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LINC00106 prevents against metastasis of thyroid cancer by inhibiting epithelial-mesenchymal transition

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Abstract. – OBJECTIVE: Thyroid cancer (TC) is a common malignant tumor of the endocrine system, and its morbidity and mortality are in the high places. Recent studies have focused on exploring biological markers and targeted therapy for TC. This research aims to elucidate the role of LINC00106 in the progression of TC and the regulatory mechanisms.

PATIENTS AND METHODS: Differential level of LINC00106 in a downloaded profile containing TC and normal tissues from GEPIA database was analyzed. Subsequently, its level in TC tissues and cell lines was detected by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). The relationship between LINC00106 level and clinical data of TC patients was assessed, including age, tumor staging, lymphatic metastasis, and overall survival. After transfection of si-LINC00106, TC cell metastasis was evaluated by wound healing and transwell assay. Relative levels of E-cadherin, N-cadherin, β-catenin, and Vimentin regulated by LINC00106 were determined using qRT-PCR and Western blot.

RESULTS: LINC00106 was downregulated in TC tissues than normal ones. Its level was correlated to tumor staging, lymphatic metastasis and overall survival in TC patients. The knockdown of LINC00106 in BCPCP and TPC-1 cells enhanced migratory and invasive abilities and triggered the process of epithelial-mesenchymal transition (EMT).

CONCLUSIONS: LINC00106 is lowly expressed in TC specimens, which attenuates migratory and invasive abilities in TC by inhibiting EMT as a tumor suppressor.

Key Words:
TC, LINC00106, Metastasis, EMT.

Introduction

Thyroid cancer (TC) is one of the most common endocrine malignant tumors in the world, accounting for 1% of all tumor cases in humans. Its incidence has sharply increased in the past decades[1]. According to the histological classification, TC is subtyped to papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) with well differentiation, poorly differentiated thyroid cancer (PDC) and anaplastic thyroid cancer (ATC)[2]. PTC is the main type of TC. Although the survival of TC has constantly increased due to advanced therapeutic strategies, the current trends of elevated incidence, younger onset, and high recurrence should be well concerned[3,4].

LncRNAs are noncoding RNAs with longer than 200 nucleotides in transcripts[5]. They are extensively involved in regulating tumor cell behaviors[6]. By affecting surrounding genes, exerting a sponge effect on miRNAs, interacting with other molecules, or inducing histone modification, lncRNAs display diverse biological functions[7-10]. At present, tumor-associated lncRNAs have been highlighted. LINC0086 presents an anti-cancer effect on nasopharyngeal carcinoma by binding miR-214[11]. High level of lncRNA CCHE1 results in a poor prognosis in cervical cancer[12]. Through activating the miR-139-5p/PDK1/AKT axis, lncRNA XIST drives proliferation of hepatocellular carcinoma[13].

Epithelial-mesenchymal transition (EMT) is a process in which epithelial cells transform into the

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mesenchymal phenotype. It is featured by downregulation of cell adhesion molecules, transformation from cytokeratin skeleton to Vimentin-based cytoskeleton, and acquisition of mesenchymal phenotype. EMT is considered as the initial event of malignant epithelial cells acquiring migratory and invasive abilities[14,15]. Typically, upregulation of mesenchymal markers (e.g., N-cadherin, Vimentin), loss of transcription factor Slug and downregulation of epithelial marker (E-cadherin) are the molecular symbols of EMT[16]. By regulating EMT in colorectal carcinoma, circ-SMAD7 alleviates metastasis of cancer cells[17]. MiR-20a-5p suppresses EMT and invasiveness in endometrial carcinoma by binding STAT3[18]. LINC00319 stimulates metastasis and EMT in cervical cancer *via* mediating the miR-3127-5p/RPP25 axis[19].

Qi et al[20] have demonstrated the prognostic value of LINC00106 in gastric cancer. This study aims to illustrate the biological function of LINC00106 in TC, and thus provides novel ideas for clinical diagnosis and treatment.

