SIRT1/LXRα signaling pathway is involved in age-related hearing loss in C57BL/6J mice and its mechanism

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Abstract

Age-related hearing loss (ARHL) is the most prevalent form of hearing impairment and a significant neurodegenerative condition associated with aging. Silent information regulator 1 (SIRT1), a key enzyme involved in diverse physiological processes, has demonstrated protective effects against multiple age-related diseases. The liver X receptor (LXR), a nuclear receptor regulating cholesterol homeostasis and macrophage activity, is also implicated in aging-related conditions. Both SIRT1 and LXR have been associated with ARHL. Although SIRT1 is an upstream regulator of LXRα and is known to be expressed in the cochlea and auditory cortex of C57BL/6J mice, the presence of LXRα in cochlear tissues and its involvement in the SIRT1/LXRα signaling pathway during ARHL remains unreported. This study aimed to investigate the expression levels of SIRT1 and LXRα in the inner ear and examine their relationship with cochlear morphology. We assessed hearing function in mice at different ages and analyzed age-related changes in cochlear histopathology and protein expression. Our goal was to elucidate the role of the SIRT1/LXRα signaling pathway in the pathogenesis of ARHL, explore its cellular and molecular mechanisms, and identify potential targets for the prevention and treatment of ARHL.

Key words: Age-related hearing loss,Sirtuin 1,Liver X receptor，Cochlea

1 Introduction

1.1 Current status of age-related hearing loss

Age-related hearing loss (ARHL) is a prevalent neurodegenerative condition and one of the most common sensory disorders among the elderly worldwide. It affects approximately one-third of individuals over the age of 65 years, with prevalence rising to over 50% in those aged 75 and older(Guerrieri et al., 2023). ARHL significantly impairs quality of life and is associated with social isolation, cognitive decline, and increased risk of mental health disorders(Liu et al., 2024). Despite its high incidence and profound impact, the molecular mechanisms underlying ARHL remain poorly understood, and there is currently no effective treatment to reverse or halt its progression(Yang et al., 2023). As global populations continue to age, the prevalence and societal burden of ARHL are expected to rise substantially. Therefore, advancing the prevention and treatment of ARHL is a critical public health priority. However, its etiology and pathogenesis remain inadequately studied, underscoring the urgent need for focused research to elucidate disease mechanisms and identify potential therapeutic targets.

1.2 ARHL and SIRT1/LXRα signaling pathway

Recent studies have highlighted the roles of Silent Information Regulator 1 (SIRT1) and Liver X Receptor Alpha (LXRα) in various aging-related diseases(Da Silva Pereira et al., 2025; Manna et al., 2023). SIRT1, a member of the Sirtuin family, is a NAD^+-dependent deacetylase expressed in diverse tissues and cell types(Chalkiadaki and Guarente, 2012). It regulates multiple biological processes, including cellular metabolism, oxidative stress response, and inflammation, by deacetylating a wide range of target proteins. These targets include transcription factors such as FOXO and p53, and metabolic regulators such as PGC-1α, thereby influencing cellular function(Han et al., 2016; Iside et al., 2020). During aging, SIRT1 expression and activity typically decline, contributing to reduced antioxidant defenses, mitochondrial dysfunction, and exacerbated inflammatory responses—hallmarks of many age-associated diseases(Iside et al., 2020). LXRα, a nuclear receptor, plays a key role in cholesterol metabolism and inflammatory regulation by binding to promoter regions of target genes and modulating their transcription(Cariello et al., 2021; Chan et al., 2020). Both SIRT1 and LXRα have demonstrated protective effects in neurodegenerative diseases, cardiovascular disorders, and metabolic syndromes. Notably, SIRT1 can activate LXRα through deacetylation, thereby enhancing its transcriptional activity(Jakobsson et al., 2012). In turn, activated LXRα regulates downstream gene expression involved in cellular metabolism and immune responses(Song et al., 2022). This signaling axis has shown promising anti-aging and anti-inflammatory effects in multiple disease contexts(Zelcer and Tontonoz, 2006; Zhao et al., 2021; Zhu et al., 2021). However, the specific roles and mechanisms of SIRT1 and LXRα in ARHL remain largely unexplored, particularly regarding their expression and function in cochlear hair cells. Further investigation into this pathway may offer new insights into the pathogenesis of ARHL and reveal novel therapeutic opportunities.

Based on the current findings, we hypothesize that LXRα is expressed in the cochlea and contributes to the regulation of ARHL via the SIRT1/LXRα signaling pathway. To test this hypothesis, we investigated whether this pathway plays a pivotal role in ARHL. If confirmed, this mechanism could offer a novel therapeutic target for ARHL and further support the notion that ARHL is closely linked to cognitive decline (Figure 1). To this end, we established a mouse model of ARHL to observe dynamic changes in cochlear synapses and morphology across different age groups, and to examine the involvement of SIRT1/LXRα signaling in ARHL progression.

