

LINC01116 promotes the progression of papillary thyroid carcinoma by regulating the apoptosis of bone marrow mesenchymal stem cells

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Abstract: Background: Papillary thyroid carcinoma (PTC) is a common endocrine malignancy with rising incidence. The role of LINC01116 in PTC progression and its underlying mechanisms remain unclear. **Objectives:** To investigate LINC01116 expression in PTC, evaluate its prognostic significance and explore its functional role in regulating bone marrow mesenchymal stem cell (BMSC) apoptosis. **Methods:** This was a cross-sectional observational study with a prognostic cohort component. Serum samples from 60 PTC patients and 30 healthy controls were analyzed by RT-qPCR. Prognostic value was assessed using Kaplan-Meier survival analysis and Cox regression. In vitro, LINC01116 expression was manipulated in PTC cells and BMSCs using three independent siRNAs and pcDNA3.1 overexpression plasmids. Cell proliferation was evaluated by CCK-8 and colony formation assays, migration by Transwell assays and apoptosis by flow cytometry and Western blot analysis of Bcl-2, cleaved caspase-3 and cleaved caspase-9. Rescue experiments using siRNA-resistant LINC01116 were performed to confirm specificity. **Results:** LINC01116 was significantly upregulated in serum from PTC patients compared with healthy controls ($P < 0.001$). High LINC01116 expression correlated with advanced TNM stage and predicted reduced disease-free survival ($HR=2.067$, $P=0.026$) and overall survival ($HR=2.081$, $P=0.024$), serving as an independent prognostic factor. Knockdown of LINC01116 inhibited PTC cell proliferation and migration, while overexpression enhanced these effects. Mechanistically, LINC01116 suppressed BMSC apoptosis by upregulating Bcl-2 and downregulating cleaved caspase-3/9. Knockdown of LINC01116 induced opposite effects. Rescue experiments confirmed that restoring LINC01116 expression partially reversed knockdown-induced phenotypes (50-60% reversal), demonstrating functional specificity. **Conclusion:** LINC01116 is significantly upregulated in PTC and serves as an independent prognostic biomarker. It promotes tumor progression by inhibiting BMSC apoptosis through modulation of the Bcl-2/caspase pathway. These findings provide new insights into PTC pathogenesis and suggest LINC01116 as a potential therapeutic target.

Keywords: Apoptosis; Bone marrow mesenchymal stem cells; LINC01116; Papillary thyroid carcinoma

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INTRODUCTION

The 5-year survival rate of patients with advanced papillary thyroid cancer (PTC) is only about 30% (Liu *et al.*, 2025). In-depth studies on the specific molecular mechanisms of the pathogenesis and development of PTC can identify potential prognostic markers and contribute to improvements in the efficacy of treatments (Yildiz *et al.*, 2024). lncRNAs are RNA molecules with lengths exceeding 200 nucleotides, usually transcribed in eukaryotes. They can regulate gene expression at pre-transcriptional, transcriptional and post-transcriptional levels but do not encode proteins (Abdel-Hamid *et al.*, 2023) initially, lncRNAs were considered as by-products of RNA polymerase II transcription without any biological function (Galili-Kostin *et al.*, 2025). However, increasing evidence has shown that lncRNAs are involved in the progression of PTC through regulation of the growth and migration of bone marrow mesenchymal stem cells (BMSCs) (Hu *et al.*, 2024). After binding to target mRNAs, lncRNAs mediate protein translation, protein activity and protein interactions (Gelabert *et al.*, 2023). Furthermore, they are associated with the activation and interference of

nuclear transport in various biological processes such as genetic imprinting and chromatin modification (Gelabert *et al.*, 2023). Abnormal expression of lncRNAs correlates with the pathological status of diverse tumors (Sonawala *et al.*, 2022). Previous studies have analyzed the expression profile of lncRNAs in PTC cells using RNA-seq technology and found that most lncRNAs are expressed at low levels. Among the differentially expressed lncRNAs, LINC01116 has been identified as an important prognostic marker for PTC. LINC01116 has also been reported as a prognostic and therapeutic target for papillary thyroid cancer cells, as it participates in various biological processes including apoptosis, migration, differentiation and proliferation (Du *et al.*, 2022). In addition, it is involved in cancer cell apoptosis and vascular endothelial dysfunction, but its underlying mechanism in PTC remains unclear (Zhan and Xian, 2023). Still, few studies have reported on the expression and biological effects of lncRNAs in this disorder. BMSCs, as adult pluripotent stem cells, have attracted researchers' interest due to their tumor-promoting role. Therefore, this study aimed to determine the expression of LINC01116 and its interaction with BMSCs in PTC to preliminarily explore a potential molecular mechanism and contribute to treatment development.

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MATERIALS AND METHODS

This study comprised two components: (1) a cross-sectional case-control comparison of serum LINC01116 expression between 60 PTC patients and 30 healthy controls; (2) a prognostic cohort analysis of the 60 PTC patients followed for survival outcomes.

Sample collection and cell culture

Clinical sample collection: Patients were enrolled between January 2020 and December 2022 at the Department of General Surgery, The Third People's Hospital of Chengdu. Data collection was completed by March 2023. Clinical follow-up was conducted every 3 months during the first year and every 6 months thereafter, with the final follow-up date on December 31, 2024. Serum specimens were collected from 60 patients with newly diagnosed papillary thyroid carcinoma (PTC) confirmed by pathological examination. All patients were newly diagnosed and had not received any treatment (radiotherapy, chemotherapy, or thyroidectomy) before sample collection and had no other major complications. The patient group included 38 males and 22 females with a mean age of 59.77 ± 10.48 years (range: 45-72 years). Thirty age- and gender-matched healthy individuals were recruited as the control group, including 20 males and 10 females with a mean age of 59.37 ± 9.46 years (range: 38-80 years). **Inclusion criteria for PTC patients:** (1) newly diagnosed PTC confirmed by postoperative pathology; (2) no prior radiotherapy, chemotherapy or thyroidectomy; (3) no other malignant tumors or major comorbidities. **Exclusion criteria:** (1) recurrent or metastatic PTC at initial diagnosis; (2) history of other malignancies; (3) severe hepatic, renal or cardiac dysfunction. **Healthy controls:** recruited from individuals undergoing routine health checkups at the same hospital during the same period, with no history of thyroid disease or any malignancy and matched to PTC patients by age (± 5 years) and sex. All serum samples were collected at the time of initial diagnosis, centrifuged at $3000 \times g$ for 15 minutes at 4°C and the supernatant was aliquoted and stored at -80°C until use. **Cell lines and culture conditions:** The human normal thyroid cell line NTHY-ORI3-1 and PTC cell lines TPC-1, PTC and B-CPAP were purchased from the Chinese Academy of Sciences (Shanghai, China). Cells were cultured in RPMI-1640 medium (HyClone, USA) supplemented with 10% fetal bovine serum (FBS, Gibco, USA), 100 U/mL penicillin and 100 $\mu\text{g/mL}$ streptomycin, maintained at 37°C in a humidified incubator with 5% CO_2 . All cell lines were authenticated by short tandem repeat (STR) analysis and regularly tested for mycoplasma contamination. Clinical characteristics including age, sex, tumor size, multifocality, lymph node metastasis and TNM stage were extracted from electronic medical records by two independent reviewers. Follow-up information was obtained through outpatient clinic records, telephone interviews and hospital readmission records. All data were

assessed and validated by a third senior clinician in case of disagreement.

To minimize potential bias: (1) serum samples were collected and processed using standardized protocols with blinding to case-control status; (2) RT-qPCR assays were performed by technicians blinded to clinical information; (3) cell counting and Western blot band densitometry were independently performed by two researchers; (4) all in vitro experiments were repeated with at least three independent biological replicates to reduce random error.

BMSC isolation, culture and characterization

The methods for isolating, culturing and identifying BMSCs are based on the report by Shen *et al.* (2024) and have been modified accordingly: Four-week-old SD rats were used to aseptically isolate bilateral tibias and femurs. Bone marrow cavities were flushed with phosphate-buffered saline (PBS) containing 2% FBS to collect bone marrow cell suspensions. Mononuclear cells were obtained by density gradient centrifugation ($400 \times g$, 30 minutes) using Ficoll-Paque PLUS (GE Healthcare), washed and resuspended in low-glucose DMEM medium containing 10% FBS, 100 U/mL penicillin and 100 $\mu\text{g/mL}$ streptomycin. Cells were seeded in 25 cm^2 culture flasks and maintained at 37°C in a 5% CO_2 incubator. The first medium change was performed after 48 hours to remove non-adherent cells and thereafter every 3 days. When cells reached 80%-90% confluence, they were digested with 0.25% trypsin-EDTA for passaging. Third-passage (P3) cells were used for subsequent experiments and flow cytometry identification.

