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MYB/*LINC00092* regulatory axis promotes the progression of papillary thyroid carcinoma

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Abstract

Introduction: Thyroid carcinoma is the most frequent malignancy in different endocrine-related tumours. In this study, we demonstrated a long non-coding RNA *LINC00092*-associated molecular mechanism in promoting the progression of papillary thyroid carcinoma (PTC).
Material and methods: The expression of *LINC00092* was analysed in the The Cancer Genome Atlas Thyroid Cancer (TCGA-THCA) patient cohorts and further determined by q-PCR. (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) (MTT) assay, and wound healing assay confirmed the function of *LINC00092* in migration and proliferation. Q-ChIP validated the transcriptional target. Luciferase reporter assay validated the miRNA-mRNA target.
Results: The analysis in patient cohorts and in PTC TPC-1 cells showed that the expression of *LINC00092* was repressed in thyroid carcinoma. In addition, the expression of *LINC00092* was negatively associated with the advanced thyroid TNM stages. *LINC00092* repressed epithelial-mesenchymal transition (EMT), migration, and proliferation of TPC-1 cells. Interestingly, we identified that MYB, a well-studied tumour promoter, is a transcription factor of *LINC00092*, thereby the expression of *LINC00092* was directly repressed by MYB. Furthermore, miR-4741 was also validated as a direct target of MYB and was induced by MYB. Notably, *LINC00092* was repressed by miR-4741 through the direct 3′-untranslational region (3′-UTR) target. Therefore, MYB induced EMT of TPC-1 cells by repressing *LINC00092* directly or indirectly via miR-4741.
Conclusions: Our study validated that *LINC00092* is a tumour suppressor lncRNA in PTC. MYB directly or indirectly represses *LINC00092,* which contributes to the PTC progression. MYB, *LINC00092*, and miR-4741 form a coherent feed forward loop. The axis of MYB-*LINC00092* promotes progression of PTC. **(Endokrynol Pol 2024; 75 (1): 27–34)**

Key words: *papillary thyroid carcinoma; LINC00092; MYB; miR-4741*

Introduction

Thyroid carcinoma is the most frequent malignancy in different endocrine-related tumours. The occurrence rate of thyroid carcinoma has been increasing, and the rate takes 9th place in all cancers [1]. Most thyroid carcinomas are categorized as papillary thyroid carcinoma (PTC), which accounts for almost 80% of all cases [2]. Recent therapeutic regimens including surgery and iodine radiotherapy keep the overall 5-year survival rate over 95%. Nevertheless, some patients still develop progressive diseases due to the PTC metastasis and recurrence. Previous studies indicate that approximately 10–15% of PTC patients receiving regular regimens will develop metastasis [3]. Therefore, there is an urgent need to uncover the molecular mechanisms of PTC metastasis and provide possible ways to prevent its progression.

Long non-coding RNAs (lncRNAs) are composed of over 200 nucleotides, which lack protein coding ability [4]. Accumulative studies have shown that the occurrence and the progression of cancers are associated with dysregulated lncRNAs [5]. Our previous study showed that lncRNA *ZFAS1* promotes the metastasis of PTC via regulation of the miR-373-3p/MMP3 axis. In addition, *ZFAS1* is a target of transcription factor CREB3, which is also involved in the regulatory program in PTC progression [6]. Our previous results indicate that dysregulated lncRNA and its associated transcription factor may play an important role in the progression of PTC. Recently, numerous studies have suggested that lncRNA *LINC00092* may serve as a tumour suppressor in different cancers, including breast cancer [7] and lung cancer [8], whereas the function of *LINC00092* in PTC is still unclear. Therefore, it is intriguing to investigate the role of *LINC00092* in PTC metastasis and progression.

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The tumour promoter MYB is a transcription factor recognizing the binding motif t/cAACt/gG in the promoter of target genes [9]. In physiological conditions, MYB mainly stays in the high turnover tissues such as the haematopoietic system and intestinal epithelial tissues [10]. MYB can be stimulated by external signals via the extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K) signalling pathways [11, 12]. The dysregulation of MYB was validated to be correlated to the progression of different cancers including breast cancer, colorectal cancer, and leukaemia [13]. Here we set out to demonstrate that MYB functions as a transcription factor of *LINC00092* in PTC.

Material and methods

Cell culture and patient samples

PTC cell line TPC-1 and a normal cell line Nthy-ori 3-1 were purchased from Sigma-Aldrich. Cells were cultured in RPMI 1640 medium with 10% foetal bovine serum (FBS, Gibco, USA), penicillin/streptomycin (2%), and amphotericin B (1%) at 37 and 5% carbon dioxide (CO_2). Papillary thyroid carcinoma tissues were collected from 5 different patients who received treatments in our hospital from January 2019 to December 2021. The experiment on human samples was approved by the Ethics Committee (No. 2021011). The work associated with human samples was conducted in accordance with the Declaration of Helsinki (1964).

