The Relationship Between Mitochondrial Mutation and Age-Related Hearing Loss

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Abstract

While many advancements in the field have been made, the exact cellular causes of age-related hearing loss (ARHL) are unknown. Current theories point heavily to the relationship between mitochondrial DNA (mtDNA) mutation and the development of ARHL. This review will discuss the cellular basis of this relationship, focusing specifically on how gene modulation from mtDNA mutation promotes processes, such as increased reactive oxygen species (ROS) production, that damage or kill peripheral auditory cells. Particular attention is given to the Bcl-2 family and its role in regulating apoptosis and mtDNA repair. Together, these mechanisms suggest that mitochondrial dysfunction (MD) contributes to ARHL through a self-propagating cycle in which products of mutation cause further mutation. Although further research is required to establish causality between these mechanisms and ARHL, understanding their interactions may provide a foundation for developing new restorative and preventative treatments.

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Background

Given the development of technology and medicine, the aging population is growing in an unprecedented manner, with the number of Americans older than 65 expected to grow 42% from 2022 to 2050 (Mather and Scommegna 2025). This unprecedented growth emphasizes the importance of addressing age-related issues, and, considering ARHL impacts over 50% of people over the age of 65, it is among the most significant (Cunningham and Tucci 2017).

ARHL, medically known as presbycusis, is characterized by decreased auditory sensitivity, loss of hair cells (HCs) and spiral ganglion neurons (SGNs), and decreased auditory processing ability (Ege et al. 2024). These symptoms reduce the efficiency of current treatments and the quality of life for those afflicted. Overall, compared to elderly people without hearing loss, those with ARHL have higher rates of hospitalization, dementia, and death (Cunningham and Tucci 2017).

Not only are current treatments ineffective in treating the symptoms of ARHL, but they are also not readily available to many people. Hearing aids are not covered by Medicare and cost, on average, $2,100 (National Council on Aging 2025). Their small size poses complications with other age-related conditions (e.g., vision loss, arthritis). Similarly, cochlear implants require surgery using anesthesia which can be expensive and risky for elderly people. In addition to the inefficacy and inaccessibility of current treatments, the increasing incidence and significant correlation between ARHL and other diseases emphasize the need for new treatments. However, for this to occur, a greater understanding of the cellular mechanisms behind ARHL is required.

How General Cellular Aging Processes Impact the Auditory System

ARHL is thought to be caused by aging-associated dysregulation of fundamental cellular mechanisms within auditory cells. In other words, the processes that cause ARHL are not specific to the auditory system–they are the same processes that cause aging in other parts of the body. On a cellular level, aging is characterized by telomere shortening, mitochondrial dysfunction and oxidative stress, and misfolded or damaged proteins (Ege et al. 2024). All of these processes ultimately lead to cellular senescence, apoptosis, and cell cycle arrest (Ege et al. 2024). Specifically, ARHL is thought to be caused by these general processes occurring in auditory tissue and causing the death of SGNs and HCs.

While there are many different processes associated with the development of ARHL, MD seems to play a significant role. Research suggests accumulation of mtDNA mutations is the most prominent cause of MD. MD is a harmful change in normal mitochondrial activity caused by structural and genetic damage and includes increased free radical production and apoptosis (Somasundaram et al. 2024). MD has a significant effect on cell health as mitochondria play a critical role in cellular function, regulating oxidative balance, calcium levels, and cellular energy (Somasundaram et al. 2024).

Mitochondrial DNA Mutation

Mitochondria contain their own DNA that is highly susceptible to mutation: mtDNA has a 15-fold higher mutation rate and less efficient repair system than nuclear DNA (Somasundaram et al. 2024). Notably, while mutations in mtDNA can occur at any point, these mutations become more common with age (Somasundaram et al. 2024). Mitochondrial mutations have been shown to result in reduced ATP production, increased production of ROS, and dysregulation of apoptosis (Somasundaram et al. 2024). In other words, mutations in mtDNA ultimately result in MD.

In combination with its foundational roles in cellular function, the high mutation rate of mtDNA leads to an established, significant role in the aging process. In fact, MD is associated with almost all aging-associated diseases (Somasundaram et al. 2024). This association is also conserved within the auditory system: many genetic syndromes associated with hearing loss, such as myoclonic epilepsy, are caused by mitochondrial defects (Someya and Prolla 2010). The prevalence of hearing loss in diseases associated with MD allows, at the very least, a correlation to be drawn between MD and ARHL.