Patients and Methods

GEPIA Database Analysis

A profile containing TC tissues (n=512) and normal ones (n=337) was downloaded from GEPIA database (http://GEPIA.cancer-pku.cn/index.html). Differential level of LINC00106 was analyzed.

Sample Collection

Fifty cases of TC tissues and adjacent normal ones were collected from The Affiliated Yantai Yuhuangding Hospital of Qingdao University, and they were immediately frozen in liquid nitrogen and preserved at -80°C. Tumor node metastasis (TNM) staging was defined based on the criteria released by the Union for International Cancer Control (UICC). Patients did not have therapeutic history of chemotherapy or radiotherapy. This study was approved by the Ethics Committee of The Affiliated Yantai Yuhuangding Hospital of Qingdao University. Signed written informed consents were obtained from all participants before the study. Inclusion criteria: patients with no severe diseases in other organs, those with no post-operative radiotherapy and those with normal thyroid function before operation. Exclusion criteria: patients with distant metastasis or metastasis of tumors, those complicated with other malignancies, those with mental disease, those complicated with myocardial infarction, heart failure or other chronic diseases, those with abnormal thyroid function prior to operation, or those previously exposed to radioactive rays.

Cell Culture

The thyroid follicular epithelial cell line (Nthy-ori3-1) and TC cell lines (BCPAP, BHP5-16, BPH2-7, TPC-1) were provided by Shanghai Institute of Biochemistry and Cell Biology (Shanghai, China). Cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640; Gibco, Rockville, MD, USA) containing 10% fetal bovine serum (FBS; Gibco, Rockville, MD, USA) and 1% penicillin-streptomycin (Gibco, Rockville, MD, USA).

Cell Transfection

Transfection of si-LINC00106 or si-NC (GenePharma, Shanghai, China) was conducted using Lipofectamine 2000 (Life Technologies Corp., Shanghai, China) once cells were grown to more than 60% confluence. Transfection efficacy was examined at 48 h by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR).

qRT-PCR

Qualified RNA was reversely transcribed into complementary deoxyribose nucleic acid (cDNA) using the PrimeScript RT reagent Kit (TaKaRa, Dalian, China). The cDNA was subjected to qRT-PCR using the SYBR Green Master Mix (Applied Biosystems, San Diego, CA, USA). Sequences were as follows: LINC00106, Forward: 5′-AGTGGTCACCTGAGATGGAGCAG-3′; Reverse: 5′-CGTCTGTCTTACGGCACGAAGC-3′; glyceraldehyde 3-phosphate dehydrogenase (GAPDH), Forward: 5′-CGGAGTCAACGGATTTGGTCGTAT-3′, Reverse: 5′-AGCCTTCTCCATGGTGGTGAAGAC-3′.

Wound Healing Assay

Cells were prepared into suspension with 1×10^5 cells/ml and implanted in 6-well plates. Until 80% of cell attachment, an artificial scratch was made using a sterilized pipette tip. Cells were washed in phosphate-buffered saline (PBS) for 2-3 times and cultured in the medium containing 1% FBS. 24 hours later, the wound closure was captured for calculating the percentage of wound healing.

Transwell Assay

Transwell chambers (BD, San Diego, CA, USA) coated with Matrigel were used. 4×10^3 cells

were implanted on the top, while 500 μL of medium was applied on the bottom. After 48 h incubation, migratory cells on the bottom were reacted with 15-min methanol, 20 min crystal violet, and captured using a microscope. Invasive cells were counted in 10 randomly selected fields per sample. Migratory cell number was similarly detected using transwell chambers without Matrigel precoating.

Western Blot

Cellular proteins were isolated using radioimmunoprecipitation assay (RIPA) lysis buffer (Beyotime, Shanghai, China), which were separated by 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and loaded on polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). After incubation in 5% skim milk for 2 h, the membranes were washed and cultivated with primary and secondary antibodies. Band exposure was conducted using enhanced chemiluminescence (ECL).