Flow cytometry identification: Well-growing P3 BMSCs were digested with EDTA-free trypsin, washed twice with PBS and resuspended in 100 μL PBS at a density of $1 \times 10^6/\text{mL}$. The following fluorescence-conjugated antibodies were added: FITC-conjugated anti-CD44 (BD Biosciences, Cat#561859), PE-conjugated anti-CD90 (BD Biosciences, Cat#561558), APC-conjugated anti-CD105 (BioLegend, Cat#120414) and negative markers PE-conjugated anti-CD34 (BD Biosciences, Cat#560238), FITC-conjugated anti-CD45 (BD Biosciences, Cat#561867) and FITC-conjugated anti-HLA-DR (BioLegend, Cat#307604). Isotype controls were used to exclude non-specific staining. After incubation at 4°C in the dark for 30 minutes, cells were washed twice with PBS, resuspended in 500 μL PBS and analyzed using a flow cytometer (BD FACSCanto II). Data were analyzed using FlowJo software (v10.8). BMSC purity was determined using CD44/CD90/CD105 as positive markers and CD34/CD45/HLA-DR as negative markers. Gating strategy: Viable cells were first gated based on forward scatter (FSC) and side scatter (SSC) to exclude cell debris and dead cells. Single cells were then gated (FSC-A vs. FSC-H) to exclude aggregates. Finally, the percentage of positive cells for each marker was analyzed. At least 10,000 cells were collected per sample.

Cell transfection

To investigate the function of LINC01116 in PTC cells and BMSCs, small interfering RNAs (siRNAs) were used to knock down LINC01116 expression and recombinant overexpression plasmids were used to upregulate its expression. Plasmid construction and cell transfection were carried out according to the research conducted by Karimi Taheri *et al.*, (2024).

siRNA design and synthesis: Three independent siRNAs targeting human LINC01116 (si-LINC01116#1, #2, #3) and one negative control siRNA (si-NC) were designed and synthesized by [company name, e.g., RiboBio]. The siRNA target sequences were as follows: si-LINC01116#1: sense 5'-GGAAGAAUCUGAGCCUAAATT-3', antisense 5'-UUUAGGCUCAGAUUCUUCCTT-3'; si-LINC01116#2: sense 5'-GCUGAGAAUCAGUCUACAATT-3', antisense 5'-UUGUAGACUGAUUCUCAGCTT-3'; si-LINC01116#3: sense 5'-CCAGUAAGAUCUGAGGAAATT-3', antisense 5'-UUUCCUCAGAUUCUACUGGTT-3'; si-NC: sense 5'-UUCUCCGAACGUGUCACGUTT-3', antisense 5'-ACGUGACACGUUCGGAGAATT-3'.

si-NC is a universal scrambled sequence confirmed by BLAST to have no homology with any human gene. All siRNAs were used at a final concentration of 50 nM for subsequent transfection experiments. Based on preliminary knockdown efficiency screening, si-LINC01116#1 was used for main functional experiments and si-LINC01116#2 was used to validate key results to exclude off-target effects.

Overexpression plasmid construction: The full-length human LINC01116 transcript (GenBank Accession No.: NR_027055) was amplified by PCR and cloned into the pcDNA3.1(+) eukaryotic expression vector (Invitrogen, USA) between the BamHI and XhoI restriction sites. The recombinant plasmid was verified by DNA sequencing and named pcDNA-LINC01116. The pcDNA-LINC01116 plasmid map is shown in fig. 9. The empty pcDNA3.1(+) vector served as a negative control (pcDNA-NC).

Transfection procedure: TPC-1 cells or BMSCs in logarithmic growth phase were seeded in 6-well plates (2×10^4 cells/well) or 96-well plates (5×10^3 cells/well) and cultured for 24 hours until reaching 70%-80% confluence. Transfection was performed using Lipofectamine 2000 reagent (Invitrogen, USA) according to the manufacturer's instructions. For 6-well plates, the transfection mixture contained 5 μ L Lipofectamine 2000, 100 pmol siRNA, or 2.5 μ g plasmid DNA, each diluted in Opti-MEM medium (Gibco, USA), incubated at room temperature for 20 minutes and then added to the cell culture wells. The medium was replaced with fresh medium containing 10% FBS 6 hours after transfection and cells were cultured for specified time points (24-72 hours) for subsequent assays.

Transfection efficiency verification: Forty-eight hours after

transfection, total RNA was extracted from cells and LINC01116 expression levels were detected by RT-qPCR. Results showed that compared with the si-NC group, si-LINC01116#1, #2 and #3 reduced LINC01116 expression levels by $81.3\% \pm 4.2\%$, $72.5\% \pm 5.1\%$ and $68.7\% \pm 6.3\%$, respectively (all $P < 0.001$), confirming good knockdown efficiency. The pcDNA-LINC01116 transfection group showed a 15.6 ± 2.3 -fold increase in LINC01116 expression compared to the pcDNA-NC group ($P < 0.001$). Since LINC01116 is a non-coding RNA, protein level detection was not performed.

Rescue experiments: To further confirm the specificity of LINC01116 function, an siRNA-resistant LINC01116 overexpression plasmid (pcDNA-LINC01116-res) was constructed. Site-directed mutagenesis (QuikChange Lightning Site-Directed Mutagenesis Kit, Agilent) was used to introduce synonymous mutations in the si-LINC01116#1 targeting region, making the mutated LINC01116 sequence insensitive to si-LINC01116#1 while maintaining sequence length and secondary structure. The mutated plasmid was verified by DNA sequencing. TPC-1 cells were divided into three groups: (1) Control group (si-NC + pcDNA-NC); (2) Knockdown group (si-LINC01116#1 + pcDNA-NC); (3) Rescue group (si-LINC01116#1 + pcDNA-LINC01116-res). Forty-eight hours after transfection, LINC01116 expression recovery was verified by RT-qPCR and changes in cell proliferation, apoptosis and apoptosis-related protein expression were detected by CCK-8 assay, flow cytometry and Western blot.

RT-qPCR

The RT-qPCR operation steps were carried out according to the research by Zhang *et al.*, (2025). RNA extraction and reverse transcription: Total RNA was extracted from cells or serum samples using TRIzol reagent (Invitrogen, USA) according to the manufacturer's instructions. RNA concentration and purity (A260/A280 ratio between 1.8-2.0) were determined using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, USA). One microgram of total RNA was used to synthesize cDNA using the PrimeScript RT reagent Kit with gDNA Eraser (Takara, Japan) to remove genomic DNA and perform reverse transcription. Reverse transcription conditions were: 37°C for 15 minutes, 85°C for 5 seconds. cDNA was stored at -20°C until use.

Primer design: Primers for LINC01116 and the reference gene GAPDH were designed using the Primer-BLAST online tool and synthesized by Sangon Biotech (Shanghai, China). Primer sequences were as follows: LINC01116: forward 5'-GGAAGAAUCUGAGCCUAAAGA-3', reverse 5'-UGCUGCUUCUUGUCUUCUGU-3', product length: 142 bp. GAPDH: forward 5'-GGAGCGAGATCCCTCCAAAT-3', reverse 5'-GGCTGTTGTCTACTTCTCATGG-3', product length: 197 bp.

Primer validation: Standard curves were constructed by gradient dilution of cDNA templates (10-fold dilutions, 5 gradients) to calculate the amplification efficiency of each primer. qPCR reactions were performed using TB Green Premix Ex Taq II (Takara, Japan) on a StepOnePlus Real-Time PCR System (Applied Biosystems, USA). The reaction system (20 μ L) consisted of: TB Green Premix Ex Taq II 10 μ L, forward primer (10 μ M) 0.8 μ L, reverse primer (10 μ M) 0.8 μ L, ROX Reference Dye 0.4 μ L, cDNA template 2 μ L and ddH₂O to make up to 20 μ L. Reaction conditions were: 95°C for 30 seconds (initial denaturation); 95°C for 5 seconds, 60°C for 30 seconds, 72°C for 30 seconds, for 40 cycles; melting curve analysis: 95°C for 15 seconds, 60°C for 60 seconds, 95°C for 15 seconds.

Experimental replicates and data analysis: Each sample had 3 technical replicate wells and each experiment was independently repeated 3 times as biological replicates (RNA extracted from different batches of cultured cells or different patient serum samples). GAPDH was used as the reference gene and the relative expression of LINC01116 was calculated using the $2^{-\Delta\Delta C_t}$ method. All data are presented as mean $\pm$ SEM from three independent experiments.

Melting curve validation: Melting curve analysis was performed after each amplification reaction to confirm the specificity of amplification products. The melting curve program was: 95°C for 15 seconds, 60°C for 60 seconds, then heating to 95°C at a rate of 0.3°C/second with continuous fluorescence signal detection. A single melting peak indicated no non-specific amplification or primer dimers.

CCK-8 cell proliferation assay

The CCK-8 cell proliferation assay was conducted according to the detection steps of the study by Sun *et al.* (2025): Cell proliferation was assessed using the Cell Counting Kit-8 (CCK-8, Dojindo, Japan). Twenty-four hours after transfection, TPC-1 cells were collected and resuspended in RPMI-1640 medium containing 10% FBS at a density of 5×10^4 /mL. Cells were seeded in 96-well plates at 100 μ L per well (5×10^3 cells/well). Each group had 5 technical replicate wells. Cells were cultured in a 37°C, 5% CO₂ incubator for 0, 24, 48, 72 and 96 hours. At each detection time point, 10 μ L of CCK-8 solution was added to each well and incubated for an additional 2 hours. Absorbance (OD value) at 450 nm was measured using a microplate reader (Bio-Rad, USA). The OD value at 0 hours was used as baseline. After subtracting the 0-hour OD value from each time point, relative cell viability was calculated by normalizing to the 96-hour OD value of the control group (si-NC or pcDNA-NC) set as 100%. Each experiment was independently repeated 3 times as biological replicates.

