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Long noncoding RNA XIST attenuates oxidative stress in hearing loss by regulating miR-454-3p/RARP1

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

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Abstract

Introduction and Objective. Long non-coding RNA XIST is implicated in various diseases, but its role in hearing loss remains unclear. The aim of the study is to investigate the function and molecular mechanism of XIST in oxidative stress-induced cochlear cell damage.

Materials and Method. XIST expression was quantified in clinical samples from presbycusis patients and normal controls. *In vitro*, the HEI-OC1 cochlear cell line was subjected to glucose oxidase (GO) treatment to mimic injury. XIST expression was knocked down using siRNA. Apoptosis was assessed by flow cytometry. Reactive oxygen species (ROS) levels were measured by DCFH-DA assay. Oxidative stress marker 4-HNE was evaluated. Dual-luciferase reporter assays and RNA pulldown analysis were employed to identify the interactions. Rescue experiments were conducted to elucidate the functional axis.

Results. Elevated serum XIST levels in presbycusis patients were associated with a diagnostic AUC of 0.855. In HEI-OC1 cells, XIST knockdown under GO treatment markedly attenuated apoptosis, reduced ROS production, and decreased 4-HNE expression. XIST was confirmed to bind to and sequester miR-454-3p. PARP1 was identified as a direct target of miR-454-3p. MiR-454-3p inhibitor or PARP1 siRNA offset the protective effects of XIST knockdown against oxidative stress and apoptosis.

Conclusions. LncRNA XIST can exacerbate oxidative stress-induced cochlear cell damage by sponging miR-454-3p and upregulating PARP1 expression.

Key words

hearing loss, lncRNA, ceRNA, oxidative stress

INTRODUCTION

Disabling hearing loss afflicts more than 5% of the world's population [1]. Diagnosis typically begins with a detailed patient history and physical examination, followed by confirmation through audiometric and tympanometric testing [2]. Aging involves complex molecular and cellular alterations that disrupt tissue and organ homeostasis, thereby contributing to the increased incidence and progression of numerous chronic conditions, among which age-related hearing loss, or presbycusis, is particularly prevalent [3, 4]. Age-related hearing loss is characterized by a progressive and irreversible reduction in auditory sensitivity. This decline is accompanied by the degeneration of sensory hair cells and auditory neurons, as well as diminished central auditory processing capabilities [3]. As human lifespans have been extended due to advances in modern medicine, the prevalence of age-related disorders such as hearing loss has become increasingly significant. Notably, hearing loss is now recognized as one of the most substantial modifiable risk factors contributing to dementia, representing up to 9% of the overall modifiable risk [5]. There is also growing acknowledgment of its profound neuropsychological and psychosocial consequences [6, 7]. Although significant progress has been made in elucidating the molecular mechanisms of aging over the past thirty years, deeper insight into the interplay between key aging pathways and the pathogenesis of hearing loss remains essential for identifying novel therapeutic targets for this prevalent condition.

Among the numerous factors contributing to hearing loss, oxidative stress emerges as a critical driver of the underlying pathological process [8, 9]. Oxidative stress occurs when the body's capacity to eliminate reactive oxygen species (ROS) through antioxidant defences is overwhelmed, leading to cellular damage, functional impairment, and ultimately cell death [10, 11]. The cochlear structures, including sensory hair cells, the stria vascularis, and spiral ganglion neurons, are highly susceptible to damage from mitochondrial ROS [12]. With age, a decline in the cochlea's antioxidant defences and mitochondrial function leads to increased oxidative stress. Although the body generally detoxifies toxins, such as 4-hydroxynonenal (4-HNE) via specialized enzymes, this

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detoxification becomes insufficient, resulting in hearing loss [13].

Recent studies over the past five years have identified long non-coding RNA (lncRNA) X-inactive specific transcript (XIST) as a critical regulator in cellular responses to oxidative stress, primarily through its involvement in apoptosis, inflammatory pathways, and antioxidant defence mechanisms [14–16]. LncRNA XIST has been shown to be upregulated under oxidative stress conditions induced by ischemia-reperfusion injury [17]. Notably, XIST often acts as a competitive endogenous RNA (ceRNA) that 'sponge' (binds and sequesters) microRNAs (miRs) targetting key oxidative stress-related genes [14, 18, 19]. For instance, XIST sponges miR-122-5p [20] or miR-125b [21], thereby modulating cell survival and apoptosis. However, the effects and potential mechanism of XIST in oxidative stress during hearing loss have not been clarified.

