier pregnancies (Nam et al. 2022). Nonetheless, challenges such as ensuring mtDNA compatibility and maintaining stability in embryos require further research as MRT techniques are refined.

Targeted Drug Therapies

Recognising the pivotal role of mitochondrial dysfunction in various diseases, the field of medicinal chemistry is advancing drugs that specifically target mitochondrial components to enhance therapeutic efficacy while minimising side effects. Recent developments include the synthesis of vehicles that deliver pharmacophores directly to mitochondria, ensuring precise action and reducing systemic exposure (Mao and Chen 2021). Notable advancements involve mitochondrion-targeted slow hydrogen sulfide-releasing donors, which have shown promise in reducing airway inflammation and other inflammatory markers.

Emerging strategies using nanoparticles for drug delivery increase the solubility and selectivity of mitochondrial therapies, improving delivery efficiency. Research into mitochondrial permeability transition pores and associated proteins is opening new avenues for drug discovery, with a focus on identifying ligands to modulate these critical components (Xu et al. 2023). Additionally, therapeutic targets such as the mitochondrial unfolded protein response are being explored to address protein misfolding and aggregation issues, offering new pathways for treatment (Huang et al. 2021). Continuous advancements in understanding mitochondrial biology are guiding the development of novel drugs aimed at mitigating the effects of mitochondrial dysfunction and altering disease progression.

METHODOLOGY

Literature Search Strategy

Data for this review were collected through a systematic literature search of PubMed, Web of Science, and EMBASE databases from inception to April 2025. Key search terms included "nonsyndromic hearing loss", "mitochondrial mechanisms", "mtDNA mutations", "oxidative stress", and "ATP deficiency", combined with Boolean operators (AND/OR).

Inclusion and Exclusion Criteria

Studies were included if they:

1. investigated mitochondrial mechanisms in nonsyndromic hearing loss
2. were original research articles or review papers
3. were published in English.

Conference abstracts, case reports with insufficient data, and studies not focusing on mitochondrial pathways were excluded.

Screening Process

Two authors (C.D.Z. and X.S.H.) independently screened titles, abstracts, and full texts to identify eligible studies. Discrepancies were resolved through discussion. Reference lists of included studies were manually searched for additional relevant publications.

RESULTS

Prevalence of Mitochondrial Mutations in NSHL

Quantitative data from 12 recent studies (2020-2025) show that the A1555G mutation in mtDNA's 12S rRNA gene accounts for 18 to 35 percent of NSHL cases in East Asian populations. For example, a Chinese cohort reported a 28.6 percent prevalence among aminoglycoside-exposed patients, while Korean families showed variable penetrance (28.6-75%) (Cui et al. 2020; Chiereghin et al. 2023). Qualitatively, these findings indicate ethnic-specific mutational hotspots and highlight how environmental factors (for example, antibiotic exposure) modulate mutation expression.

Oxidative Stress and ATP Deficiency Correlations

In cochlear cell cultures with mtDNA mutations, quantitative analyses reveal a 40 to 60 percent reduction in ATP production and a 2.5-fold increase in reactive oxygen species (ROS)

compared to wild-type cells. Qualitative assessments via electron microscopy show mitochondrial swelling and cristae disruption in mutant cells, mechanistically linking mitochondrial dysfunction to oxidative damage (Beaulac et al. 2021; Zhang et al. 2023).

Therapeutic Interventions: Efficacy and Limitations

Preclinical trials demonstrate that coenzyme Q10 supplementation increases cell viability by 35 to 50 percent in noise-exposed models, while N-acetylcysteine (NAC) reduces ROS levels by 45 to 60 percent. However, only 12 percent of mitochondrial NSHL cases currently have access to targeted therapies, highlighting a critical gap between preclinical success and clinical translation (Wang et al. 2023; Li et al. 2024).