Statistical Analysis

Experimental data were expressed as mean ± standard deviation, and processed using GraphPad Prism 6.0 (La Jolla, CA, USA). Differences between two groups were analyzed by using the Student's *t*-test. Comparison between multiple groups was done using One-way ANOVA test followed by Post-Hoc Test (Least Significant Difference). Kaplan-Meier curves were plotted for survival analysis on TC according to LINC00106 level. $p<0.05$ was considered as statistically significant.

Results

LINC00106 Was Downregulated in TC Tissues and Cells

We first compared LINC00106 levels in a profile containing TC tissues (n=512) and normal ones (n=337) using GEPIA database, and the lower level of LINC00106 was detected in the former (Figure 1A). Subsequently, its level was further detected in 50 pairs of TC and adjacent normal ones, and it was downregulated in TC tissues as well (Figure 1B). LINC00106 was downregulated in TC cells compared with that of thyroid follicular epithelial cells (Figure 1C).

Correlation Between LINC00106 and Prognosis in TC

The correlation between LINC00106 and clinical pathology of TC was analyzed. No significant difference in LINC00106 level was detected in TC patients older than 45 years or younger (Figure 2A). In TC patients with a larger tumor size (≥1 cm), they had a lower level of LINC00106 in comparison to those with a smaller one (Figure 2B). In addition, TC patients in advanced stage (III+IV) or had lymphatic metastasis expressed lower level of LINC00106 than those of controls (Figure 2C, 2D). Kaplan-Meier curves uncovered poor overall survival in TC patients expressing low level of LINC00106 (Figure 2E). It is concluded that low level of LINC00106 predicted poor prognosis in TC.

Knockdown of LINC00106 Stimulated TC Metastasis

Transfection of si-LINC00106 effectively downregulated LINC00106 in BCPAP and TPC-

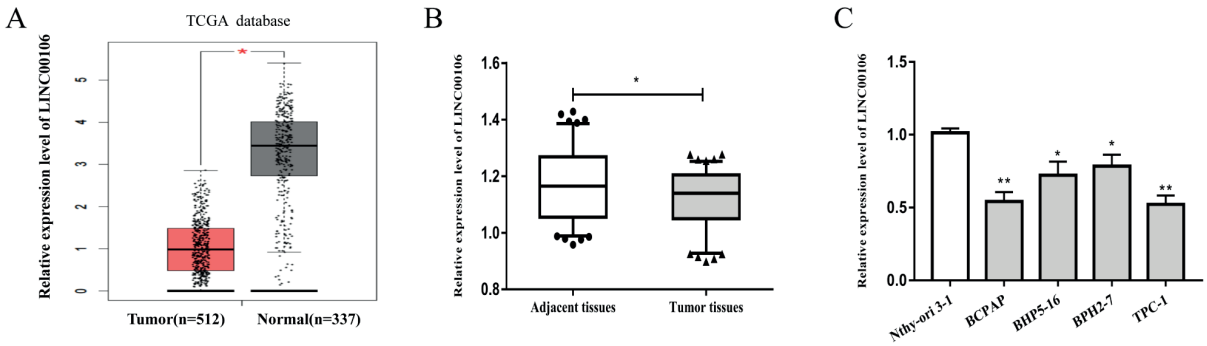

Figure 1. LINC00106 was downregulated in TC tissues and cells. **A,** Downregulated LINC00106 in TC tissues than normal ones as analyzed in GEPIA database. **B,** Downregulated LINC00106 in TC tissues than normal ones analyzed by qRT-PCR. **C,** Downregulated LINC00106 in TC cell lines than the thyroid follicular epithelial cell line. *$p<0.05$, **$p<0.01$.