The aim of the study is to determine the clinical relevance of XIST in presbycusis by assessing its expression levels, and subsequently to decipher its functional role in oxidative stress and the associated molecular mechanisms in hearing loss via *in vitro* models.

MATERIALS AND METHOD

Acquisition of human blood samples. Venous blood was collected from 80 elderly participants, comprising 40 normal-hearing controls (female/male: 18/22; 67.3 ± 4.3 years) and 40 presbycusis patients (female/male: 17/23; 66.7 ± 5.1 years) with bilateral high-frequency hearing loss, all audiometrically confirmed. The study protocol was approved by the Medical Ethics Committee of Kunshan Women and Children's Health Care Hospital.

HEI-OC1 cell culture and modelling. HEI-OC1 cells were cultured in high-glucose DMEM containing 10% foetal bovine serum. The cells were seeded into 96-well plates for 48 hours. Subsequently, to establish an oxidative stress model, they were treated with glucose oxidase (GO, 40 U/L) for three hours [22].

Cell transfections. For siRNA-mediated depletion of XIST or PARP1, an siRNA of human XIST (siXIST) or PARP1 was used (koPARP1) (Ribobio, China). As a negative control, non-targeting siRNAs (siNC or koNC) were used (Ribobio, China). The miR-454-3p mimic, negative control (mimicNC), miR-454-3p inhibitor (in454-3p), and NC inhibitor (in NC) were constructed by Guangzhou RiboBio Co. (China). HEI-OC1 cells at 70% confluency were transfected in triplicate either with 10 μM of siRNAs or 50 nM of mimics/inhibitors with Lipofectamine™ 3000 Reagent (Invitrogen, USA). After 48 hours of transfection, cells were harvested, and transfection efficiency was quantified by qPCR.

RNA extraction, cDNA creation, and qPCR. Samples were stored in RNAlater stabilisation reagent (Ambion). RNA was extracted from both blood samples and cells using the RNeasy mini kit (QIAgen, USA). RNA was confirmed for the concentration, then treated with DNAse 1 (Sigma-Aldrich, USA) before cDNA creation. mRNA-encoding cDNA was made using Superscript II Reverse Transcriptase (Invitrogen, USA). MicroRNA cDNA was made using the miRCURY LNA RT Kit (Qiagen, USA). qPCR was carried out on a CFX Connect qPCR machine (Bio-Rad, USA), using Sso-Advanced Master Mix (Bio-Rad, USA) for XIST and PARP1 or the miRCURY LNA SYBR Green PCR Kit (Qiagen, USA) for miR-454-3p. Relative expression levels were calculated using the $2^{-\Delta\Delta ct}$ equation. Hprt was used as an internal control for XIST and PARP1, and Jag1 as an internal control for miR-454-3p [23].

Determination of ROS levels. Intracellular ROS levels were detected by incubating the cells with DCFH-DA (ROS Assay Kit, Beyotime, China) for three hours, followed by flow cytometric analysis. The gating strategy of cell population was as follows: the screening of live cells was conducted using forward scattered light (FSC) and lateral scattered light (SSC) as the primary parameters. The subsequent identification of positive populations was facilitated by the use of DCFH-DA fluorescence intensity (X-axis) in conjunction with appropriate background fluorescence (Y-axis).

Cell apoptosis detection. The differences in apoptosis rates among different groups were detected using Annexin V-FITC/PI Apoptosis Kit (TransGen, China). After processing all samples according to the kit instructions, the percentage of apoptotic cells was quantified by gating on Annexin V and PI double-positive cells via flow cytometry.

Analysis of 4-HNE. To evaluate oxidative stress levels, the content of 4-hydroxynonenal (4-HNE) in cell lysates was measured using a specific 4-HNE ELISA Kit (Abcam, UK). After treatment, cells were washed and lysed, and the supernatant detected according to the kit instructions. The 4-HNE concentration in each sample was calculated based on the standard curve and normalized.