Vector cloning

Overexpression of *LINC00092* and MYB was performed by transfected with the pcDNA3.1 system. The construction of ectopic vector containing the entire mRNA of *LINC00092* and CDS region of MYB was accomplished and validated by Maokang Bio (Shanghai, China). For luciferase assay, 3′-UTR of *LINC00092* was cloned into pGL3-control vector (Promega, USA). The seed match sequence of miR-4741 in the 3′-UTR of *LINC00092* was mutated by using Mut Express II Fast Mutagenesis Kit V2 (Vazyme, China) according to the manufacturer's instructions.

Transfection

For cell transfection, cells were seeded into 6-well plates at a density of 2×10^5 cells/well and cultivated overnight. When cell confluence reached 80%, the transfection process was performed based on the manufacturer's instructions. Briefly, for transfection of vectors, Lipofectamine 2000 (Invitrogen, USA, 10 μL) was used and mixed with vectors (2.0 μg) in Opti-MEM media (Gibco, USA). The mixture was incubated at room temperature for 5 min, and then added to the 6-well plate dropwise for 48-hour incubation. For transfection of miRNAs, HiPerFect (Qiagen, Germany, 10 μL) was used and mixed with miRNAs (25 nM) in Opti-MEM media. The mixture was incubated at room temperature for 5 min and then added to the 6-well plate dropwise for 48-hour incubation.

Quantitative real-time polymerase chain reaction (qPCR)

qPCR was performed after different treatments. Total RNAs were isolated by using a High Pure RNA Isolation Kit (Roche, Switzerland) following the manufacturer's instructions. A verso cDNA Synthesis Kit (Thermo Fisher, USA) was used to reverse transcribe RNA to cDNA. Gene expression was measured by qPCR with SYBR Green on the LightCycler 480 platform (Roche, Switzerland). The primers used in qPCR analysis were listed in Table 1 (5′–3′). The relative expression of genes was calculated by using the 2^(-ΔΔCt) method.

Table 1. ***Primers used in quantitative polymerase chain reaction (q-PCR) analysis***

LINC00092 Forward	TGATTCGGAGGAACGGGTTG
LINC00092 Reverse	CCATTACTCTCAGGCGTCCC
E-cadherin Forward	CGAGAGCTACACGTTCACGG
E-cadherin Reverse	GGGTGTCGAGGGAAAAATAGG
VIM Forward	GACGCCATCAACACCGAGTT
VIM Reverse	CTTTGTCGTTGGTTAGCTGGT
GAPDH Forward	GGAGCGAGATCCCTCCAAAAT
GAPDH Reverse	GGCTGTTGTCATACTTCTCATGG

Wound-healing assay

Cells were seeded into a 6-well plate at the density of 5×10^5 cells/well. After 24–48 hours, and when the cell confluence reached 90%, the cells were scratched with a 20 μL tip. The debris was removed by washing with Hank's balanced salt solution (HBSS) twice. After one-hour incubation, the image of the scratch was taken as the initial stage of wound healing (d_0, μm). After 48 hours, the image of the scratch was taken as the end stage of wound healing (d_t, μm). The migration rate (%) was determined by the following formula: $(d_t\text{-}d_0)/d_0 \times 100\%$.

Chromatin immunoprecipitation qPCR (ChIP-qPCR)

Q-ChIP was performed based on the protocol of Auto iDeal ChIP-qPCR Kit (Diagenode, USA). MYB was overexpressed in TPC-1 cells for 24 hours, and then cells were lysed to isolate chromatin. Obtained chromatin was sonicated for 30 seconds and 30 cycles to obtain DNA fragments of appropriate size (less than 400 bp). The enrichment of *LINC00092* was evaluated by q-PCR.

Bioinformatics analysis

The data of the patient cohorts were obtained from Genomic Data Commons Data Portal (https://portal.gdc.cancer.gov/). The microRNA target prediction was performed through miRDB (http://mirdb.org/custom.html). The transcription factor screening was performed using Cistrome DB (http://cistrome.org/db/#/) and JASPAR (https://jaspar.genereg.net/).

Statistics

All data are presented as mean ± standard deviation (SD) (at least 3 independent experiments were included). Analyses were achieved by 2-way analysis of variance and t-test. All analyses were performed using GraphPad Prism8 software. P-values of < 0.05 or < 0.01 were considered statistically significantly.