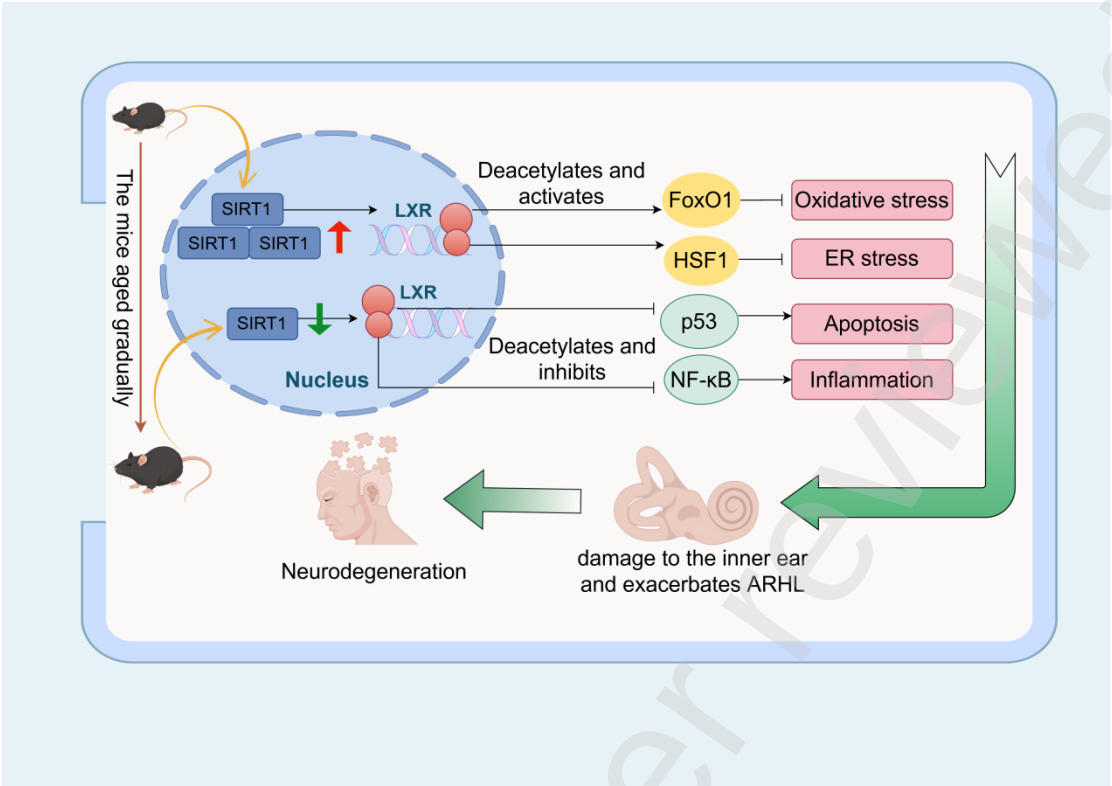

Fig. 1 The SIRT1/LXRα pathway is involved in the occurrence and development of age-related hearing loss (ARHL), and there is a correlation between ARHL and cognitive ability.

2. Materials and methods

2.1 Animals

In this study, C57BL/6J mice were obtained from the Animal Experimental Center of Southern Medical University. Each mouse underwent auricle reflex testing and otoscopic examination to rule out external auditory canal lesions and otitis media. Animals were housed in a temperature-controlled environment (23°C) under a standard 12-hour light/dark cycle, with food and water available ad libitum. The experimental protocol was approved by the Animal Ethics Committee of the Third Affiliated Hospital of Southern Medical University and adhered strictly to institutional animal welfare guidelines.

2.2 Auditory function evaluation

Auditory brainstem response (ABR) testing was conducted in a sound-proof, electromagnetically shielded room using an ABR recording system (Tucker-Davis Technologies). The recording electrode was placed at the cranial midline, aligned with the superior edge of the auricles. The reference electrode was positioned beneath the ipsilateral ear, and the ground electrode under the contralateral ear. ABR thresholds were assessed using click stimuli and tone bursts at 4, 8, 16, 24, and 32 kHz. Stimulus intensity was decreased in 10 dB increments, and then in 5 dB steps near the threshold. Hearing thresholds were determined based on wave III responses and defined as the lowest stimulus level that produced a reproducible waveform with discernible peaks. ABR measurements were taken 24 hours before and 72 hours after drug administration in each group.

2.3 Immunohistochemistry

For immunostaining of LXRα, NFκB, and SIRT1, cochlear sections were rehydrated and subjected to antigen retrieval using 0.01 M sodium citrate buffer (pH 6.0) heated in a microwave oven for 2 minutes. After PBS washing, tissues were blocked with 5% normal goat serum for 30 minutes, followed by incubation with primary antibodies overnight at 4°C: rabbit polyclonal LXRα (14351-1-AP, 1:300, Proteintech, Wuhan, China), SIRT1 (13161-1-AP, 1:300, Proteintech), and NF-κB p65 (WL01273b, 1:500, Wanleibio, Shenyang, China). The next day, sections were extensively washed and incubated with horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG secondary antibody (1:500, Biodragon Immunotechnologies, Beijing, China) for 1 hour at 37°C. Signal amplification was performed using the Vectastain Avidin-Biotin Complex kit (Vector Laboratories), followed by visualization with 3,3-diaminobenzidine (Thermo Scientific) and counterstaining with Mayer's hematoxylin (Sigma-Aldrich). Digital images were captured using a fluorescence microscope (OLYMPUS BX-51, Japan).