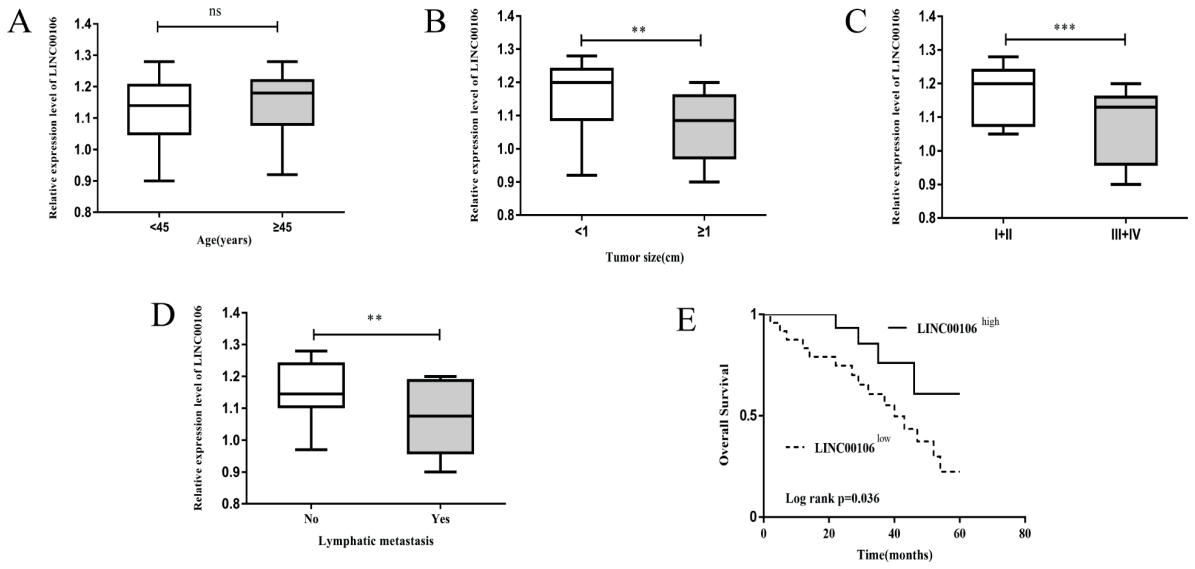

Figure 2. Correlation between LINC00106 and prognosis in TC. **A,** No significant difference in LINC00106 in TC patients younger or older than 45 years. **B,** Lower level of LINC00106 in TC cases with larger tumor size (≥ 1cm) than smaller ones (< 1 cm). **C,** Lower level of LINC00106 in stage III+IV TC cases than stage I+II ones. **D,** Lower level of LINC00106 in TC cases with lymphatic metastasis than non-metastasis cases. **E,** Lower overall survival in TC patients expressing low level of LINC00106 than those with high level. Ns, no significant difference; **p<0.01, ***p<0.001.

1 cells (Figure 3A). A larger distance of wound healing was detected in TC cells transfected with si-LINC00106 at 24 h compared with those transfected with si-NC, indicating the promoted migratory potential (Figure 3B). Furthermore, the knockdown of LINC00106 enhanced migratory and invasive cell numbers in TC, suggesting the stimulated metastasis potential (Figure 3C, 3D).

Knockdown of LINC00106 Triggered EMT in TC

Regulatory effect of LINC00106 on EMT was evaluated by determining relative levels of EMT markers in TC cells. Knockdown of LINC00106 downregulated E-cadherin and β-catenin, as well as upregulated N-cadherin and Vimentin in TC cells at both mRNA and protein levels (Figure 4A, 4B). We believed that LINC00106 inhibited EMT in TC.

Discussion

TC is mainly originated from thyroid follicular or perifollicular cells[21,22]. Major pathogenic risks for TC include ionizing radiation, excessive or insufficient intake of iodine, genetic factors, etc[23,24]. PTC covers more than 90% of TC cases, which has a relatively well prognosis. Nevertheless, about 59% of patients develop lymphatic metastasis, and 10-20% have local infiltration or distant metastasis[25,26]. For a long period, surgery combined radioactive iodine therapy for removal of residue cancer cells is preferred to TC patients. Rapid growth of TC case number and improvement of the prognosis are clinical challenges for now[27].