It is also worth noting that the cells that compose cochlear tissue (long-lived, oxygen-consuming postmitotic cells) are the same cell type that compose other tissues (e.g., brain, heart) that are known to accumulate mtDNA mutations and are the site of many age-related diseases (Someya and Prolla 2010). This implies that mtDNA mutations accumulate in cochlear tissue, and that cochlear tissue is susceptible to age-related disease (e.g., ARHL).

mtDNA Mutation Accumulation and Gene Modulation

Further study of mtDNA mutation within the auditory tissue of mouse models has supported the correlation between MD and ARHL. Specifically, ARHL is thought to be caused by MD initiated by an accumulation of mutations in mtDNA within auditory tissue (Someya and Prolla 2010). The accumulation of mtDNA mutations in auditory cells causes modulation of genes responsible for MD. This modulation increases MD, resulting in the death of SGNs and HCs.

This mechanism is supported by a foundational study published in Neurobiology of Aging in which mice were engineered to carry a mutation (D257A) that disrupts the enzyme responsible for repair of mtDNA (mitochondrial DNA polymerase gamma–POLG). This mutation inhibits the already inefficient mtDNA repair system, resulting in a several hundred-fold increase in mtDNA point mutations (Someya et al. 2008). Compared to the control mice, mutated mice showed significant modulation of the genes responsible for the biological processes associated with ARHL, including the up-regulation of genes involved in apoptosis and the stress response and down-regulation of genes involved in energy metabolism, cytoskeletal regulation, and hearing function (Someya et al. 2008). In addition to gene identification, hearing tests and histological examination of cochlear tissue from both groups were performed and compared. While the mice in both groups were age-matched (9 months), measurements showed significant disparities in hearing abilities and cochlear tissue integrity. Mutated mice showed significant hearing loss and decreased SGN and HC concentrations, none of which was observed in the control group (Someya et al. 2008). These findings are further supported by a later study in Hearing

Research which found that, compared to control mice of the same age, all D257A mutated mice had more hearing loss and significantly worse outer hair cell function (Crawley and Keithley 2011).

Developments in bioinformatics and genetic databases have allowed for more direct identification of specific genes involved in ARHL. In a study published by BMC Genomics, Ma et al. identified 28 mitochondrial genes that were differentially expressed in mice with ARHL. Out of the 28, three genes (Aco2, Bcs11, and Ndufs1) shown to play central roles in normal mitochondrial function were significantly downregulated in ARHL (Ma et al. 2025). Downregulation of these genes caused, amongst other effects, increased ROS production and decreased gene integrity and cellular metabolism, all of which are processes implicated in the development of ARHL (Ma et al. 2025).

Overall, these studies provide strong evidence for a causal relationship between the accumulation of mtDNA mutations and ARHL. When these mutations accumulate in auditory cells, SGNs and HCs are damaged or die. Since auditory cell death is thought to be the structural cause of ARHL, these studies define mtDNA mutation accumulation as at least one cellular cause of ARHL. In normal aging, mtDNA mutations accumulate over time, resulting in a gradual decline in auditory cell function and concentration. After a certain point, so many cells have died that hearing ability is notably impacted. This accumulation mechanism is in line with the gradual development of ARHL. In a similar light, the incidence of ARHL increases with age similar to how mtDNA mutation increases with age.

A Direct Example of Gene Expression Modulation in ARHL: The Bcl-2 Family

It has been established that an increase of mtDNA mutations results in upregulation of genes that cause apoptosis. One of the most notable families of proteins associated with this process is the Bcl-2 family. This family includes the protein Bak, which promotes the apoptosis pathway related to permeabilization of the outer mitochondrial membrane (Someya et al. 2009; Salam et al. 2021). By promoting permeabilization of the outer mitochondrial membrane, this protein causes caspase activation and cell death (Someya et al. 2009; Salam et al. 2021). When these processes occur in auditory tissue, they lead to SGN and HC death and cause ARHL. While there are hundreds of genes associated with mtDNA mutation, this family is especially notable as the associated proteins seem to be required for the development of ARHL. Removal of the Bak gene prevents the death of SGNs and HCs which, in turn, prevents hearing loss from occurring (Someya et al. 2009).

A study published in the journal PNAS tested the role of Bak in ARHL development by studying mice mutated to have a deficiency in the Bak gene. Middle-aged (15 months old) mice with a Bak deficiency were shown to have significantly less hearing loss than the middle-aged control mice (Someya et al. 2009). In fact, the middle-aged, mutated mice had hearing ability similar to young (5 months old) control mice (Someya et al. 2009). In addition, using cell counting, the Bak mice showed increased SGN and HC survival with no difference in SGN and HC concentration between the middle-aged, mutated mice and the young control mice (Someya et al. 2009). So, removal of Bak prevented the apoptosis that causes ARHL. This study implies that the Bak gene regulates the activation of the apoptosis that causes ARHL. Bak's role as an apoptosis instigator is further supported by an additional measurement of nuclear DNA

fragmentation (a hallmark of apoptosis) that showed mice without Bak showed decreased fragmentation compared to age-matched WT mice (Someya et al. 2009). These results were supported by a study in Biomedicine and Pharmacotherapy where application of a drug that downregulates Bak, thymoquinone, resulted in less HC death, greater cochlear and SGN integrity, and less hearing loss than control mice (Salam et al. 2021).