Dual-Luciferase reporter assays. The Luciferase reporter plasmids of XIST or PARP1 wild type (wildXIST or wildPARP1) and mutant type (mutantXIST or mutantPARP1) were constructed by Sangon Biotech (China), according to the binding sites of XIST or PARP1 with miR-124-3p. The plasmids were co-transfected with the mimicNC and mimic454-3p into HEI-OC1 cells. A Promega dual luciferase reporter assay system (USA) was used to read the luciferase activity after 48 hours of incubation.

RNA pulldown assays. RNA pulldown assays were performed using biotin-labeled RNA probes. Briefly, biotinylated non-coding control RNA (Bio-NC), biotinylated miR-454-3p mutant (Bio-miR-454-3p-Mut), and biotinylated miR-454-3p wild-type (Bio-miR-454-3p-WT) were synthesized by Sigma-Aldrich. Cell lysates from HEI-OC1 cells were incubated with each of these biotinylated RNAs, respectively. Streptavidin-coated magnetic beads were then added to each mixture and incubated for two hours to capture RNA-protein complexes. After thorough washing, bound RNAs were isolated, and the enrichment of XIST and PARP1 mRNA was quantified via qPCR.

Statistical analysis. Data were first assessed for normality and homogeneity of variance using the Shapiro-Wilk test, Bartlett's test, and Levene's test. Based on the results of these tests, appropriate tests for group comparisons were selected. For the XIST qPCR data in blood samples, the Mann-Whitney U-test was chosen to determine significance.

For the cell experimental data, the Student t-test, one-way or two-way ANOVA were used, followed by Bonferroni correction for multiple testing. Statistical significance was defined as a *P* value below the threshold of 0.05.

RESULTS

XIST was upregulated in hearing loss. A significant upregulation of XIST was observed in presbycusis patients compared to normal-hearing elders ($P < 0.001$) (Fig. 1A). Based on ROC curve analysis results (Fig. 1B), the XIST expression archived an AUC of 0.855 in discriminating hearing loss from the control elders (sensitivity 87.5%, specificity 77.5%).

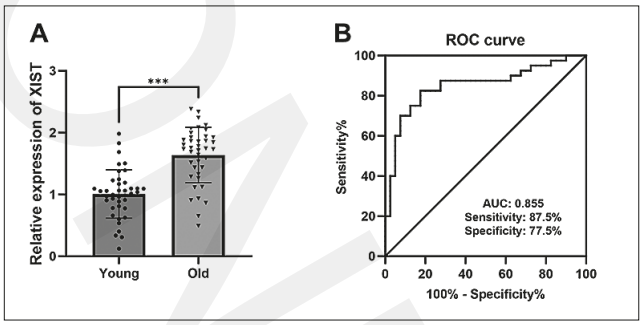

Figure. 1. Dysregulation of XIST in hearing loss. (A) The expression of XIST in the normal hearing elderly group and presbycusis group. (B) The ROC curve and AUC results of XIST for the discrimination of hearing loss.
*** $P < 0.001$

XIST attenuated oxidative stress in hearing loss. Under identical GO treatment conditions, XIST expression was knocked down in HEI-OC1 cells using specific siRNA ($P < 0.00$) (Fig. 2A). Apoptosis was assessed by flow cytometry with Annexin V-FITC/PI staining, revealing a significant increase in the rate of apoptosis following GO treatment, which was brought down by XIST knockdown ($P < 0.001$) (Fig. 2B). DCFH-DA fluorescence intensity measurements indicated that ROS levels were significantly lower in cells with XIST-knockdown than in negative control cells ($P < 0.001$) (Fig. 2C). Similarly, the expression level of 4-HNE was also reduced upon XIST knockdown ($P < 0.001$) (Fig. 2D).