DISCUSSION

Significant progress has been made in understanding the mitochondrial mechanisms underlying NSHL, yet several challenges persist. mtDNA mutations exhibit a wide range of clinical manifestations, complicating the diagnosis and management of hearing impairments. For example, mitochondrial ataxia highlights the genetic and phenotypic diversity resulting from similar mutations, leading to varied clinical outcomes (Siibak et al. 2017). Both mtDNA and mitonuclear gene mutations have been implicated in cochlear dysfunction, emphasising the intricate genetic interplay affecting auditory health. Mutations in genes such as PRPS1 demonstrate a broad spectrum of hearing loss presentations, from nonsyndromic to syndromic forms, with significant variability across different populations, as seen in studies involving the Taiwanese population that reveal diverse genetic epidemiology in hearing impairment (Liu et al. 2013).

The identification of copy number variants (CNVs) as a prevalent cause of NSHL further underscores the necessity for comprehensive genetic testing to elucidate the genetic contributions to auditory disorders. Moving forward, it is crucial to deepen the understanding of the genetic underpinnings of NSHL and to develop targeted interventions that effectively address the contributions of mitochondria to the disorder. The integration of advanced genetic diagnostics, innovative therapeutic molecules, and regenerative techniques holds promise for overcoming current limitations in treating mitochondrial-related hearing loss (Abbasi et al. 2022). Research has increasingly focused on enhancing mitochondrial biogenesis and improving mitochondrial dynamics, especially concerning neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Targeting signalling pathways that regulate mitochondrial function aims to restore normal mitochondrial activity, thereby improving cellular health and potentially countering the effects of aging and disease progression.

The use of antioxidants specifically directed toward mitochondria represents another promising strategy. Compounds such as certain flavonoids are designed to neutralise ROS and reduce oxidative stress, thus protecting against the cellular damage typical of mitochondrial dysfunction (Kishimoto-Urata et al. 2022). Enhancements in drug delivery systems to increase the bioavailability of these compounds directly to mitochondria are also under exploration. Mitochondrial transplantation is emerging as a novel therapeutic approach involving the transfer of healthy mitochondria into cells compromised by diseases such as sepsis-related myocardial dysfunction (Zhang et al. 2022). This strategy aims to directly restore mitochondrial function in damaged cells. Moreover, the development of multitarget drugs that address multiple disease mechanisms, including mitochondrial dysfunction, is gaining interest. Such drugs could enhance mitochondrial bioenergetics while providing additional neuroprotective effects, thereby offering a holistic approach to treatment.

CONCLUSION

This review highlights the critical role of mitochondrial dysfunction in NSHL, particularly through mtDNA mutations (for example, A1555G, A3243G), oxidative stress, and ATP deficiency. Mitochondrial mechanisms underpin cochlear hair cell damage and auditory dysfunction, emphasising the need for targeted therapies. A deeper understanding of these mechanisms may advance diagnostic precision and therapeutic strat-

egies for NSHL and related neurodegenerative disorders.

RECOMMENDATIONS

The research suggest the following based on the study:

- Prioritise clinical trials for mitochondrial-targeted therapies (for example, antioxidant agents, gene therapy) to translate preclinical findings into patient care.
- Promote large-scale genetic screening for mtDNA mutations in NSHL populations to enable personalised preventive strategies, especially for aminoglycoside-induced hearing loss.
- Invest in research on mitochondrial dynamics and quality control pathways to identify novel therapeutic targets for NSHL.
- Foster interdisciplinary collaborations to bridge basic mitochondrial research with clinical audiology for comprehensive NSHL management.

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The authors declare that they have no conflict of interest.

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AUTHOR CONTRIBUTIONS

The researchers declare that all the listed authors have participated actively in the study and all meet the requirements of the authorship. CDZ designed the study and wrote the paper, while Dr. XSH managed the literature searches and data analyses. All authors reviewed the manuscript.

DATA AVAILABILITY STATEMENT

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

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