The mechanism behind the Bcl-2 protein's role in the development of ARHL seems to be related to its impact on mtDNA repair. These proteins inhibit the repair of mtDNA mutation, subsequently increasing the rate of apoptosis. In cancer cells, Bcl-2 proteins have been found to inhibit mitochondrial endonuclease activity (mtAPE1–the enzyme involved in mtDNA repair) (Xie et al. 2015). Conversely, depletion of Bcl-2 proteins resulted in increased mtAPE1 activity and decreased mtDNA mutation (Xie et al. 2015). In other words, removing these proteins increased repair of mtDNA mutations. Thus, Bcl-2 proteins increase mtDNA mutations by decreasing mtDNA repair. The Bcl-2 protein family is not the only proapoptotic protein that has increased expression from mtDNA mutation, but it is the most significant. Other proteins certainly increase apoptosis, but not to the magnitude observed in ARHL. In theory, the requirement for Bcl-2 proteins in ARHL could stem from the magnitude of its effect on the rate of apoptosis, though these findings would need to be translated to auditory cells.

The Bcl-2 proteins contribute to the self-propagating loop mechanism of ARHL development. As mtDNA mutation accumulates with age, expression of genes that encode Bcl-2
proteins increase. The resulting Bcl-2 protein concentrations in the cell inhibit the enzymes that repair mtDNA mutations, further increasing mutation accumulation. This increase in mtDNA mutation results in increased proapoptotic gene expression (i.e., Bcl-2), subsequently restarting the cycle.

Byproducts Generated by Mitochondrial Dysfunction

Byproducts released by mitochondria due to MD can result in subsequent mutation of mtDNA, damaging other structures and cells in the process. ROS are formed during mitochondrial oxidative metabolism and are known to cause oxidative damage within the cell (Someya and Prolla 2010; Salam et al. 2021). As organisms age, mtDNA mutations accumulate and mitochondria begin to produce more ROS, increasing their levels to harmful concentrations (Someya and Prolla 2010; Salam et al. 2021). At these harmful concentrations, ROS can damage different molecules within the cell, including mtDNA (Ege et al. 2024). Damaging mtDNA can lead to mutation, and this mutation can lead to further ROS release. Similarly, ROS can damage the antioxidants responsible for ROS breakdown. In addition to causing mtDNA mutation, ROS could increase apoptosis by damaging the mitochondria's outer membrane.

Several studies confirm this relationship by showing that modulating the concentration of antioxidant enzymes (e.g., Sod1, Gpx1, and catalase) that break down ROS results in a modulation of the structural changes associated with ARHL. Decreasing ROS breakdown increases ARHL while increasing ROS breakdown decreases ARHL. One study found that loss of cytosolic Sod1 results in degeneration of SGNs, decreased stria vascularis (another region implicated in ARHL) thickness, and more ARHL (Someya and Prolla 2010). Loss of Sod1 or Gpx1 results in more HC death and greater susceptibility to

noise-induced hearing loss (Someya and Prolla 2010). Conversely, overexpressing catalase results in more ROS breakdown and is found to reduce HC loss (Someya and Prolla 2010).

It is well known that noise exposure results in hearing loss typically by damaging or even killing HC. In a similar light, cochleae exposed to high-intensity noise are shown to generate ROS, directly linking ROS to HC death (Someya and Prolla 2010; Crawley and Keithley 2011). Considering noise exposure is a compounding cofactor in ARHL development (a disease caused, in part, by HC death), this supports the claim that ROS increase ARHL. Furthermore, this indirectly implicates mitochondria as they are the main source of ROS.

The Self-Propagating Loop of Mitochondrial Dysfunction

Research implies that mutations in mtDNA are a significant basis for the development of ARHL. However, as shown, aging and mtDNA mutation accumulation do not have a simple linear relationship. While mtDNA mutation does increase with age, aging is not the only source of mutation. mtDNA mutation results in the release of molecules (i.e., ROS) that cause further mutation. Furthermore, mtDNA mutation results in an increase in expression of genes that ultimately reduce mtDNA mutation repair. This indirectly increases mutation accumulation. Overall, the role of mtDNA mutation in the development of ARHL seems to function in a self-propagating loop with mtDNA mutation causing more mtDNA mutation. Ultimately, mtDNA mutations result in a decrease in cell function and an increase in apoptosis. These processes occurring in auditory tissue result in the death of cells required for auditory sensory perception.