XIST targeted miR-454-3p. LncRNAs can interact with miRNAs. There are three sets of binding sites for miR-454-3p and XIST based on ENCORI/starBase database (Fig. 3A). The dual-luciferase reporter assays were used to validate the interaction between miR-454-3p and XIST. Compared with the negative control group, the relative luciferase activity in the experimental group carrying wild-type XIST plasmids and mimic454-3p decreased significantly ($P < 0.05$), whereas there was no significant change in the relative luciferase activity in the experimental group carrying mutant XIST plasmids (Fig. 3B). To further validate the interaction between XIST and miR-454-3p in HEI-OC1 cells, an RNA pulldown assay was performed. The results demonstrated a significant enrichment of XIST pulled down with biotinylated wild-type miR-454-3p (Bio-miR-454-3p-WT), compared to the mutant version (Bio-miR-454-3p-Mut), where the XIST binding sites were disrupted ($P < 0.001$) (Fig. 3C). The qPCR analysis data demonstrated the expression of miR-454-3p increased after XIST knockdown in HEI-OC1 cells ($P < 0.001$) (Fig. 3D).

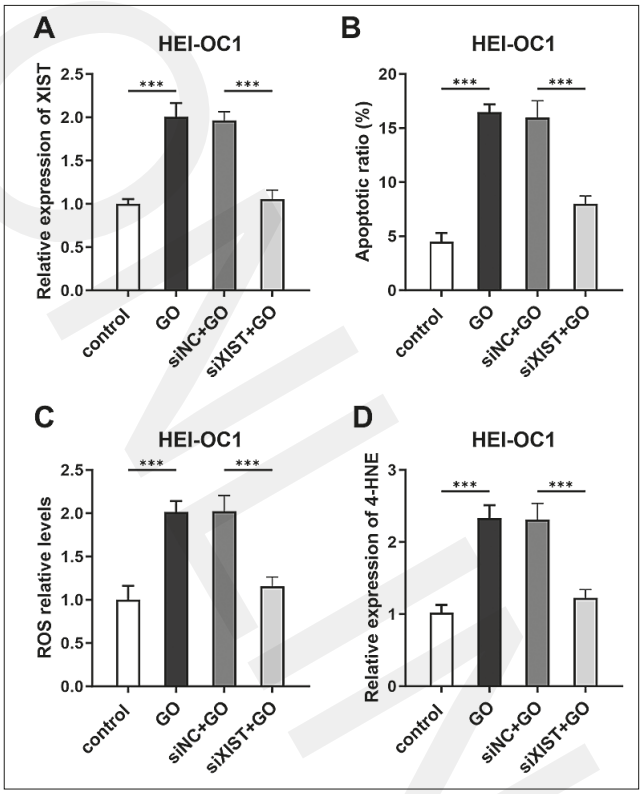

Figure 2. Changes in ROS levels and cell apoptosis in HEI-OC1 cells with XIST knockdown under oxidative stress. (A) Transfection efficiency of siRNA in HEI-OC1 cells (n=3). (B) Apoptosis rate in HEI-OC1 cells under oxidative stress post-transfection (n=3). (C) ROS levels in HEI-OC1 cells under oxidative stress post-transfection (n=3). (D) Relative 4-HNE expression in HEI-OC1 cells under oxidative stress post-transfection (n=3).
*** $P < 0.001$

PARP1 was a target gene of miR-454-3p. Based on the binding sites between miR-454-3p and PARP1, the results of dual-luciferase reporter assays showed that miR-454-3p mimics influenced the luciferase intensity of HEI-OC1 cells carrying wild-type PARP1, but not cells carried mutant PARP1 ($P < 0.05$) (Fig. 4A). RNA pulldown assay results indicated a marked enrichment of PARP1 captured by the biotin-labeled wild-type miR-454-3p (Bio-miR-454-3p-WT) relative to the mutant form (Bio-miR-454-3p-Mut), in which the PARP1 binding sites had been abolished ($P < 0.001$) (Fig. 4B). The qPCR analysis data demonstrated the expression of PARP1 mRNA reduced after XIST knockdown, but increased after miR-454-3p inhibition in HEI-OC1 cells ($P < 0.001$) (Fig. 4C).