Results

LINC00092 is downregulated in PTC

To determine the expression level of *LINC00092* in thyroid carcinoma, we analysed TCGA-THCA patient cohorts. In the unpaired and paired comparisons, the expression of *LINC00092* was significantly repressed in thyroid carcinoma tissues (Fig. 1A and 1B). In ad-

dition, the expression of *LINC00092* was negatively correlated to the advanced TNM stages of thyroid carcinoma compared to normal groups (Fig 1C–E). Therefore, the downregulation of *LINC00092* suggests promoted progression of thyroid carcinoma. To validate the findings of bioinformatics analysis, we performed q-PCR analysis on *LINC00092* expression in 5 paired tissues of PTC patients. Indeed, the expression of *LINC00092* was downregulated in PTC tissues compared to paired adjacent normal tissues (Fig. 1F). Furthermore, the expression of *LINC00092* was also repressed in the TPC-1 cell, a cell line derived from a papillary thyroid carcinoma of a female patient (Fig. 1G). Collectively, *LINC00092* is downregulated in PTC, which indicates that *LINC00092* may play a tumour suppressive role in PTC.

LINC00092 represses EMT of PTC

Because the results of bioinformatics analysis indicated that *LINC00092* may function as a tumour suppressor, here we evaluated the function of *LINC00092* in the migration of PTC. Ectopic expression of *LINC00092* repressed the migration ability of TPC-1 cells, whereas silencing *LINC00092* promoted the migration ability of TPC-1 cells (Fig. 2A). In addition, ectopic *LINC00092* induced E-cadherin and repressed vimentin (VIM)