2.4 Western blot

Three cochleas from each group were dissected, collected on ice, stored at −80 °C, and lysed in RIPA buffer (Biyotime, Shanghai, China). Protein concentrations were determined using the Micro BCA kit (Solarbio, Beijing, China). Protein samples were separated via SDS-PAGE and transferred to PVDF membranes (Millipore, MA, USA), which were blocked with 5% nonfat dry milk in TBS containing 0.1% Tween-20. The membranes were then incubated overnight at 4 °C with primary antibodies: rabbit anti-LXRα (14351-1-AP, 1:300, Proteintech, Wuhan, China), anti-SIRT1 (13161-1-AP, 1:300, Proteintech), anti-NFκB (WL01273b, 1:500, Wanleibio, Shenyang, China), and anti-β-actin (WL01372, 1:1000, Wanleibio). Following extensive washing, membranes were incubated with a secondary antibody (ZB-2306, 1:5000, ZSGB-BIO, Beijing, China), and immunoreactive bands were visualized using enhanced chemiluminescence (KF001, Affinity Biosciences, OH, USA). Densitometric analysis was performed using ImageJ (Bethesda, MD, USA), with β-actin serving as the loading control.

2.5 Statistical analyses

Statistical analyses were conducted using GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, CA, USA). Data are presented as mean ± standard error of the mean (SEM). One-way or two-way ANOVA was used for multiple comparisons, followed by Tukey's post hoc test. A p-value < 0.05 was considered statistically significant.

3 Results

3.1 Hearing test results of C57BL/6J mice at different ages

Auditory brainstem responses (ABRs) were measured in C57BL/6J mice at 2, 6, 9, and 12 months of age to assess age-related changes in hearing, as shown in Figure 2-1. Under click (broadband) stimulation, hearing thresholds progressively increased with age (Fig. 2-1A). Compared with 2-month-old mice, 9- and 12-month-old mice exhibited significantly elevated thresholds ($P < 0.0001$), indicating moderate to severe hearing loss, with average thresholds of 54.5 dB and 63.0 dB, respectively. Additionally, pure tone ABRs were conducted at frequencies ranging from 4 kHz

(low) to 32 kHz (high) in 2- and 12-month-old mice. As shown in Fig. 2-1B, 12-month-old mice displayed significantly higher thresholds than 2-month-old mice across all frequencies tested ($P < 0.0001$). These results demonstrate that 2-month-old mice have normal hearing, which progressively declines with age, leading to moderate to severe hearing loss by 9 months—characteristic of age-related hearing loss (ARHL). Therefore, 2-month-old mice can be classified as young with normal hearing, while mice aged 9 months and older can be considered aged with hearing impairment. Moreover, age-related declines were also accompanied by reduced mobility and loss of auricular reflexes.

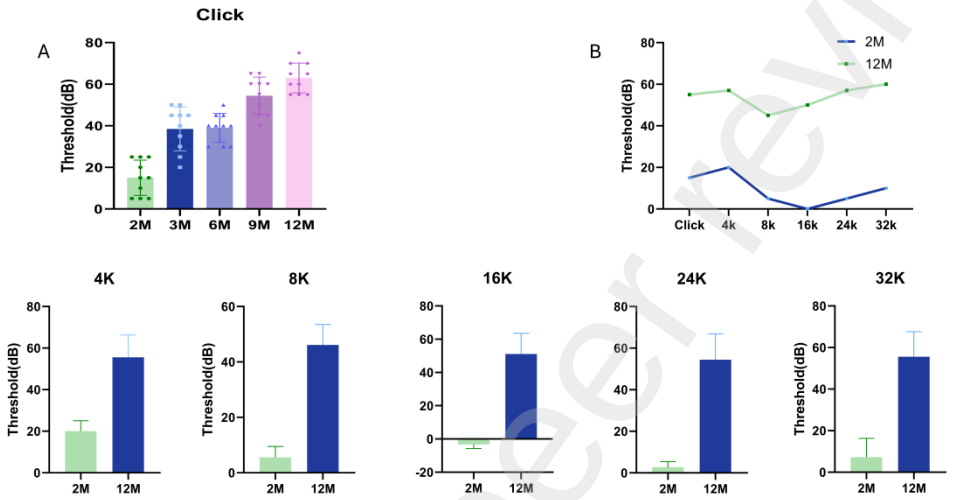

Fig. 2 Hearing thresholds of C57 mice of different ages. A: Hearing thresholds of 2-month-old, 3-month-old, 6-month-old, 9-month-old, and 12-month-old mice when stimulated with short sounds (clicks), showing that the hearing threshold gradually increases with age; n = 10. B: Hearing thresholds of 2-month-old and 12-month-old mice when stimulated with short sounds and pure tones (tones) at various frequencies. The hearing thresholds of the elderly mice were significantly higher than those of the young mice at all frequencies; $P < 0.0001$, n (2M) = 14, n (12M) = 9.