PAXBP1-AS1 functioned by regulating miR-454-3p/RARP1. We conducted rescue experiments to explore the mechanism by which XIST functions in HEI-OC1 cells. The qPCR results (Fig. 5A) showed that HEI-OC1 cells transfected with XIST siRNA exhibited reduced PARP1 mRNA expression, whereas cotransfection of XIST siRNA and miR-454-3p inhibitors increased the expression of PARP1 mRNA, which was then reduced by PARP1 siRNA ($P < 0.01$). The ROS level assays demonstrated that miR-454-3p inhibitors led to an increase in ROS levels, while PARP1 siRNA reduced the ROS levels ($P < 0.05$) (Fig. 5B). The increased cell apoptosis under GO treatment was reduced by XIST knockdown; however, apoptosis was increased by miR-454-3p mimics, and this effect was reversed by PARP1 inhibition ($P < 0.001$) (Fig. 5C).

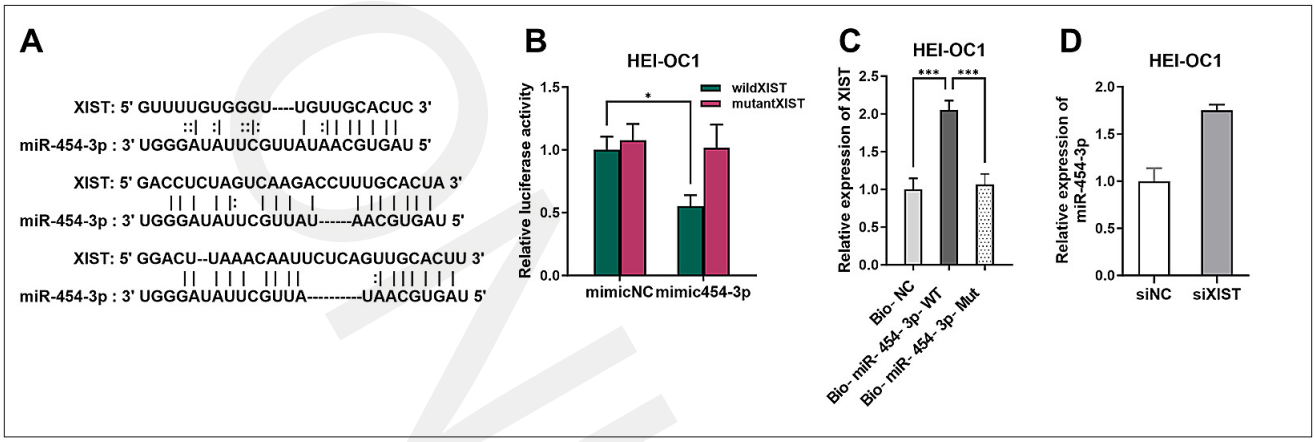

Figure 3. Interaction between XIST and miR-454-3p in HEI-OC1 cells. (A) Predicted binding sites of XIST and miR-454-3p from the StarBase database. (B) Luciferase activity in HEI-OC1 cells (n = 3). (C) RNA pull-down assay using biotinylated wild-type (Bio–miR-454-3p–WT) or mutant (Bio–miR-454-3p–Mut) probes; enrichment of XIST was measured via qPCR (n = 3). (D) miR-454-3p expression levels in HEI-OC1 cells after XIST knockdown, detected by qPCR (n = 3).
* $P < 0.05$. *** $P < 0.001$