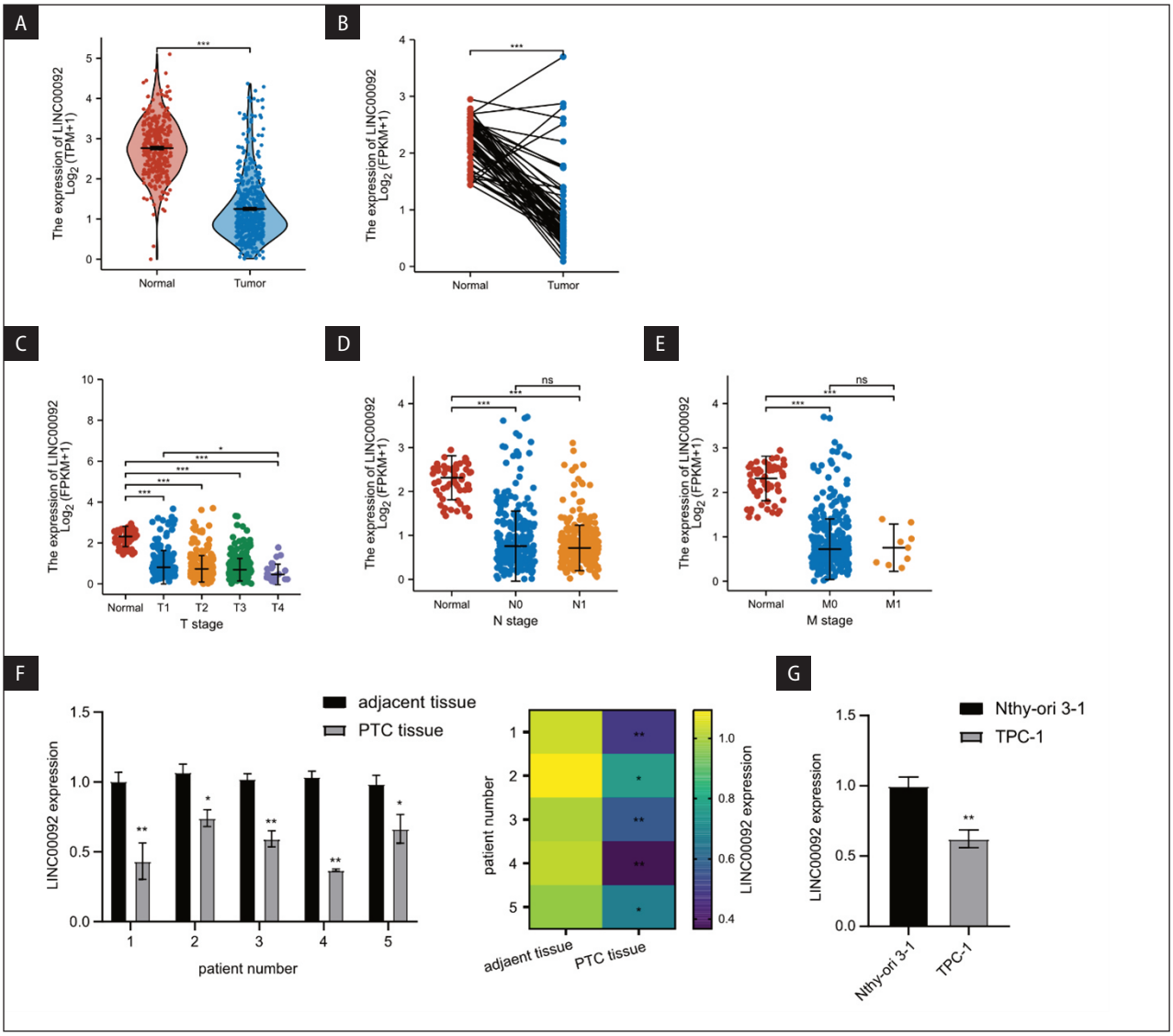

Figure 1. *LINC00092 is downregulated in papillary thyroid carcinoma (PTC).* **A.** *The expression of LINC00092 analysed from TCGA-THCA patient cohorts;* **B.** *The expression of LINC00092 analysed from paired TCGA-THCA patient cohorts;* **C.** *The expression of LINC00092 in different T stages of thyroid carcinoma. The expression in T1–T4 stages was compared to normal tissues;* **D.** *The expression of LINC00092 in different N stages of thyroid carcinoma. The expression in N0-N1 stages was compared to normal tissues;* **E.** *The expression of LINC00092 in different M stages of thyroid carcinoma. The expression in M0-M1 stages was compared to normal tissues;* **F.** *Quantitative polymerase chain reaction (q-PCR) analysis of LINC00092 in PTC tissues from different patients (n = 5);* **G.** *q-PCR analysis of LINC00092 in TPC-1 cells compared to Nthy-ori 3-1 cells. *p < 0.05, **p < 0.01, ***p < 0.001*

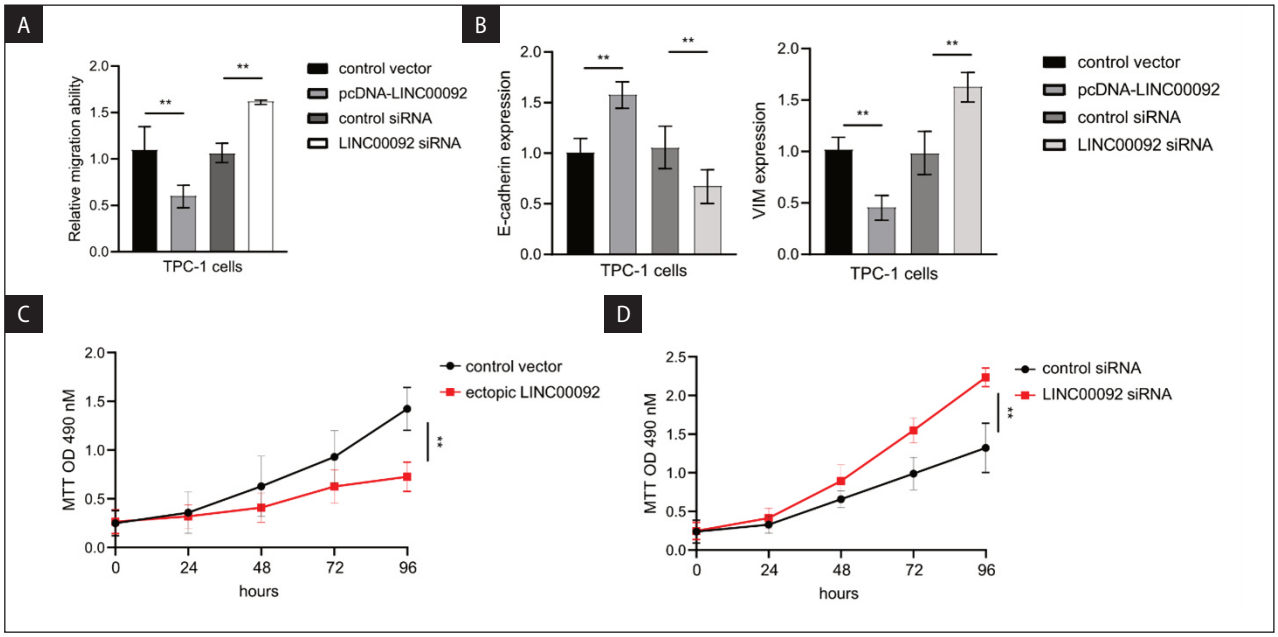

Figure 2. *LINC00092 represses epithelial-mesenchymal transition (EMT) and proliferation of TPC-1 cells.* **A.** *Migration ability of TPC-1 cells was evaluated by wound-healing assay after transfected with the indicated vectors for 48 hours. The quantification of migration ability was presented;* **B.** *Quantitative polymerase chain reaction (q-PCR) analysis of the expression of E-cadherin (left panel) and vimentin (VIM) (right panel) after transfected with indicated vectors and RNAs. Cell proliferation was evaluated by (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) assay after transfected with LINC00092 vector (***C***) and LINC00092 siRNA (***D***) for 48 hours in TPC-1 cells. **p < 0.01*