3.2 Expression and localization of the LXRα and SIRT1 proteins in the mouse cochlea

To further confirm the expression and distribution of LXRα in the mouse cochlea, we prepared paraffin sections from 2-month-old mice and performed immunohistochemistry. LXRα expression was also examined in the cochleae of 5-day-old neonatal and 12-month-old aged mice. We observed that LXRα was expressed in both neonatal and aged cochleae; however, its expression levels were significantly lower compared to those in young mice (Fig. 3). In the 2-month-old cochleae, LXRα was localized to inner and outer hair cells, spiral ganglion cells, the spiral ligament, and the stria vascularis within the apical, middle, and basal turns. No staining was observed when the primary antibody was replaced with PBS, confirming the specificity of the signal and excluding false positives(Fig. 4).

To assess age-related changes in other regulatory molecules, we examined the

expression of SIRT1 and NFκB across different age groups using immunohistochemical staining. SIRT1 expression decreased with age, while NFκB expression increased. In particular, SIRT1 was weakly positive in the spiral ganglion cells of 12-month-old mice compared to 6-month-old mice, whereas NFκB showed strong positivity in the few remaining spiral ganglion cells of aged mice (Fig. 5). These findings indicate that aging is associated with reduced SIRT1 expression and impaired suppression of NFκB, contributing to increased inflammation and apoptosis in cochlear cells (spiral ganglion cells) and potentially accelerating age-related hearing loss.

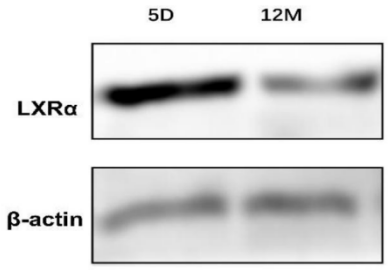

Fig. 3 LXRα can be detected in large quantities in the cochlea of 5-day-old neonatal mice, and a small amount of LXRα expression still exists in the cochlea of 12-month-old mice.

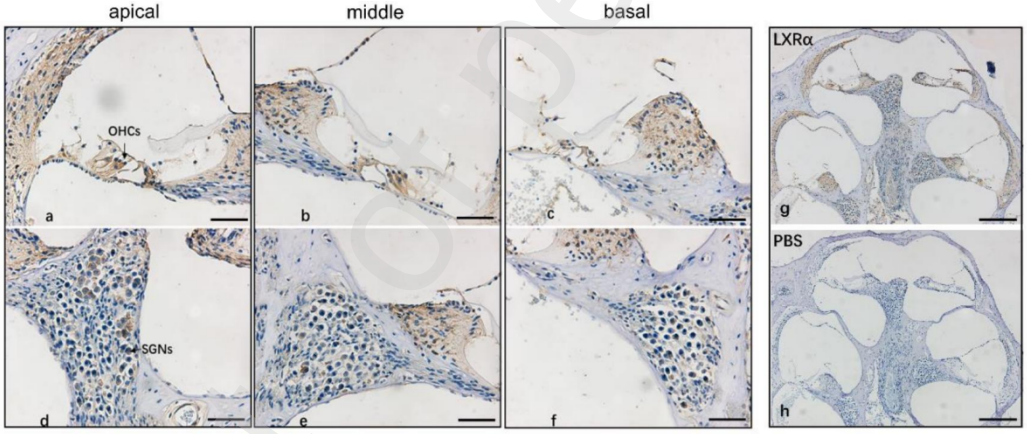

Fig. 4 Expression and localization of LXRα in the mouse cochlea. LXRα was expressed in the hair cells and spiral ganglion cells of the apical, middle and basal turns of 2-month-old mice (a, b, c, d, e, f, scale bar: 20 μm); no staining was observed in the negative control (g, h, scale bar: 200 μm).