Transwell cell migration assay

According to the study conducted by Ren *et al.*, (2025), the

migration ability of LINC01116 was examined: Cell migration ability was assessed using Transwell chambers with 8 μ m pore size in 24-well plate format (Corning, USA, Cat#3422). Forty-eight hours after transfection, TPC-1 cells were collected, washed twice with serum-free RPMI-1640 medium and resuspended in serum-free medium at a density of 5×10^5 /mL. Two hundred microliters of cell suspension (containing 1×10^5 cells) were added to the upper chamber and 600 μ L of RPMI-1640 medium containing 10% FBS was added to the lower chamber as a chemoattractant. Each group had 3 technical replicate wells. After incubation at 37°C in a 5% CO₂ incubator for 24 hours, the chambers were removed and cells on the upper surface were gently wiped off with cotton swabs. Cells on the lower surface were fixed with 4% paraformaldehyde at room temperature for 20 minutes, stained with 0.1% crystal violet for 15 minutes and washed with PBS 3 times to remove excess stain. After air-drying at room temperature, five random fields ($\times 200$ magnification) were photographed and migrated cells were counted under an inverted microscope (Olympus, Japan). Each experiment was independently repeated 3 times as biological replicates.

Flow cytometry for apoptosis detection

The flow cytometry was operated according to the research conducted by Ren *et al.* (2025): Apoptosis was detected using the Annexin V-FITC/PI apoptosis detection kit (BD Biosciences, USA, Cat#556547) according to the manufacturer's instructions. BMSCs or TPC-1 cells (including floating cells) were collected 48 hours after transfection, washed twice with pre-chilled PBS and resuspended in $1 \times$ binding buffer at a density of 1×10^6 /mL. One hundred microliters of cell suspension (containing 1×10^5 cells) were mixed with 5 μ L Annexin V-FITC and 5 μ L PI, gently vortexed and incubated at room temperature in the dark for 15 minutes. Four hundred microliters of $1 \times$ binding buffer were added and samples were analyzed within 1 hour using a flow cytometer (BD FACSCanto II, USA). At least 10,000 cells were collected per sample. Data were analyzed using FlowJo software (v10.8, USA). Annexin V-positive/PI-negative cells were considered early apoptotic cells and Annexin V-positive/PI-positive cells were considered late apoptotic/necrotic cells. The total apoptosis rate (early + late) was calculated. Each experiment was independently repeated 3 times as biological replicates.

Western blot

The Western blot experiment was based on the report by Ma *et al.* (2024) and modified accordingly: BMSCs or TPC-1 cells were collected 48 hours after transfection, washed twice with pre-chilled PBS and lysed on ice for 30 minutes with RIPA lysis buffer (Beyotime, China) containing protease inhibitor cocktail (Roche, Switzerland), with vortexing every 10 minutes. After centrifugation at $12,000 \times g$ for 15 minutes at 4°C, the supernatant was collected. Protein concentration was determined using the

BCA protein assay kit (Thermo Fisher Scientific, USA) according to the standard curve.

Electrophoresis and transfer: Thirty micrograms of total protein were mixed with 5× loading buffer and boiled at 100°C for 5 minutes for denaturation. Protein samples were separated by 10% or 12% SDS-PAGE gel electrophoresis (constant voltage 80 V for 30 minutes, then 120 V for 60 minutes) and transferred to PVDF membranes (Millipore, USA) by wet transfer method (constant current 300 mA, 90 minutes, on ice).

Immunodetection: After transfer, membranes were blocked with 5% non-fat milk in TBST buffer at room temperature for 1 hour. Primary antibodies were added and incubated overnight at 4°C. Primary antibodies used included: rabbit anti-Bcl-2 monoclonal antibody (Abcam, USA, Cat#ab32124, dilution 1:1000), rabbit anti-cleaved caspase-3 polyclonal antibody (Cell Signaling Technology, USA, Cat#9661, dilution 1:1000), rabbit anti-cleaved caspase-9 polyclonal antibody (Cell Signaling Technology, USA, Cat#7237, dilution 1:1000) and mouse anti-GAPDH monoclonal antibody (Proteintech, USA, Cat#60004-1-Ig, dilution 1:5000). The next day, membranes were washed 3 times with TBST for 10 minutes each. Horseradish peroxidase-conjugated secondary antibodies were added and incubated at room temperature for 1 hour. Secondary antibodies included: HRP-conjugated goat anti-rabbit IgG (Cell Signaling Technology, USA, Cat#7074, dilution 1:3000) and HRP-conjugated goat anti-mouse IgG (Cell Signaling Technology, USA, Cat#7076, dilution 1:3000). After incubation, membranes were washed 3 times with TBST for 10 minutes each.

Exposure and quantification: Enhanced chemiluminescence solution (ECL, Millipore, USA) was applied to the membranes and images were captured using a chemiluminescence imaging system (ChemiDoc XRS+, Bio-Rad, USA). Band intensities were analyzed using Image Lab software (Bio-Rad, USA) or ImageJ software (NIH, USA). The relative expression of target proteins was expressed as the ratio of target protein gray value to GAPDH gray value and normalized to the control group set as 1. Each experiment was independently repeated 3 times as biological replicates.

Definition of outcome variables

Disease-free survival (DFS) was defined as the time from the date of surgery to the date of first documented disease recurrence (local, regional, or distant), or death from any cause, whichever occurred first. Overall survival (OS) was defined as the time from the date of surgery to the date of death from any cause. Patients alive and recurrence-free at the last follow-up were censored at that date. TNM staging was performed according to the 8th edition of the AJCC/UICC staging system and was analyzed both as a stratification variable and as a potential confounder in multivariable models.

Statistical analysis

Statistical analysis was performed using SPSS 27.0 software. Measurement data were expressed as mean ± standard error of the mean (SEM). For comparisons between two groups, Student's t-test was used for normally distributed data with homogeneous variance and the Mann-Whitney U test was used for non-normally distributed data with homogeneous variance. For comparisons among multiple groups, one-way analysis of variance (ANOVA) followed by Tukey's HSD post-hoc test was used. Repeated measurement data were analyzed by repeated measures ANOVA. Survival curves were plotted using the Kaplan-Meier method and differences in survival between groups were compared using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model to calculate hazard ratios (HR) and their 95% confidence intervals (CI). Multivariate analysis used backward stepwise regression to screen for independent prognostic factors. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic value of serum LINC01116 expression for PTC, calculating the area under the curve (AUC), sensitivity, specificity and Youden index. The correlation between LINC01116 expression and clinicopathological parameters was analyzed using the chi-square test or Fisher's exact test. All in vitro experiments were independently repeated 3 times as biological replicates, with 3-5 technical replicates each time. All statistical tests were two-sided and $P < 0.05$ was considered statistically significant.

Sample size justification: The sample size of 60 PTC patients and 30 controls was determined based on a power calculation using G*Power 3.1. Assuming a two-sided $\alpha = 0.05$, power=0.80 and an expected effect size (Cohen's d) of 0.65 for serum LINC01116 expression difference between PTC and controls based on a pilot study ($n=10$ per group), the minimum required sample was 52 PTC patients and 26 controls. Considering a 15% dropout rate, we enrolled 60 PTC patients and 30 controls. For survival analysis, PTC patients were divided into high- and low-LINC01116 expression groups using the median serum expression level ($2^{-\Delta \Delta Ct} = 3.87$) as the cut-off value. Patients with expression above the median were assigned to the high-expression group ($n=30$) and those below or equal to the median to the low-expression group ($n=30$).

Variables entered into the multivariable Cox regression model included: age (continuous), sex (male/female), TNM stage (I/II vs. III/IV), lymph node metastasis (yes/no), tumor size (≥ 2 cm vs. < 2 cm) and LINC01116 expression level (high/low). Variable selection was performed using backward stepwise regression (entry criterion $P < 0.10$, removal criterion $P > 0.05$). No missing data were present for the main exposure (LINC01116) and key clinical variables. For survival analysis, patients who were lost to follow-up ($n=3$, 5%) were censored at their last known follow-up date.