Noncoding RNAs constitute the vast majority of mammal genomes[28,29]. LncRNAs are capable of transcriptionally or post-transcriptionally regulating gene expressions[30]. Abnormally expressed lncRNAs are of significance in various biological processes[31,32]. Several lncRNAs associated with TC have been identified. Of note, lncRNA UCA1 stimulates proliferative and migratory capacities in TC by exerting a miRNA sponge effect on miR-497-3p[33]. The knockdown of lncRNA DLX6-AS1 suppresses metastasis of TC cells by upregulating UPF1[34]. By regulating the PI3K/AKT signaling, the hknockdown of lncRNA H19 weakens viability and induces apoptosis in TC cells[35]. By analyzing GEPIA database, it is found that LINC00106 was downregulated in TC tissues, which was identically indicated in clinical samples of TC collected in our hospital. LINC00106 level was closely linked to tumor size, TNM staging, and lymphatic metastasis in TC patients. Moreover, Kaplan-Meier curves demonstrated that low lev-

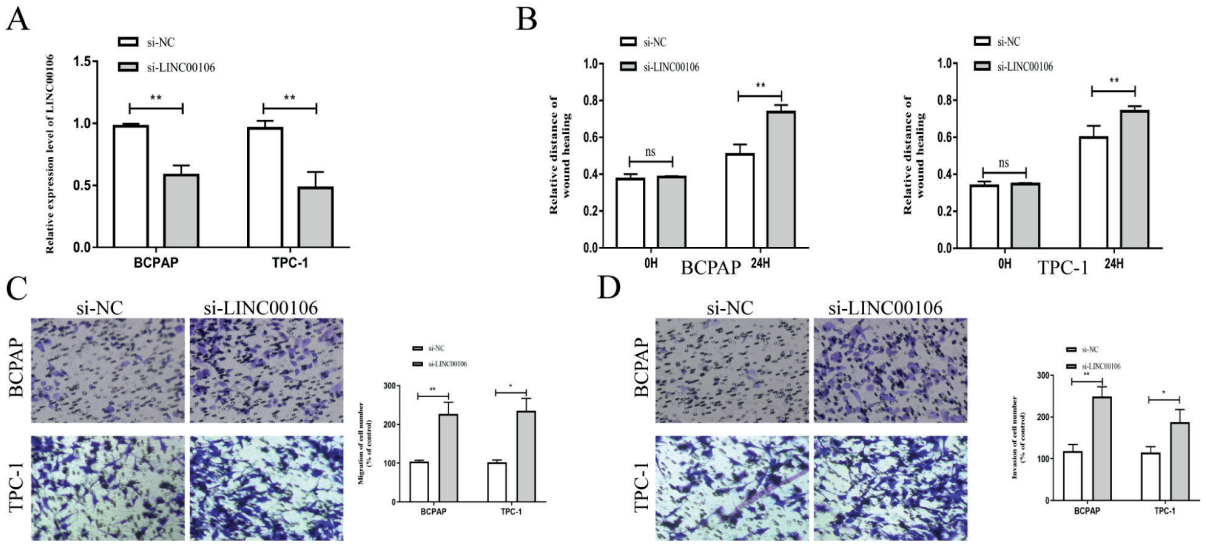

Figure 3. Knockdown of LINC00106 stimulated TC metastasis. **A,** Transfection of si-LINC00106 significantly downregulated LINC00106 in BCPAP and TPC-1 cells. **B,** Transfection of si-LINC00106 promoted migratory ability in BCPAP and TPC-1 cells. **C,** Transfection of si-LINC00106 promoted migratory ability in BCPAP and TPC-1 cells (magnification: 20×). **D,** Transfection of si-LINC00106 promoted invasive ability in BCPAP and TPC-1 cells (magnification: 20×). Ns, no significant difference; *p<0.05, **p<0.01.