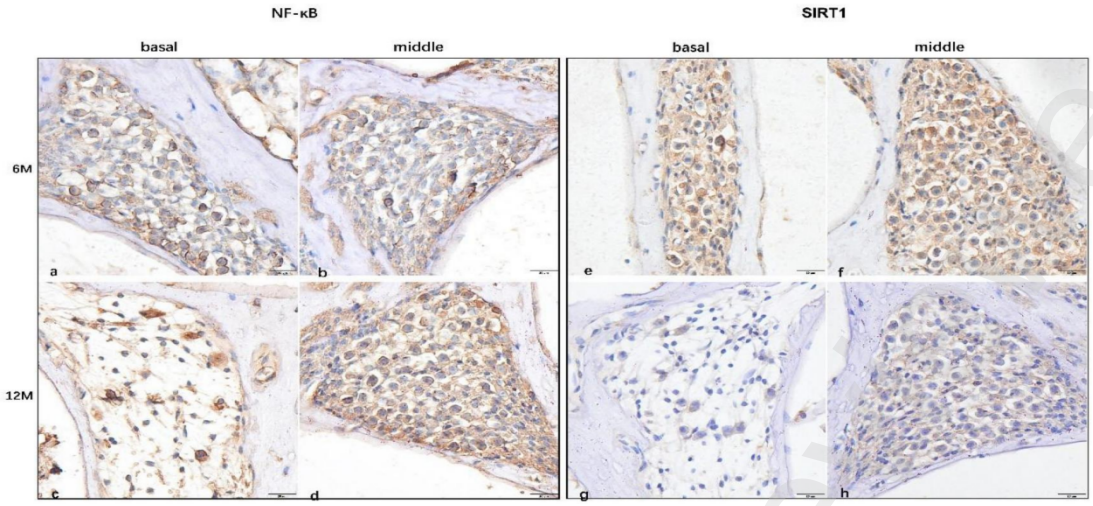

Fig. 5 The expression of NFκB and SIRT1 in the cochlea of mice of different ages. The results showed that the expression of NFκB in spiral ganglion cells of the cochlea increased with age: in 12-month-old mice, it was strongly positive, with dark brown staining granules visible within the cells; while in 6-month-old mice, there were light brown staining granules within the spiral ganglion cells (a, b, c, d). The content of SIRT1 in spiral ganglion cells of the cochlea of 12-month-old mice decreased significantly, and the expression of SIRT1 within the cells was weakly positive; while in 6-month-old mice, dark brown staining granules were visible, and the expression was strongly positive (e, f, g, h); scale bar: 20 μm.

3.3 Expression of SIRT1, LXRα, and NFκB in the cochleae of mice at different ages

Immunohistochemical staining of paraffin-embedded cochlear sections revealed strong LXRα expression in young mice and weak expression in aged mice (Fig. 6A). Quantitative analysis of LXRα-positive spiral ganglion cells in the apical, middle, and basal turns showed a significantly lower number of positive cells in aged mice compared to young mice (Fig. 6B). These findings paralleled the expression pattern of SIRT1 in the cochlea (Fig. 8). To further validate these results, Western blot analysis was performed. The expression levels of both LXRα and SIRT1 were found to decline significantly with age (Fig. 6C).

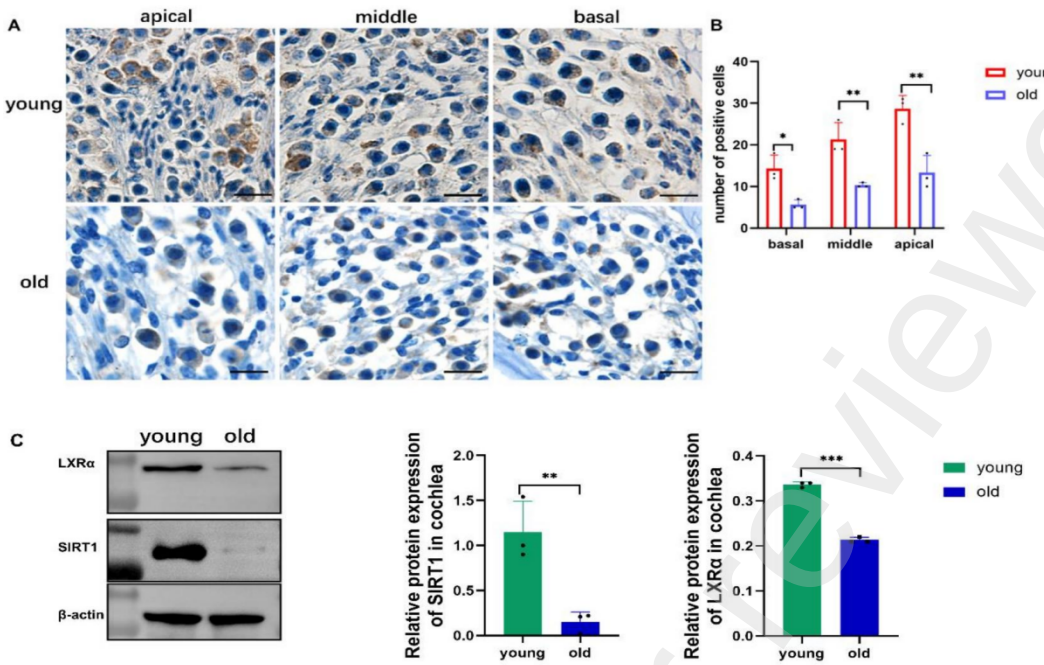

Fig.6 The expression levels of SIRT1 and LXRα in the cochlea of aged mice decreased. A: Immunohistochemistry: LXRα was strongly expressed in the spiral ganglion cells of young mice, and dark brown staining granules could be seen in a large number of cells after staining; LXRα was weakly expressed in the spiral ganglion cells of the cochlea of aged mice, with a significantly reduced expression level compared to young mice, and only a few cells showed light brown staining granules after staining; scale bar: 20 μm. B: Under the same field of view, the number of positive cells in the spiral ganglion of the basal turn in aged mice was significantly reduced compared to young mice, $P < 0.05$; the number of positive cells in the spiral ganglion of the middle turn ($P < 0.01$) and the apical turn ($P < 0.01$) in aged mice was significantly reduced compared to young mice; $n = 3$. C: The expression levels of SIRT1 and LXRα in the cochlear tissues of mice of different ages. The expression levels of LXRα and SIRT1 in the cochlear tissues of aged mice were significantly lower than those of young mice, $P < 0.001$, $n = 3$.