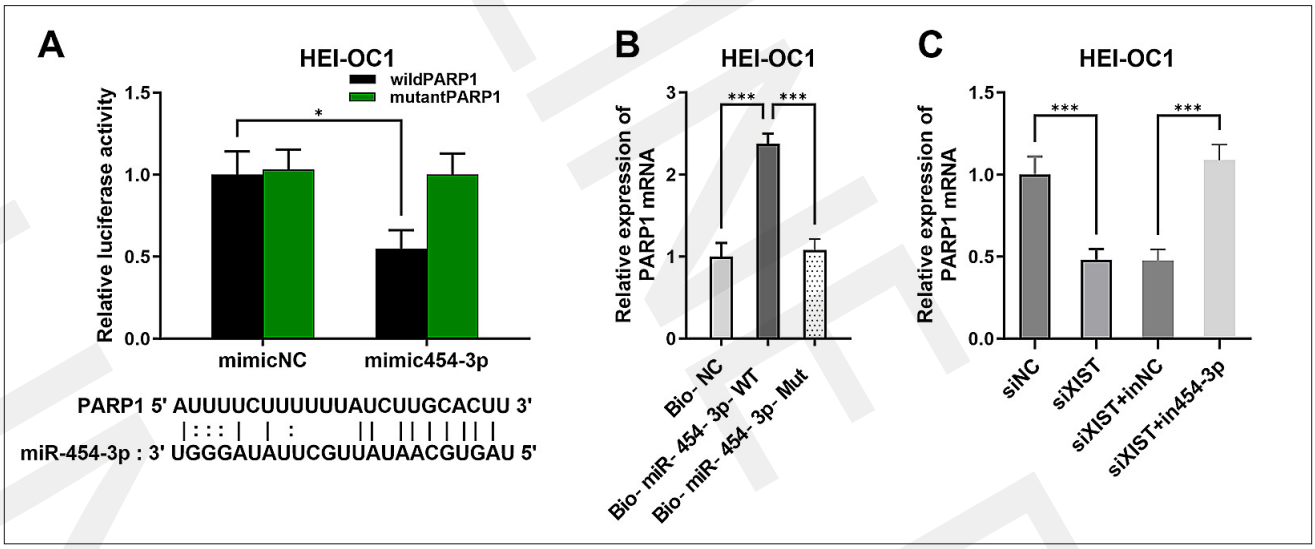

Figure 4. Interaction between miR-454-3p and PARP1 in HEI-OC1 cells. (A) Luciferase activity of PARP1 reporter vectors in HEI-OC1 cells transfected with miR-454-3p mimics or mimic NC, based on predicted binding sites (n = 3). (B) RNA pull-down assay using biotinylated wild-type (Bio–miR-454-3p–WT) or mutant (Bio–miR-454-3p–Mut); enrichment of PARP1 mRNA was detected by qPCR (n = 3). (C) miR-454-3p expression levels after transfection with XIST siRNA and/or a miR-454-3p inhibitor, measured by qPCR (n = 3).
* $P < 0.05$. *** $P < 0.001$

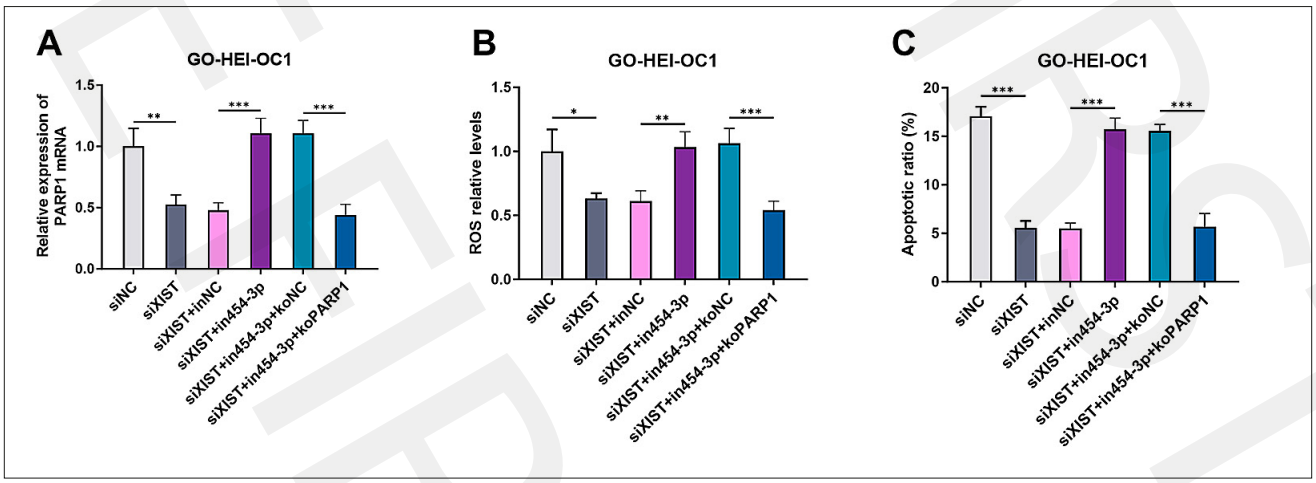

Figure 5. XIST functioned via moderating miR-454-3p and PARP1 in HEI-OC1 cells. (A) Verification of transfection effect after siRNA and/or inhibitor transfection of HEI-OC1 cells (n = 3). (B) ROS levels in HEI-OC1 cells under oxidative stress after siRNA and/or inhibitor transfection (n = 3). (C) Changes in the apoptosis ratio of HEI-OC1 cells under oxidative stress after siRNA and/or inhibitor transfection (n = 3).
* $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$