expression in TPC-1 cells (Fig. 2B), indicating that *LINC00092* represses migration of PTC via regulation of the EMT process. Furthermore, MTT assay results showed that ectopic *LINC00092* significantly repressed the proliferation of TPC-1 cells (Fig. 2C). Conversely, silencing *LINC00092* promoted the proliferation of TPC-1 cells (Fig. 2D). Taken together, our findings suggest that *LINC00092* functions as a tumour suppressor via repressing the EMT of PTC.

LINC00092 is a direct target of MYB

Next, we set out to clarify the potential regulator of *LINC00092* in PTC. By screening with the JASPR online tool, MYB appeared to be a transcription factor of *LINC00092* (Fig. 3A). Indeed, the chromatin immunoprecipitation-sequencing (ChIP-seq) data of previous studies obtained from the Cistrome DB online tool showed that MYB was enriched in the promoter region of *LINC00092*, represented by significant ChIP peaks (Fig. 3B). Ectopic expression of MYB repressed the expression of *LINC00092* (Fig. 3C). In addition, q-ChIP analysis validated that *LINC00092* is a direct target of MYB (Fig. 3D). Furthermore, the newly synthesized RNA of *LINC00092* was suppressed by ectopic MYB in TPC-1 cells (Fig. 3E). Therefore, *LINC00092* is a direct target of MYB, and MYB directly represses the expression of *LINC00092*.

miR-4741 is a direct target of MYB, and miR-4741 represses LINC00092

Because previous studies have shown that lncRNAs are widely regulated by miRNAs via the 3′-UTR target, herein we screened the potential target miRNAs of *LINC00092*. In the screened miRNA candidates, miR-4741 was upregulated in PTC tissues and TPC-1 cells (Fig. 4A and 4B). Luciferase assay validated that *LINC00092* is a target of miR-4741 (Fig. 4C). Ectopic expression of miR-4741 largely repressed the expression of *LINC00092* in TPC-1 cells (Fig. 4D). In addition, ectopic expression of miR-4741 largely abrogated the effect of *LINC00092* on EMT markers of TPC-1 cells (Figs. 4E and 4F). Interestingly, the ChIP-seq data from a previous study, obtained from the Cistrome DB online tool, indicated that MYB is enriched in the promoter of *MIR4741* gene (Fig. 4G), thereby miR-4741 may serve as a direct target of MYB. Next, we performed qChIP analysis and validated that MYB is a transcription factor of miR-4741 (Fig. 4H). In addition, ectopic MYB induced the expression of miR-4741 and the nascent mRNA of *MIR4741* (pri-miR-4741) in TPC-1 cells (Figs. 4I and 4J). Furthermore, inhibition of miR-4741 largely abrogated the effect of MYB on repressing *LINC00092* in TPC cells (Fig. 4K). Collectively, MYB could repress *LINC00092* by inducing the expression of miR-4741.