3.4 Detection of GPX activity in the serum of mice at different ages

We also measured serum glutathione peroxidase (GPX) activity in young and old mice. GPX activity was significantly lower in aged mice ($P < 0.05$), indicating a decline in systemic antioxidant capacity with age(Fig. 7).

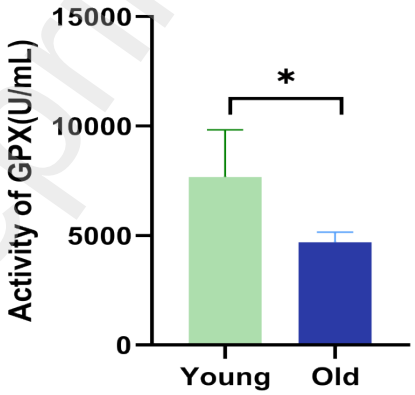

Fig.7 The GPX activity in the serum of mice of different ages was measured. The GPX activity in the serum of aged mice was lower than that of young mice, $P < 0.05$, $n \geq 3$.

Additional immunohistochemical analysis of cochleae from mice at different ages showed that LXRα expression was highest in young mice, declined by 9 months of age, and exhibited a slight increase in 12-month-old mice (Fig.8). Quantification revealed fewer LXRα-positive spiral ganglion cells in 9- and 12-month-old mice than in 2-month-old mice (Fig. 8J). Concurrently, SIRT1 expression decreased and NFκB expression increased with age. Notably, NFκB staining was weak in spiral ganglion cells of 2-month-old mice but strong in the remaining cells of 12-month-old mice (Fig.8K). These data support the conclusion that aging reduces SIRT1 expression and its regulatory control over NFκB, promoting inflammation and apoptosis in cochlear tissues and contributing to the development of age-related hearing loss.

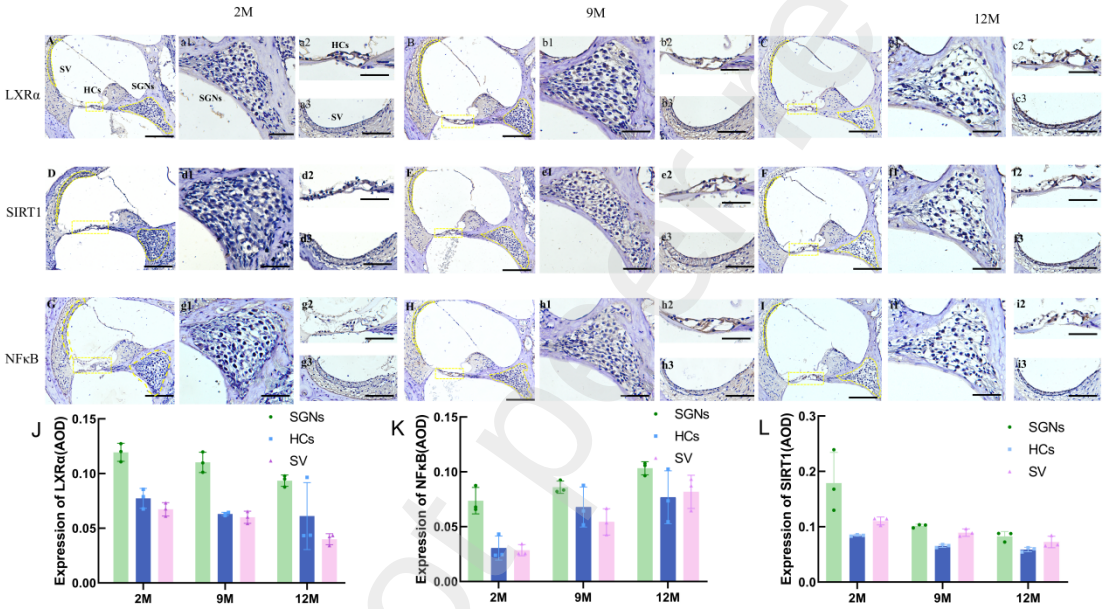

Fig.8 The expression of NFκB, LXRα and SIRT1 in the cochlea of mice of different ages. The results showed that the expression of NFκB in the cochlea increased with age: deep brown staining granules were observed in the spiral ganglion cells, stria vascularis and Corti's organ of the mice, and the number of granules increased with age (g-i1, 2, 3, K); the content of LXRα and SIRT1 in the cochlea decreased significantly with age (a-f1, 2, 3, J, L); scale bar: (a-i1, 2, 3: 20 μm; A-I: 100μm)

4. Discussion

Based on our findings, we confirmed that the expression levels of SIRT1 and LXRα decline significantly in the aging cochlea, accompanied by abnormal activation of the NFκB signaling pathway and elevated release of inflammatory cytokines. These results suggest a potential link between this molecular shift and the development of age-related hearing loss (ARHL). Specifically, the functional decline of the SIRT1/LXRα signaling axis may contribute to ARHL pathogenesis by amplifying the inflammatory response. The underlying mechanism is discussed in the context of current evidence.