DISCUSSION

The study has demonstrated that the long non-coding RNA XIST was significantly upregulated in the blood of elderly individuals with presbycusis and exhibited high diagnostic accuracy for age-related hearing loss, as indicated by ROC analysis (AUC = 0.855). Functional experiments in HEI-OC1 auditory cells revealed that knockdown of XIST under GO-induced oxidative stress resulted in decreased apoptosis, reduced levels of ROS, and lipid peroxidation marker 4-HNE. Mechanistically, XIST was confirmed to directly bind to miR-454-3p, thereby modulating the expression of its target gene PARP1. Functional validation via rescue assays underscored that the XIST/miR-454-3p/PARP1 axis was instrumental in mediating oxidative stress and apoptosis.

LncRNAs have increasingly been recognized as key regulators in the pathogenesis of hearing loss [24]. For instance, lncRNA H19 exerts a protective effect against oxidative stress in cochlear hair cells by regulating miR-653-5p and then SIRT1 [25]. LncRNA Gm44593 can sponge miR-29b and thus upregulate WNK1, thereby attenuating oxidative stress in age-related hearing loss [26]. LncRNA H19 can increase cell viability, but reduce the cell apoptosis ratio in H_2O_2-stimulated HEI-OC1 cells [25].

The study also identified XIST as a novel player in hearing loss. A range of evidence has suggested that XIST can function as a key regulator in crucial cellular functions, such as proliferation and apoptosis, by regulating the expression level of target genes via epigenomic, transcriptional, or post-transcriptional approaches [27]. Recent research reveals that lncRNA XIST can assemble many proteins within the inactive X chromosome and initiate X-chromosome inactivation [28]. In addition to its original role in X chromosome dose compensation, lncRNA Xist participates in the development of human diseases as a ceRNA [28]. In the current study it was found that XIST knockdown reduced apoptosis in HEI-OC1 cells under stress by targeting the miR-454-3p/PARP1 axis, suggesting a context-dependent protective role. This may reflect the complex regulatory networks between lncRNAs and miRNAs in cochlear homeostasis, serving as a new strategy for targeted treatment of hearing loss.

Oxidative stress is a well-established contributor to both age-related and noise-induced hearing loss, causing damage to auditory cells [9]. Recent studies have highlighted the involvement of redox imbalance and lipid peroxidation in promoting cochlear degeneration [29]. It has been identified that individuals with presbycusis exhibit an increase in oxidative stress [30]. XIST knockdown has been identified to suppress the inflammatory damage and ROS production in deep venous thrombosis [16]. PARP1 can contribute to oxidative stress in age-related hearing loss through the PAR-Ca^{2+}-AIF pathway in cochlear strial marginal cells [31]. miR-454 can attenuate oxidative stress, evidenced by reduced ROS levels, and decrease neuronal apoptosis [32]. In the current study, GO-induced oxidative injury increased ROS and 4-HNE levels, but XIST knockdown can relieve this damage. A previous study has revealed that the impact of XIST on cellular plasticity can be attributed to the cells' capacity to adapt to environmental changes [33]. Here, the decrease in ROS upon XIST knockdown suggests that XIST may facilitate adaptive redox signalling necessary for cellular homeostasis under stress. Furthermore, through regulation of the miR-454-3p/PARP1 pathway, XIST appears to influence both apoptotic processes and oxidative stress responses, highlighting its multifaceted role in auditory cell survival.

CONCLUSIONS

In conclusion, this study demonstrated that XIST was significantly elevated in presbycusis patients, and in auditory cells under oxidative stress. It can function as a molecular sponge for miR-454-3p and lead to the dysregulation of PARP1, resulting in exacerbated oxidative stress, increased ROS production, and accelerated apoptosis in cochlear hair cells under stress conditions. Therefore, the XIST/miR-454-3p/PARP1 regulatory axis constitutes a novel mechanism contributing to the development of presbycusis.

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