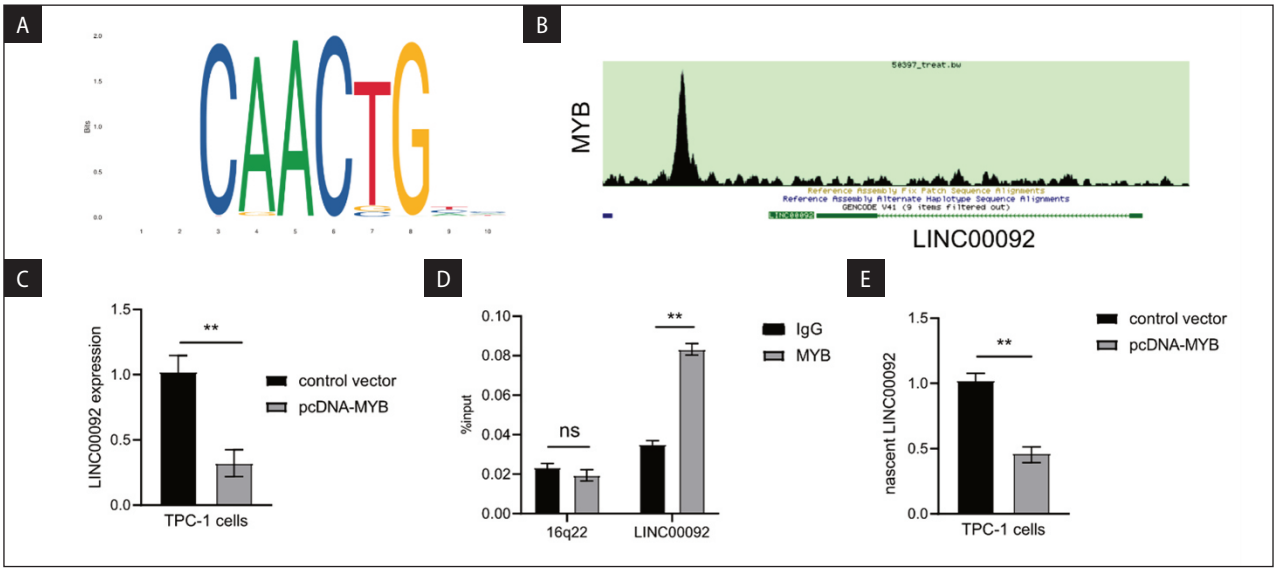

Figure 3. *LINC00092 is a direct target of MYB.* **A.** *The MYB binding motif in the promoter region of LINC00092;* **B.** *The chromatin immunoprecipitation-sequencing (ChIP-seq) data from online database showed MYB binding peak in the promoter of LINC00092;* **C.** *Quantitative polymerase chain reaction (q-PCR) analysis of LINC00092 after transfected MYB overexpression vector in TPC-1 cells;* **D.** *Q-ChIP analysis confirmed LINC00092 is a direct target of MYB. 16q22 served as a negative control;* **E.** *q-PCR analysis of nascent LINC00092 mRNA after overexpression of MYB in TPC-1 cells. **$p < 0.01$*

MYB promotes the EMT of PTC by repressing LINC00092

Because we had identified that MYB directly or indirectly represses *LINC00092*, we would like to ascertain whether MYB promotes EMT of PTC via regulation of *LINC00092*. Ectopic expression of MYB induced *VIM* expression and repressed *E-cadherin* expression in TPC-1 cells, whereas ectopic *LINC00092* largely abrogated the effect of MYB (Figs. 5A and 5B). The above results indicate that MYB promotes EMT via repression of *LINC00092*. The proliferation of TPC-1 cells was promoted by ectopic MYB (Fig. 5C). Furthermore, this effect was reversed by ectopic *LINC00092* (Fig. 5C). Therefore, MYB promotes the progression of PTC via repression of *LINC00092*.

Discussion

In this study, we demonstrated that *LINC00092* functions as a tumour suppressor in PTC. In addition, the tumour promoter MYB can directly or indirectly repress *LINC00092*, as summarized in Fig. 5D. Our previous study shows that lncRNA *ZFAS1* plays an oncogenic role in PTC via induction of MMP3 by repressing miR-373-3p [6]. The transcription factor CREB3 directly induces the expression of *ZFAS1*, thereby promoting the progression of PTC. Herein, we validated that *LINC00092*, a downregulated lncRNA in PTC, inhibits the EMT of PTC. Similarly, the expression of *LINC00092* is also controlled by a specific transcription factor, MYB. Therefore, the regulatory pattern of transcription factor/lncRNA/miRNA could be critical in cancer progression. Of note, the function of *LINC00092* is contradictory in different cancers. *LINC00092* is highly expressed in ovarian cancer [14]. *LINC00092* drives glycolysis and progression of ovarian cancer. However, the lower expression of *LINC00092* indicates a poorer prognosis in lung adenocarcinoma and colon cancer [8, 15]. In addition, *LINC00092* suppresses the malignant progression of breast cancer by inducing SFRP1 through the miR-1827 target. Our findings suggest that *LINC00092* plays a tumour suppressive role in PTC.

The transcription factor MYB is highly conserved, ranging from plant to vertebrates [16], suggesting that MYB has an essential function in different cells and organisms. Previous studies have identified that MYB targets genes at a global level: over 10,000 promoters can be targeted by MYB in MCF-7 cells [17]. The validated targets of MYB include *MYC*, *CCNB1*, *JUN*, and *KLF4*. In line with previous findings, herein we show that MYB plays an oncogenic role in PTC, inducing EMT and proliferation. Interestingly, MYB repressed the expression of *LINC00092* by acting as a transcription factor. Our results imply that reversing the expression of genes repressed by MYB could counteract the effect of MYB.