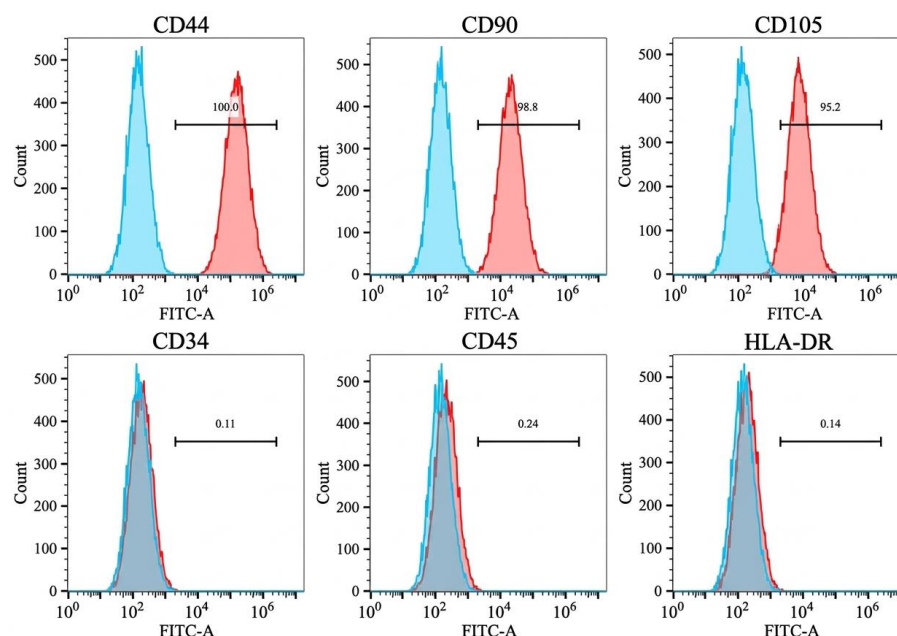


Fig. 1: Flow cytometric identification of rat BMSCs.

Note: CD44, CD90, CD105; negative markers: CD34, CD45, HLA-DR. Numbers represent the percentage of positive cells (mean $\pm$ SEM, $n=3$).

Table 1: Baseline characteristics.

Characteristic	PTC patients (n=60)	Healthy controls (n=30)	P value
Age (years, mean $\pm$ SD)	59.77 $\pm$ 10.48	59.37 $\pm$ 9.46	0.862
Sex			0.732
	Male 38(63.33)	20(66.67)	
	Female 22(36.67)	10(33.33)	
Tumor size			-
	≥ 2 cm 32(53.33)	-	-
	<2 cm 28(46.67)	-	-
Lymph node metastasis			-
	yes 25(41.67)	-	-
	no 35(58.33)	-	-
TNM stage			-
	III+IV 22(36.67)	-	-
	I+II 38(63.33)	-	-
LINC01116			-
	high 30(50.00)	-	-
	low 30(50.00)	-	-

Complete-case analysis was used for multivariable models. The median follow-up duration was 42 months (range: 6 – 60 months). During follow-up, DFS events occurred in 23 patients (38.3%) and OS events occurred in 19 patients (31.7%). Subgroup and interaction analyses were not performed due to the limited sample size and insufficient statistical power. Sensitivity analyses were performed by excluding patients lost to follow-up ($n=3$) to assess the robustness of survival results; the findings remained consistent (data not shown).

RESULTS

Baseline characteristics

A total of 78 patients with suspected PTC were initially screened. Among these, 12 were excluded due to prior treatment ($n=5$), other malignancies ($n=4$) or incomplete clinical data ($n=3$). An additional 6 patients declined to participate. Finally, 60 patients were enrolled and included

in the analysis. Among the 60 patients, 57 (95%) completed follow-up and 3 (5%) were lost to follow-up. For the control group, 42 healthy individuals were screened, of whom 12 were excluded due to age/sex mismatch ($n=8$) or abnormal thyroid function ($n=4$), leaving 30 controls enrolled. The baseline demographic and clinicopathological characteristics of the enrolled participants are summarized in table 1.

Flow cytometry identification of BMSCs

To confirm that the isolated and cultured cells possessed BMSC characteristics, third-passage cells were subjected to flow cytometry analysis. After gating viable cells based on FSC/SSC and further gating single cells to exclude aggregates, the results showed that the obtained cells highly expressed the positive BMSC markers CD44 (90.0%), CD90 (99.99%) and CD105 (94.48%), while the negative markers CD34 (0.21%), CD45 (0.91%) and HLA-DR (0.25%) were expressed at rates below 2% (Fig. 1).

LINC01116 is highly expressed in PTC

LINC01116 expression was significantly increased in serum samples from PTC patients compared with healthy controls ($P < 0.05$) (Fig. 2A). Survival analysis found that patients with high LINC01116 expression had a lower disease-free survival (DFS) rate ($HR=2.067$, $P=0.0264$) (Fig. 2B) and patients with high LINC01116 expression had a significantly lower overall survival (OS) rate compared with those with low LINC01116 expression ($HR=2.081$, $P=0.0244$) (Fig. 2C). The ROC curve shows that the expression level of LINC01116 is highly sensitive to the diagnosis of the disorder (Fig. 2D).

Analysis of independent risk factors for survival of papillary thyroid carcinoma

TNM stage ($P=0.035$) and serum expression of LINC01116 ($P=0.028$) were independent risk factors for DFS of PTC patients (Figs. 3A-B). TNM stage ($P=0.033$) and serum expression of LINC01116 ($P=0.013$) were independent risk factors for OS (Figs. 3C-D).

LINC01116 promotes PTC cell proliferation and migration

To characterize LINC01116 expression in PTC, we examined its basal expression levels in human normal thyroid cell lines and PTC cell lines. RT-qPCR results showed that compared with the normal thyroid cell line NTHY-ORI3-1, LINC01116 was significantly upregulated in PTC cell lines TPC-1, PTC and B-CPAP ($P < 0.05$) (Fig. 4A). TPC-1 cells showed the highest LINC01116 expression and were therefore selected for subsequent functional experiments. To investigate the biological function of LINC01116, we knocked down LINC01116 expression in TPC-1 cells using siRNA and overexpressed LINC01116 using the pcDNA3.1 vector. RT-qPCR results 48 hours after transfection showed that compared with the si-NC group, si-LINC01116#1 significantly reduced LINC01116 expression ($P < 0.001$) (Fig. 4B); compared with the pcDNA-NC group, the pcDNA-LINC01116 transfection group showed significantly increased LINC01116 expression ($P < 0.001$) (Fig. 4C), confirming good transfection efficiency. CCK-8 assay results showed that after LINC01116 knockdown, TPC-1 cell viability was significantly lower than the si-NC group starting from 24 hours, with the inhibitory effect increasing over time. At the 96-hour time point, the OD value of the si-LINC01116#1 group was reduced by 37.3% compared to the si-NC group ($P < 0.001$) (Fig. 4D). Conversely, after LINC01116 overexpression, cell viability significantly increased, with the OD value at 96 hours increased by 37.0% compared to the pcDNA-NC group ($P < 0.001$) (Fig. 4F). Transwell migration assays examining the effect of LINC01116 on TPC-1 cell migration showed that compared with the si-NC group (156.8 ± 1.1 cells/field), LINC01116 knockdown significantly reduced the number of migrated cells to 77.8 ± 0.8 cells/field ($P < 0.001$), representing a 50.4% inhibition rate (Fig. 4E). Conversely, after LINC01116 overexpression, the number of migrated

cells increased from 142.6 ± 11.3 cells/field in the pcDNA-NC group to 241.8 ± 18.5 cells/field ($P < 0.001$) (Fig. 4G).

Verification of LINC01116 knockdown effect on cell migration using a second independent siRNA

To exclude potential off-target effects from a single siRNA, we repeated the Transwell migration assay using a second independent siRNA (si-LINC01116#2) to verify the specificity of LINC01116 knockdown on TPC-1 cell migration. Transwell migration assay results (Fig. 5) showed that the si-LINC01116#2 group had 78.5 ± 0.8 migrated cells/field, significantly reduced compared to the si-NC group (156.8 ± 1.1 cells/field) ($t=12.38$, $P < 0.001$), with an inhibition rate of 49.9%. This result was highly consistent with the migration inhibition rate observed with si-LINC01116#1 (50.4%, 77.8 ± 0.8 migrated cells/field), with no significant difference between the two siRNA groups ($t=0.62$, $P=0.57$). These results demonstrate that two independent siRNAs targeting LINC01116 produced consistent migration inhibition phenotypes, confirming the specificity of LINC01116 regulation of TPC-1 cell migration and excluding off-target effects.

LINC01116 promotes the development of PTC by regulating the apoptosis of BMSCs

As revealed by flow cytometry, after knocking down the expression of LINC01116, knockdown of LINC01116 significantly increased BMSC apoptosis ($P < 0.05$; Fig. 6A), while overexpression of LINC01116 significantly reduced BMSC apoptosis ($P < 0.05$) (Fig. 6B). To further depict the impact on apoptosis, we conducted Western blot to detect cell apoptosis-related proteins. It was found that silencing of LINC01116 decreased the expression of Bcl-2 and increased the expression of Cleaved Caspase3 and Cleaved Caspase9 (Fig. 6C). After overexpression of LINC01116, the expression of Bcl-2 was significantly increased and the expressions of Cleaved Caspase3 and Cleaved Caspase9 declined (Fig. 6D), indicating that LINC01116 promotes PTC progression by regulating BMSC apoptosis.