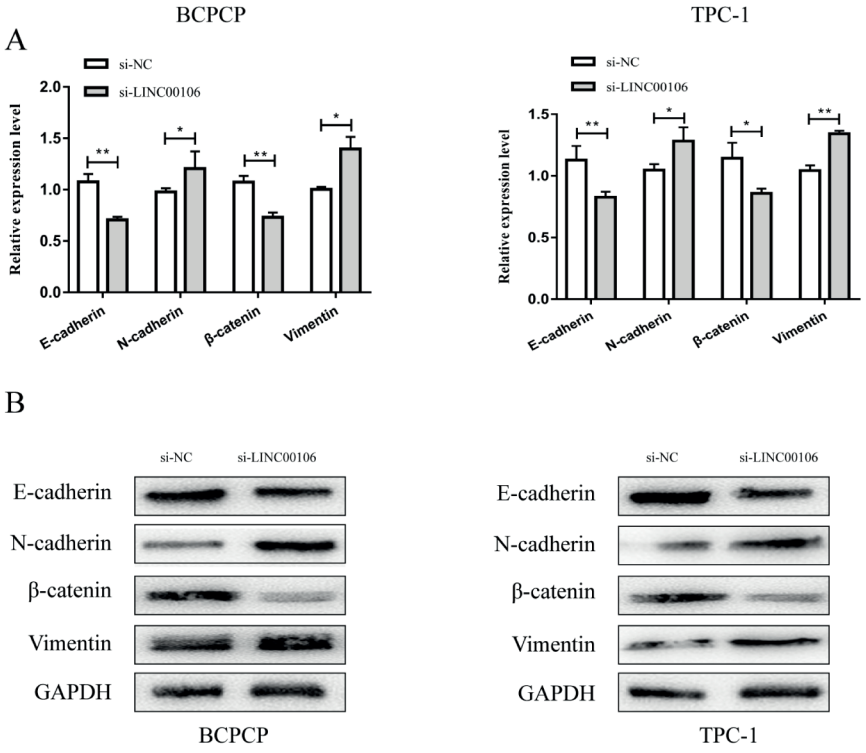

Figure 4. Knockdown of LINC00106 triggered EMT in TC. **A,** Transfection of si-LINC00106 reduced mRNA levels of E-cadherin and β-catenin, and elevated mRNA levels of N-cadherin and Vimentin in BCPAP and TPC-1 cells. **B,** Transfection of si-LINC00106 reduced protein levels of E-cadherin and β-catenin, and elevated protein levels of N-cadherin and Vimentin in BCPAP and TPC-1 cells. *p<0.05, **p<0.01.

el of LINC00106 was unfavorable to overall survival of TC. *In vitro* experiments suggested that LINC00106 attenuated migratory and invasive abilities in BCPAP and TPC-1 cells.

EMT leads to massive changes of cell phenotypes and abilities of adhesion and metastasis[36]. It occurs in the early phase of tumor metastasis, leading to strengthened migratory and invasive capacities[37]. MiR-451a promotes the growth of TC cells by inducing EMT[38]. LncRNA SLC26A4-AS1 contributes to EMT inhibition in PTC[39]. Here, we detected mRNA and protein levels of EMT markers in TC cells with LINC00106 knockdown. Silence of LINC00106 downregulated E-cadherin and β-catenin, as well as upregulated N-cadherin and Vimentin in TC cells. It is indicated that LINC00106 inhibited EMT in TC cells as an anti-cancer lncRNA. This article first proposed the abnormally low expression of LINC00106 in TC, and proved that LINC00106 may suppress the metastasis of TC *via* regulating the EMT progression. It is innovative at the source and provides theory for the clinical diagnosis and treatment of TC. However, whether LINC00106 was involved in regulating various cellular processes, such as proliferation, apoptosis, and invasion by targeting multiple genes, need to be further explored.

Conclusions

Altogether, LINC00106 is lowly expressed in TC specimens, which attenuates migratory and invasive abilities in TC by inhibiting EMT. LINC00106 exerts an anti-cancer role against TC metastasis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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