Interestingly, *LINC00092* was also regulated by MYB indirectly via miR-4741. Herein, we confirmed that *MIR4741* gene is a direct target of MYB; hence, ectopic MYB induces the expression of miR-4741. Furthermore, *LINC00092* was identified as a target of miR-4741, which enables miR-4741 to mediate the function of MYB by

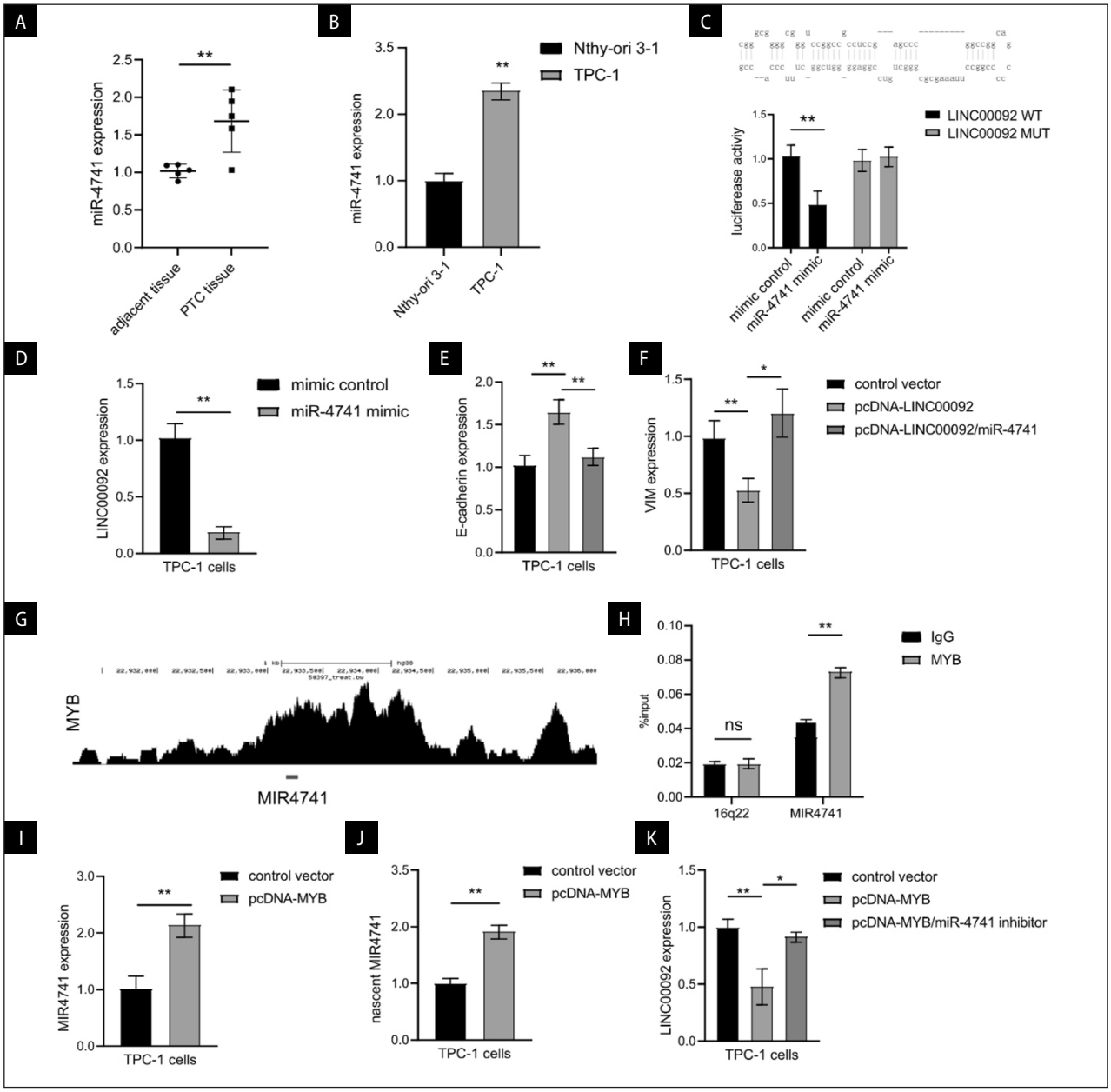

Figure 4. *miR-4741 is a direct target of MYB, and it represses LINC00092.* **A.** *Quantitative polymerase chain reaction (q-PCR) analysis of miR-4741 in papillary thyroid carcinoma (PTC) tissues from different patients (n = 5);* **B.** *q-PCR analysis of miR-4741 in TPC-1 cells compared to Nthy-ori 3-1 cells;* **C.** *Luciferase assay validated the target between LINC00092 3'UTR and miR-4741. The target scheme was also presented;* **D.** *q-PCR analysis of LINC00092 after overexpression of miR-4741 in TPC-1 cells. q-PCR analysis of E-cadherin (***E***) and vimentin (VIM) (***F***) after transfected indicated vectors and miRNA mimic in TPC-1 cells;* **G.** *The chromatin immunoprecipitation-sequencing (ChIP-seq) data from an online database showed MYB binding peak in the promoter of the MIR4741 gene;* **H.** *Q-ChIP analysis confirmed that MIR4741 is a direct target of MYB. 16q22 served as a negative control;* **I.** *Q-PCR analysis of MIR4741 after transfected MYB overexpression vector in TPC-1 cells.* **J.** *qPCR analysis of nascent MIR4741 after overexpression of MYB in TPC-1 cells;* **K.** *qPCR analysis of LINC00092 following ectopic MYB and/or miR-4741 inhibition. *p < 0.05, **p < 0.01*