LXRα, a member of the nuclear receptor family, plays dual roles in regulating lipid metabolism and suppressing inflammation(Shiragannavar et al., 2020). It

promotes the expression of cholesterol transporters such as ABCA1 by binding to target gene promoters, thereby contributing to the maintenance of ionic balance in the cochlear endolymph (Madashetty et al., 2024; Marwarha et al., 2011). SIRT1 enhances LXRα transcriptional activity through deacetylation, while activated LXRα inhibits NFκB-mediated inflammatory signaling. Together, SIRT1 and LXRα act synergistically to attenuate cochlear inflammation by downregulating pro-inflammatory cytokines such as IL-6 and TNF-α (Nunez and Guo, 2025; Pang et al., 2019; Tang et al., 2023). Although SIRT1 has been previously implicated in ARHL treatment (Takumida et al., 2016; Xiong et al., 2015), the expression and role of LXRα in the cochlea had not been thoroughly investigated. To date, only one study (Song et al., 2022) (2022) has examined the role of LXRβ in ARHL, reporting that its deficiency leads to spiral ganglion cell death and progressive hearing loss. While LXRβ is broadly expressed across tissues, LXRα exhibits tissue-specific distribution, prompting our investigation into its cochlear expression. Using Western blot analysis, we confirmed the presence of LXRα in mouse cochlear tissue. During our observations, we noted that the external ear is fully developed by postnatal day 5, while the auricular reflex progressively weakens with age and disappears by 12 months. Accordingly, cochlear tissues were collected from 5-day-old and 12-month-old mice. LXRα was found to be highly expressed at postnatal day 5 but markedly reduced in the aged cochlea. To further characterize LXRα localization, cochlear paraffin sections were subjected to immunohistochemistry. LXRα was broadly distributed across inner and outer hair cells of the basal, middle, and apical turns, as well as spiral ganglion cells, the stria vascularis, and the spiral ligament—paralleling the distribution of SIRT1. Notably, LXRα expression declined significantly with age, potentially disrupting cochlear homeostasis by impairing metabolic-inflammation balance. This downregulation may contribute to lipid metabolism disorders, stria vascularis dysfunction, and destabilization of the endolymphatic potential. Simultaneously, reduced LXRα may relieve NFκB inhibition, promoting inflammatory cell infiltration and hair cell damage. Collectively, these findings support the hypothesis that SIRT1 and LXRα function as a synergistic anti-inflammatory network, potentially through epigenetic regulation or protein-protein interactions. Their age-related decline likely exacerbates the inflammatory cascade in cochlear tissue, contributing to ARHL progression.

Secondly, as a NAD^+-dependent histone deacetylase, SIRT1 plays a critical role in maintaining cellular redox homeostasis and suppressing inflammatory responses (Miwa, 2021; Zhao and Tian, 2022). It delays aging by regulating mitochondrial function, mitigating oxidative stress, and inhibiting inflammation. Previous studies have demonstrated that SIRT1 expression is significantly downregulated in the cochlea, leading to mitochondrial dysfunction and hair cell apoptosis (Han et al., 2016; Salam et al., 2021; Zhu et al., 2021). Mechanistically, SIRT1 deacetylates the p65 subunit of NF-κB, thereby inhibiting its transcriptional activity and reducing the release of pro-inflammatory cytokines such as IL-6 and TNF-α (Chalkiadaki and Guarente, 2012; Yun et al., 2012). Additionally, SIRT1 promotes mitochondrial biogenesis and limits reactive oxygen species (ROS) accumulation by activating PGC-1α, ultimately