Rescue experiments confirm the functional specificity of LINC01116

LINC01116 expression recovery: RT-qPCR results (Fig. 7A) showed that LINC01116 expression in the knockdown group (si-LINC01116#1 + pcDNA-NC) decreased to $19\% \pm 3\%$ of the control group ($P < 0.001$); the Rescue group (si-LINC01116#1 + pcDNA-LINC01116-res) showed LINC01116 expression restored to $75\% \pm 6\%$ of the control group, significantly higher than the knockdown group ($t=8.24$, $P < 0.001$), representing a 69.1% recovery rate. Cell proliferation recovery: CCK-8 assay results (Fig. 7B) showed that cell viability in the knockdown group was significantly reduced at 96 hours compared to the control group ($P < 0.001$); the Rescue group showed significantly increased cell viability compared to the knockdown group ($P=0.002$), reversing the proliferation inhibition caused by knockdown.

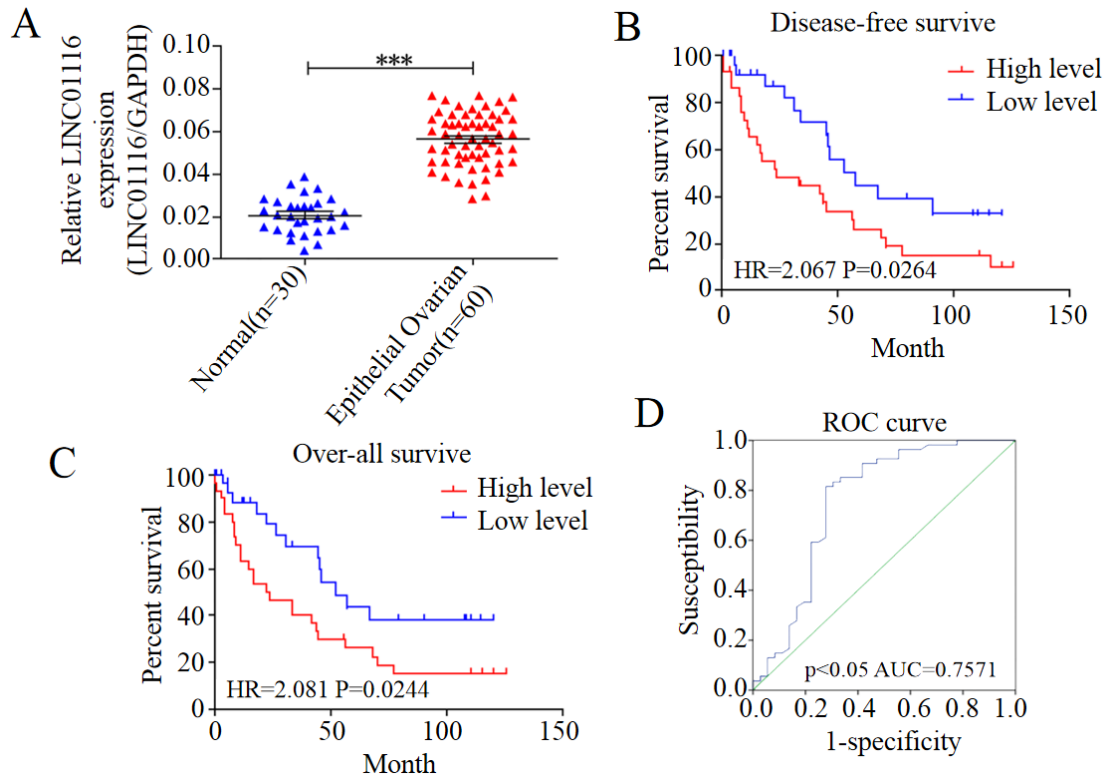


Fig. 2: Up-regulation of LINC01116 in serum of PTC patients (A). RT-qPCR analysis of LINC01116 expression in serum samples from 60 PTC patients and 30 healthy controls. Data are presented as scatter plots with mean $\pm$ SEM. ***P < 0.001 vs. control group. (B). Kaplan-Meier survival curves for disease-free survival (DFS) according to LINC01116 expression levels (high vs. low, n=30 per group). (C). Kaplan-Meier survival curves for overall survival (OS) according to LINC01116 expression levels (n=30 per group). (D). ROC curve analysis of serum LINC01116 expression for PTC diagnosis

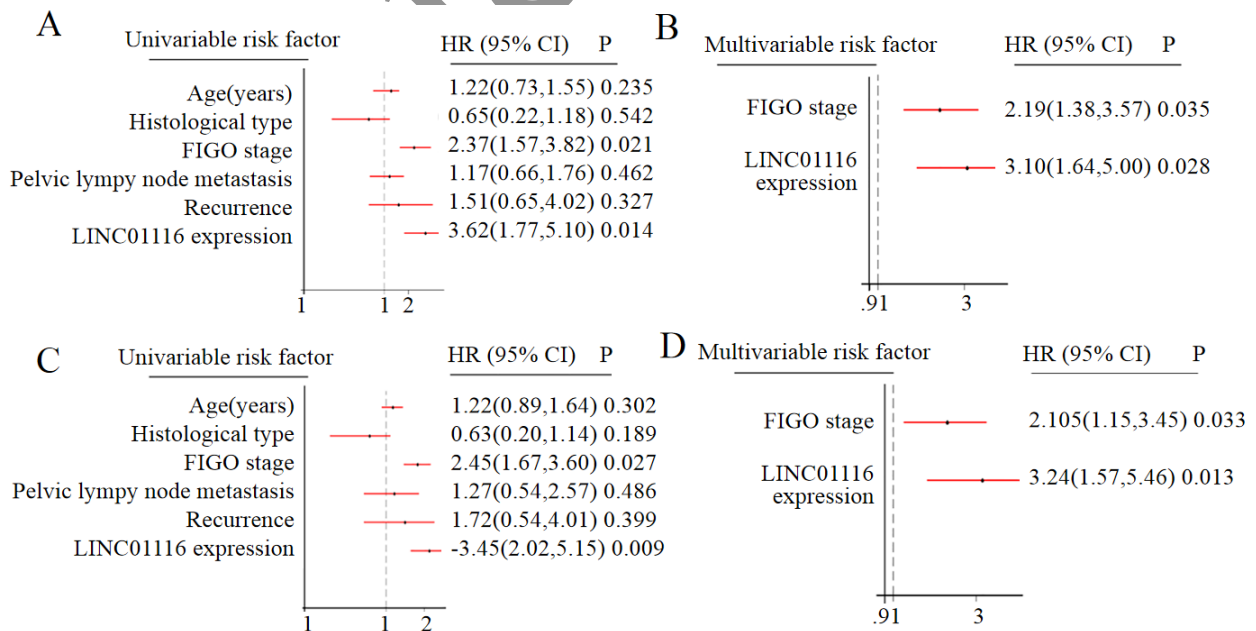


Fig. 3: Analysis of independent risk factors for survival of papillary thyroid carcinoma. (A-B). COX univariate and multivariate analysis between LINC01116 serum expression level and DFS. (C-D). COX univariate and multivariate analysis between LINC01116 serum expression level and OS.