repressing downstream *LINC00092*. Our findings reveal a robust regulation between MYB and *LINC00092*, which confers the progression of PTC. MYB, *LINC00092*, and miR-4741 form a coherent feed forward loop. Because MYB regulates downstream genes in a global level, the validation and demonstration of more potential target miRNAs are warranted. In addition, the function of *LINC00092* and the correlated regulatory axis require *in vivo* evidence.

Conclusion

Our study validated that *LINC00092* is a tumour suppressor in PTC. *LINC00092* is regulated by MYB di-

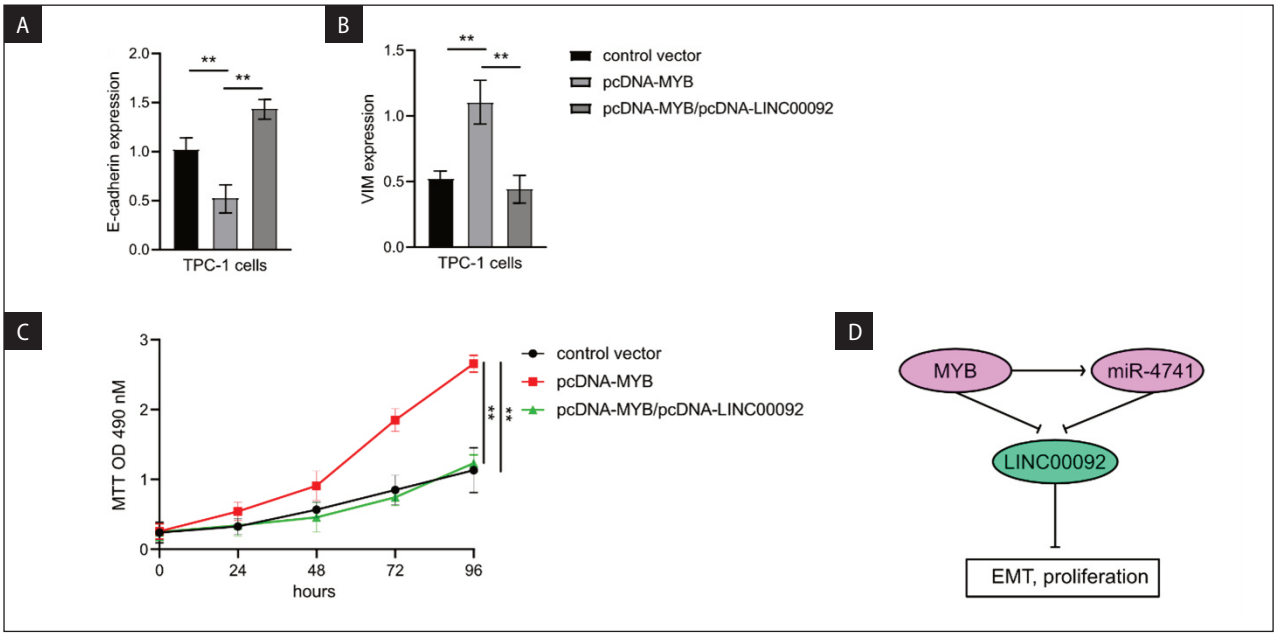

Figure 5. *MYB promotes epithelial-mesenchymal transition (EMT) of papillary thyroid carcinoma (PTC) by repressing LINC00092. Quantitative polymerase chain reaction (qPCR) analysis of E-cadherin (***A***) and vimentin (VIM) (***B***) after transfected indicated vectors in TPC-1 cells.* **C.** *Cell proliferation was evaluated by (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) (MTT) assay after transfection with indicated vectors in TPC-1 cells.* **D.** *Regulation model of the MYB/LINC00092 axis in PTC. **$p < 0.01$*

rectly through promoter binding or indirectly through the miR-4741 target. The axis of MYB-*LINC00092* promotes progression of PTC.

Data availability statement

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

Ethics statement

The experiment on human samples was approved by the Ethics Committee of Southwest Medical University (No. 2021011).

Author contributions

L.C. and X.D. designed the study. L.C. performed experiments and analysed the results. Y.L. performed bioinformatics analysis. L.C. and X.D. wrote the paper. All authors read and approved the paper.

Conflict of interest

The authors declare that there is no conflict of interest for this study.

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