suppressing the NF-κB-mediated apoptotic pathway(Hou et al., 2022; Liu et al., 2022; Xie et al., 2022). In this study, decreased SIRT1 expression in the cochlear tissues of middle-aged and aged mice likely weakens its inhibitory control over NF-κB, contributing to excessive NF-κB signaling. This overactivation appears closely linked to age-related declines in NAD^+ levels and increased oxidative stress, which together may drive the formation of a chronic inflammatory microenvironment in the cochlea(Keithley, 2020; Pak et al., 2020; Rivas-Chacón et al., 2021). To investigate whether the SIRT1/LXRα signaling pathway contributes to the pathogenesis of age-related hearing loss (ARHL), we conducted a preliminary analysis of SIRT1 and LXRα expression in the cochleae of mice at different ages using immunohistochemistry and immunoblotting techniques. The results revealed a significant age-dependent decline in both SIRT1 and LXRα expression. Aged mice exhibited markedly fewer SIRT1- and LXRα-positive cells in the spiral ganglion, with weak expression levels in the remaining positive cells. Histological analysis of cochlear sections using H&E staining further showed a significant reduction in the number of neurons and glial cells in the spiral ganglion of 12-month-old mice. Structural degeneration, including atrophy of the stria vascularis and deterioration of the spiral ligament, was particularly pronounced in the cochlear base. These observations align with previously reported findings. Due to the relatively early onset of hearing loss in mice, we also observed mild neuronal loss in the spiral ganglia of 6-month-old mice, along with looser neuronal arrangements compared to 2-month-old mice. This suggests that early pathological changes in ARHL may involve auditory nerve degeneration. Taken together, histological alterations and reduced expression of SIRT1 and LXRα with age suggest that degeneration of cochlear structure in ARHL may be closely linked to downregulation of the SIRT1/LXRα signaling axis.

Further analysis revealed a strong correlation between persistent activation of the NF-κB pathway and cochlear tissue pathology. Increased nuclear translocation of NF-κB and elevated expression of inflammatory mediators such as COX-2 and iNOS in aged cochleae may contribute to the following pathological processes(Ege et al., 2024; Shih et al., 2025): (1) mitochondrial dysfunction and activation of apoptosis in hair cells(Huang et al., 2024); (2) abnormal extracellular matrix remodeling in spiral ligament fibroblasts(Lao et al., 2024); (3) impaired ion transport in marginal cells of the stria vascularis. These changes collectively lead to structural degeneration of the organ of Corti and disruption of auditory signal transmission. Notably, pretreatment with SIRT1 agonists (e.g., resveratrol) or LXRα agonists (e.g., GW3965) significantly inhibited NF-κB activation and mitigated cochlear inflammation, providing a compelling experimental basis for targeted therapeutic intervention in age-related hearing loss(Rivas-Chacón et al., 2023; Wan et al., 2024; Wang et al., 2023; Zhao et al., 2023).

Several critical questions remain to be addressed in this study: (1) Is the observed downregulation of SIRT1/LXRα expression linked to aging-associated epigenetic modifications, such as DNA methylation or histone alterations? (2) Does NFκB activation exacerbate cochlear degeneration by promoting pyroptosis or driving the senescence-associated secretory phenotype (SASP)? (3) Is metabolic

reprogramming—such as inhibition of fatty acid oxidation—involved in modulating the SIRT1/LXRα/NFκB signaling axis? Additionally, factors such as sex-based differences, cochlear region specificity (e.g., basal vs. apical turns), and potential synergistic effects of ototoxic stressors require further investigation.

We observed that SIRT1 and LXRα expression were significantly reduced, whereas NFκB expression was elevated in the aging cochlea of mice. These findings suggest that the age-related decline in SIRT1 and LXRα may compromise antioxidant defenses and amplify inflammatory responses. Notably, similar expression patterns were found in brain tissue, indicating that this regulatory axis may be broadly relevant across auditory and central nervous systems. In young cochleae, SIRT1 and LXRα were highly expressed, but their levels markedly declined with age. Taken together, our results support the hypothesis that SIRT1/LXRα signaling plays a central role in age-related hearing loss (ARHL). With advancing age, reduced SIRT1 expression leads to diminished LXRα activity, impairing energy metabolism regulation, lowering antioxidant capacity, and intensifying inflammation—all of which contribute to cell apoptosis, loss of hair cells and spiral ganglion neurons, and ultimately, irreversible hearing impairment. These findings offer novel insights for the development of early interventions and therapeutic strategies targeting ARHL.

5 Conclusions

This study proposes a new mechanistic framework for ARHL: age-dependent downregulation of SIRT1/LXRα leads to chronic, low-grade cochlear inflammation via disinhibition of NFκB, culminating in progressive hearing deterioration. This model not only deepens our understanding of ARHL's molecular underpinnings but also establishes a theoretical basis for anti-inflammatory therapies targeting the SIRT1/LXRα axis. Although this project represents a preliminary exploration—limited to evaluating SIRT1 and LXRα expression and their putative roles in ARHL pathogenesis—future studies should employ pharmacological modulators or gene-editing approaches to manipulate SIRT1/LXRα activity. These interventions will enable direct assessment of auditory function and cochlear pathology, thereby validating the functional relevance of this signaling pathway in ARHL.

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CRediT authorship contribution statement

Guangyong Tian, and Piao Xu conceived the ideas for experimental designs, analyzed the data. Dafei Li, Qiongping Lin, Tingting Zhao, Yue Meng and Hongjuan Chu performed the experiments, analyzed the data, and drafted the manuscript. Guangyong Tian revised the manuscript. All authors read and approved the final manuscript.

Ethics statement

The animal study was reviewed and approved by Animal Ethics Committee of the Third Affiliated Hospital of Southern Medical University.

Declaration of competing interest

None of the authors has a conflict of interest to declare.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

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