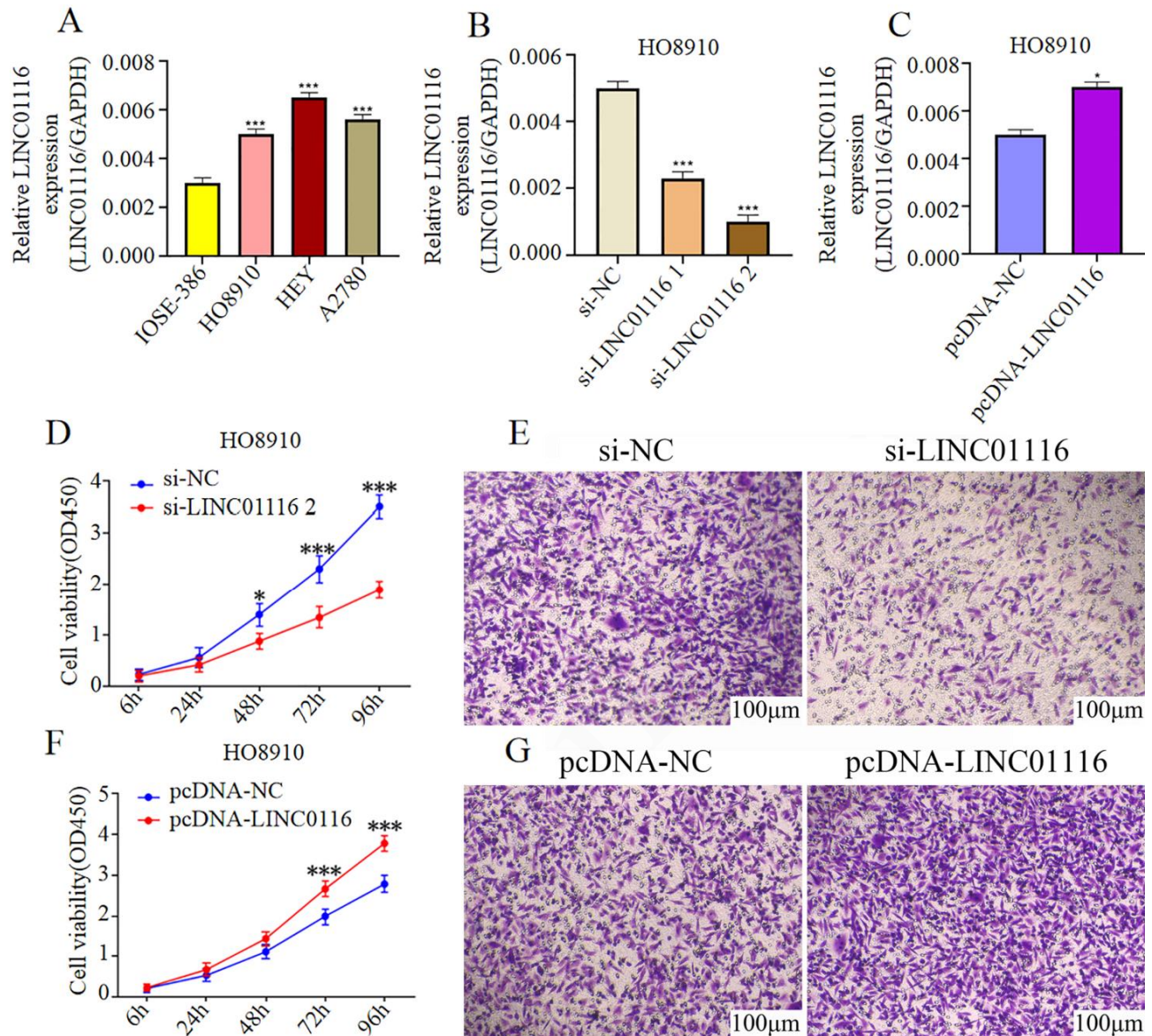


Fig. 4: High LINC01116 expression promotes PTC cell proliferation and migration.

(A).RT-qPCR analysis of LINC01116 expression in NTHY-ORI3-1 and PTC cell lines (TPC-1, PTC, B-CPAP).

(B-C). RT-qPCR validation of LINC01116 knockdown (B) and overexpression (C) efficiency in TPC-1 cells after transfection. (D-E).CCK-8 assay detection of cell viability after transfection with si-LINC01116 (D) or pcDNA-LINC01116 (E). (F-G).Transwell migration assay detection of cell migration ability after transfection with si-LINC01116 (F) or pcDNA-LINC01116 (G). Left panels show representative migration images, right panels show quantitative analysis of migrated cells per field. Scale bar = 100 μ m. Data are presented as mean $\pm$ SEM from three independent experiments.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. respective control groups.

Apoptosis recovery: Flow cytometry results (Fig. 7C) showed that the total apoptosis rate in the knockdown group was significantly increased compared to the control group ($P < 0.001$); the Rescue group showed a reduced apoptosis rate, significantly lower than the knockdown group ($P = 0.001$), reversing the apoptosis promotion caused by knockdown. **Apoptosis-related protein recovery:** Western blot results (Fig. 7D) showed that compared with the control group, Bcl-2 expression was decreased ($P <$

0.001) and cleaved caspase-3 and cleaved caspase-9 expression were increased (both $P < 0.001$) in the knockdown group; compared with the control group, Bcl-2 expression in the Rescue group was decreased (but higher than the knockdown group, $P < 0.01$) and cleaved caspase-3 and cleaved caspase-9 expression were higher than the control group (but lower than the knockdown group, both $P < 0.01$).

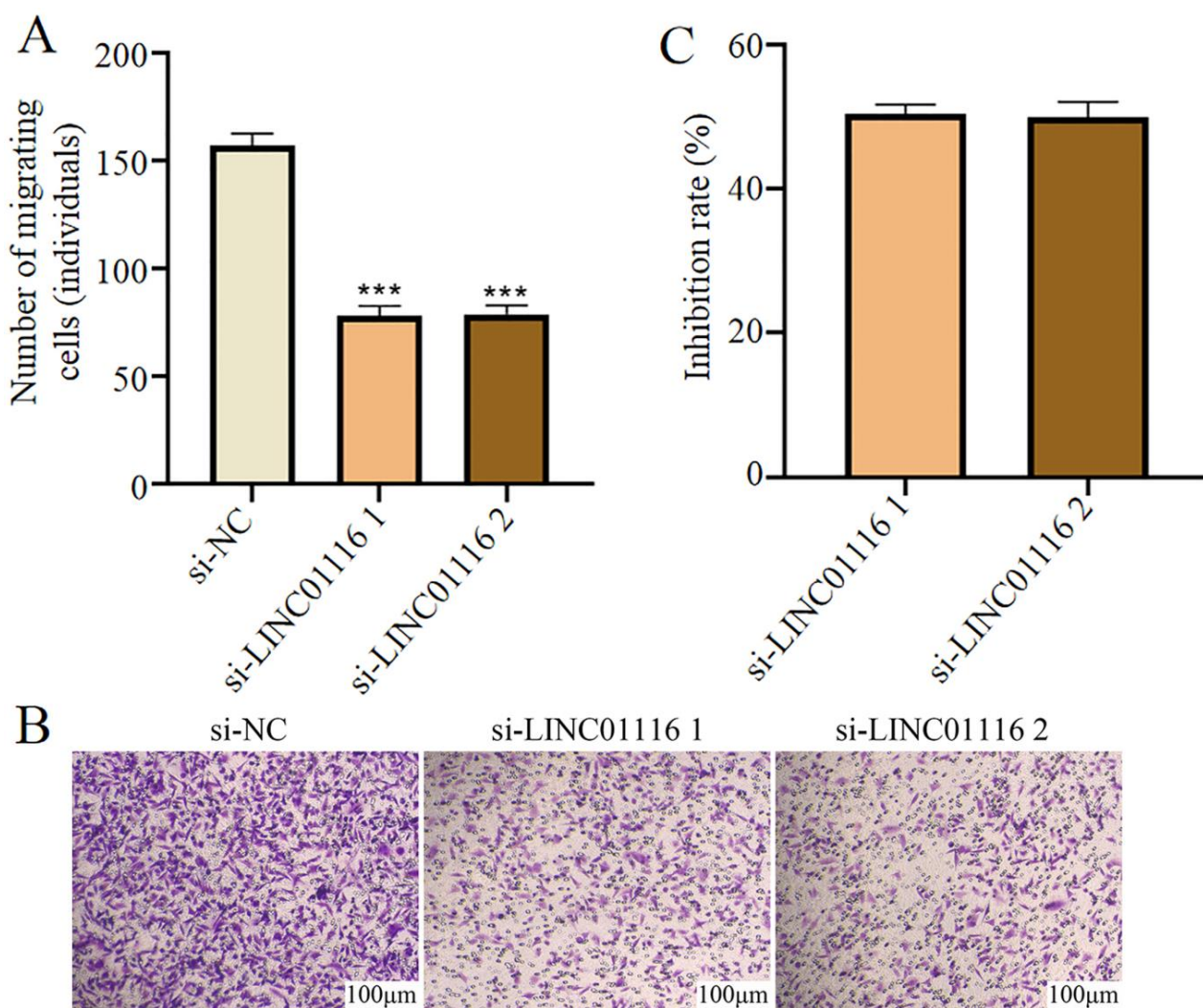


Fig. 5: Verification of LINC01116 knockdown effect on TPC-1 cell migration using a second independent siRNA. (A). Transwell migration assay detecting changes in TPC-1 cell migration ability after si-LINC01116#2 transfection. Data are presented as mean $\pm$ SEM from three independent biological replicates, with 3 technical replicates per experiment and 5 random fields counted per well. *** $P < 0.001$ vs. si-NC group; n.s., not significant; (B) Representative migration images (scale bar: 50 μ m); (C) Comparison of migration inhibition rates.

RT-qPCR primer validation

To ensure the accuracy and specificity of RT-qPCR detection, we validated the primers for LINC01116 and the reference gene GAPDH using standard curve and melting curve analysis. Standard curves were constructed using 5 gradients of 10-fold diluted cDNA templates. Results showed that the amplification efficiency of LINC01116 primers was 96.3% (slope -3.41, $R^2=0.998$) and the amplification efficiency of GAPDH primers was 98.1% (slope -3.37, $R^2=0.999$), both within the recommended range of 90%-110%, indicating good amplification efficiency (Figs. 8A, 8C). Melting curve analysis showed single sharp peaks for both LINC01116 and GAPDH amplification products, with melting temperatures of 83.5°C and 86.2°C, respectively. No primer dimers or non-specific amplification peaks were observed (Figs. 8B, 8D), confirming high primer specificity.

DISCUSSION

PTC is a common endocrine malignancy that poses a serious threat to patient health. Approximately 30-40% of patients develop local lymph node metastasis and 1-4% develop distant metastasis. Patients with multi-organ metastasis have a particularly poor prognosis, with a 5-year survival rate of only 15.3% (Abutalib *et al.*, 2023). Although research into the molecular mechanisms of PTC development and progression has deepened in recent years, effective diagnostic markers and therapeutic targets remain limited. Long non-coding RNAs (lncRNAs) are a class of non-coding RNA molecules exceeding 200 nucleotides in length, mainly transcribed by RNA polymerase II.