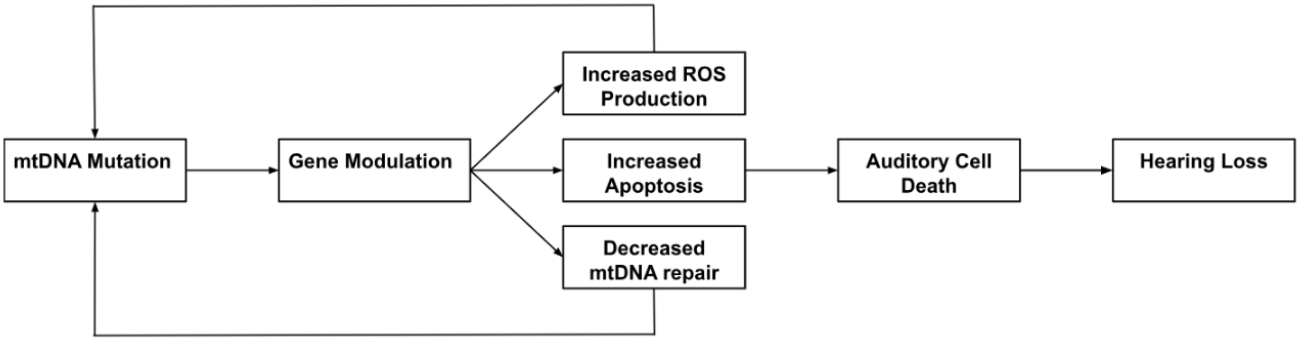


Figure 1: A simplified model of the proposed self-propagating mechanism of ARHL

The Clinical Application of the Mechanisms Behind Mitochondrial Dysfunction

While there are no approved treatments for ARHL, the mechanisms of mtDNA mutation serve as a promising potential basis for new developments. Research in this regard has begun, but it is still at the beginning stages. A greater understanding of the foundational cellular mechanisms behind aging is required for effective preventive and restorative treatments to be developed.

Calorie restriction has been shown to reduce ROS release and Bak expression by reducing mitochondrial activity (Ege et al. 2024). Ultimately, these changes reduce the accumulation of mtDNA mutations, subsequently decreasing the development of ARHL. However, this method has not been studied extensively in elderly people and poses specific complications related to other age-related cofactors (e.g., disease, low blood sugar). Another potential treatment lies in the genes encoding Bcl-2 proteins. Removal and downregulation of these genes in mice have been shown to slow the development of ARHL, and one possible mechanism for treatment in humans is CRISPR gene editing. CRISPR-Cas9 gene editing has already been shown to be successful in other sensory-related disabilities. One study found people with blindness caused by genetic mutation experienced improvements in vision following one CRISPR treatment (Pierce et al. 2024). Using this mechanism, targeting the Bak gene or mtDNA mutations could significantly reduce the development of ARHL, though this is speculative and further direct research is required.

Overall, while significant progress in the field has been made, the cellular basis of ARHL is still not widely understood. Like many other diseases, ARHL is a complicated and multifactorial issue. The structural changes associated with ARHL are not solely caused by a single cellular mechanism. Besides mtDNA mutation, autophagy, proteostasis, and telomere attrition are shown to contribute to ARHL development (Ege et al. 2024). This makes it difficult to isolate and identify which mechanisms are causing SGN and HC death. In addition to the simultaneous contribution of multiple different cellular mechanisms, individual differences play a significant role. For example, therapeutic drugs, smoking, and noise exposure all negatively impact the cellular mechanisms behind the development of hearing loss (Ege et al. 2024). Even if treatments addressing these mechanisms are developed, the complex nature of ARHL would make it difficult to identify which mechanisms are causing ARHL in a specific individual. The impact of these cofactors on the foundational cellular mechanisms behind ARHL makes further research necessary to fully isolate and solidify the mechanism of these structural changes.

Conclusion

While scientists are only in the preliminary stages of research, there is significant evidence suggesting that mtDNA mutation is an important contributing mechanism of the structural changes behind ARHL. The accumulation of mtDNA mutations modulates gene expression and promotes the release of harmful byproducts, with both of these processes leading to auditory cell damage and death. These processes cause further mtDNA mutation, seemingly creating a self-propagating cycle. Additional research on these mechanisms must be done to both translate current findings from model systems to humans and to establish the role of mitochondria in ARHL such that it could be used to develop new treatments. However, considering what is currently known about the wide impact and the proposed self-propagating mechanism of mtDNA mutation, it seems to be an important contributing mechanism of ARHL that should be further investigated.

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