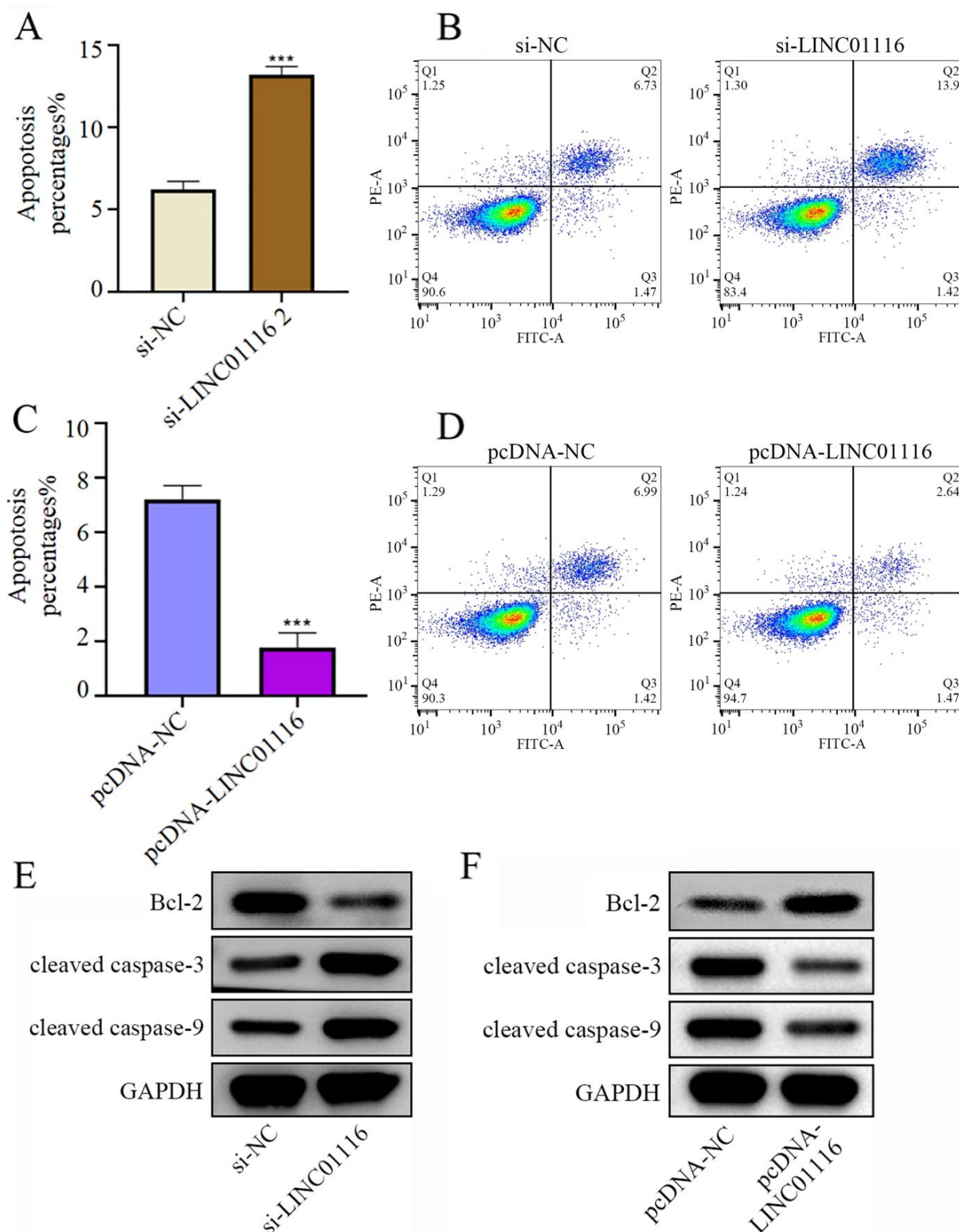


Fig. 6: LINC01116 inhibits the apoptosis of BMSCs.

(A-D). Flow cytometry of apoptosis of BMSCs upon transfection with si-LINC01116 or pcDNA-LINC01116, or NC; (E-F). Western blot analysis of Bcl-2, Cleaved Caspase3 and Cleaved Caspase9 expression upon transfection.

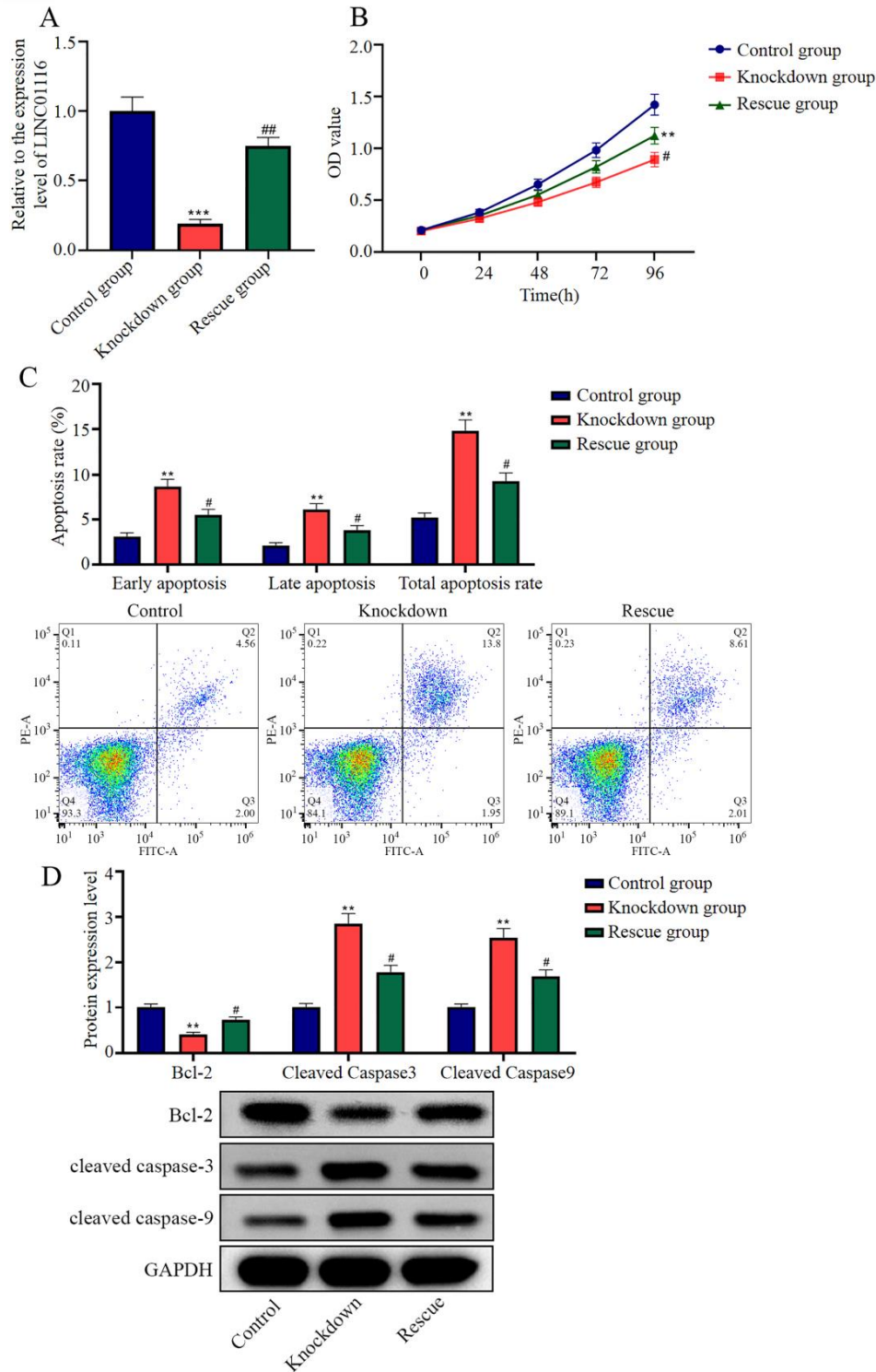


Fig. 7: Rescue experiments confirm the functional specificity of LINC01116.

(A) RT-qPCR detection of LINC01116 expression levels in each group of rescue experiments. Control group (si-NC + pcDNA-NC), knockdown group (si-LINC01116#1 + pcDNA-NC), rescue group (si-LINC01116#1 + pcDNA-LINC01116-res). *** $P < 0.001$ vs. control group; ## $P < 0.01$ vs. knockdown group; (B) CCK-8 assay detection of cell viability in each group of rescue experiments. ** $P < 0.01$ vs. control group; # $P < 0.05$ vs. knockdown group; (C) Flow cytometry detection of apoptosis rates in each group of rescue experiments. ** $P < 0.01$ vs. control group; # $P < 0.05$ vs. knockdown group; (D) Western blot detection of Bcl-2, cleaved caspase-3, and cleaved caspase-9 expression in each group of rescue experiments.

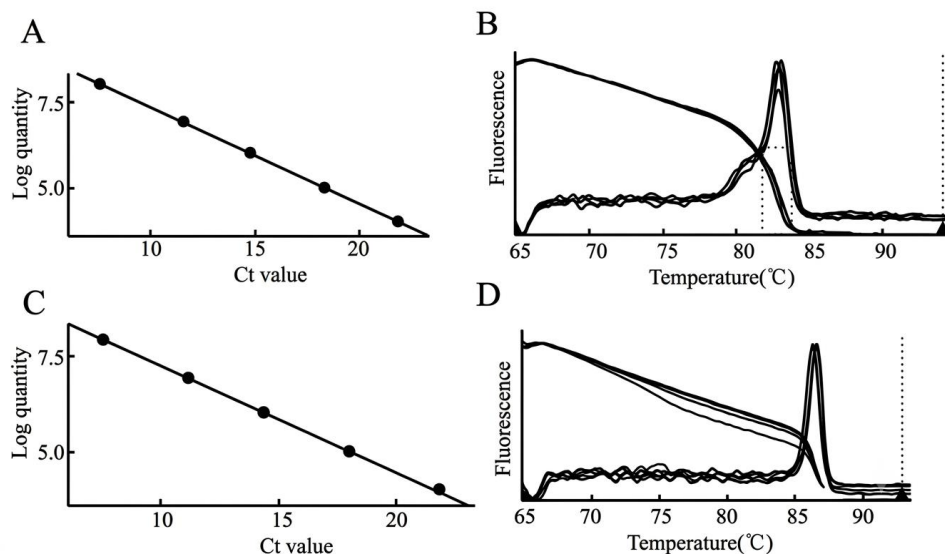


Fig. 8: Standard curve and melting curve analysis validating the efficiency and specificity of LINC01116 and GAPDH primers. (A) Standard curve for LINC01116 primers; (B). Melting curve for LINC01116 primers; (C). Standard curve for GAPDH primers; (D). Melting curve for GAPDH primers. Data are presented as mean $\pm$ SEM from three technical replicate experiments. All experiments were repeated three times with similar results.

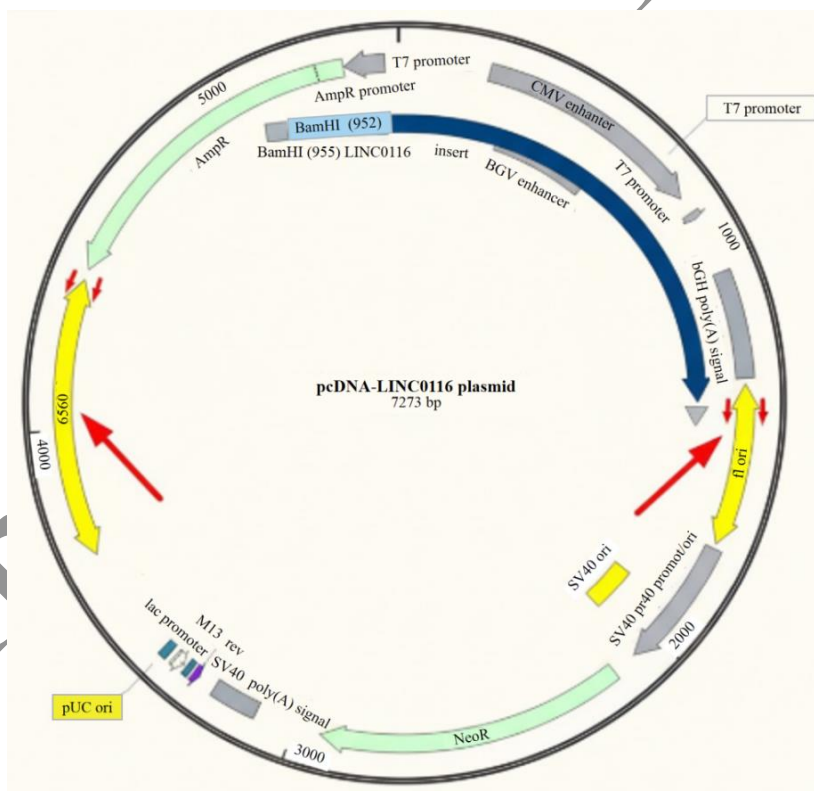


Fig. 9: pcDNA-LINC01116 plasmid map.

Although lncRNAs do not encode proteins, molecular biology studies have confirmed their involvement in regulating malignant biological behaviors such as cell proliferation, apoptosis and migration, thus playing key roles in tumor regulation (Miao *et al.*, 2024, Hussain *et al.*, 2024). LINC01116, as a newly discovered lncRNA, is

aberrantly expressed in various cancers including lung cancer, gastric cancer, colorectal cancer, glioma and osteosarcoma (Zhang *et al.*, 2024). Related studies have indicated that LINC01116 is closely associated with cellular senescence and apoptosis and can be used to predict prognosis and tumor immune microenvironment in

lung adenocarcinoma patients (Fang *et al.*, 2022). However, the expression characteristics and biological functions of LINC01116 in PTC remain unclear.

This study found that high LINC01116 expression significantly correlated with lower DFS and OS in PTC patients. Multivariate Cox regression analysis showed that TNM stage and LINC01116 expression levels were independent prognostic factors for DFS and OS. ROC curve analysis demonstrated that serum LINC01116 expression had good diagnostic value for PTC ($AUC=0.892$). These findings suggest that LINC01116 may serve as both a diagnostic marker and a prognostic indicator for PTC. The tumor microenvironment plays a crucial role in tumor progression, with bone marrow mesenchymal stem cells (BMSCs) serving as important stromal cells that regulate tumor cell proliferation, migration and drug resistance through paracrine pathways and cell-cell interactions (Wang *et al.*, 2024). However, the specific mechanism of BMSCs in PTC progression has not been fully elucidated. Our functional experiments revealed that LINC01116 overexpression inhibited BMSC apoptosis, manifested by upregulated Bcl-2 expression and downregulated cleaved caspase-3/9 expression, while LINC01116 knockdown induced BMSC apoptosis. This suggests that LINC01116 may promote PTC progression by regulating BMSC apoptosis and remodeling the tumor microenvironment.

Furthermore, this study confirmed the functional specificity of LINC01116 through multiple independent siRNA knockdown experiments and rescue experiments. Three independent siRNAs targeting different regions of LINC01116 effectively knocked down its expression. Using a second independent siRNA (si-LINC01116#2) to repeat migration experiments yielded consistent migration inhibition phenotypes with si-LINC01116#1, excluding off-target effects. Further rescue experiments using an siRNA-insensitive LINC01116 overexpression plasmid showed that restoring LINC01116 expression partially reversed the proliferation inhibition, apoptosis promotion and apoptosis-related protein changes caused by knockdown. This confirms that the observed phenotypic changes are specifically mediated by LINC01116. Several limitations of this study should be acknowledged. First, the sample size (60 PTC patients and 30 controls) is relatively small, which may limit the generalizability and statistical power for subgroup analyses. Second, this is a single-center study, which may introduce selection bias and limit external validity. Third, although we used three independent siRNAs and rescue experiments to minimize off-target effects, unmeasured confounding cannot be entirely excluded in the clinical observational component. Fourth, the prognostic analysis was based on a relatively short follow-up period (median 42 months) and longer follow-up is needed to confirm the survival associations. Fifth, external validation in an independent PTC cohort is lacking. Sixth, the direct molecular target of LINC01116

was not identified and the causal relationship between LINC01116 and BMSC apoptosis requires further validation using co-culture systems and in vivo models.

The findings of this study are derived from a single-center Chinese PTC cohort with a predominance of middle-aged and elderly patients. While LINC01116 showed consistent expression and functional effects across multiple PTC cell lines, the generalizability of these results to other PTC populations—particularly those with different ethnic backgrounds, younger age groups, or distinct histological subtypes—requires further validation in multi-center, diverse cohorts. Nonetheless, the consistent effects observed with multiple independent siRNAs and the conserved nature of the Bcl-2/caspase apoptosis pathway suggest that LINC01116 may play a similar role in broader PTC populations, warranting future external validation studies.

CONCLUSION

In conclusion, this study demonstrates that LINC01116 is highly expressed in PTC, correlates with poor patient prognosis and promotes PTC progression by inhibiting BMSC apoptosis. These findings provide new insights into the molecular mechanisms of PTC and offer a theoretical basis for targeting LINC01116 in PTC treatment strategies.

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Author's contributions

Huan He: Research design and conception, experimental operations (cell culture, transfection, RT-qPCR, CCK-8, flow cytometry, Western blot), data collation and analysis, Fig. preparation, initial draft writing; Kehao Liu: Overall research guidance and supervision, Experimental operations (BMSC isolation and characterization, Transwell migration assays, plasmid construction), data collection, manuscript review and revision, final version approval and statistical analysis, literature review. All authors have read and approved the publication of this manuscript.

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Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical approval

This study was approved by the Ethics Committee of The Third People's Hospital of Chengdu (Approval No.: 2025-S-2863). This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflict of interest

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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