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LINC01857 promotes the development of gastric cancer by regulating microRNA-200b

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Abstract. – OBJECTIVE: The aim of this study was to investigate the expression characteristics of LINC01857 in gastric cancer (GCa), and to further study whether it could promote GCa development by modulating microRNA-200b.

PATIENTS AND METHODS: Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) was used to examine LINC01857 expression in 60 pairs of GCa tissues and adjacent tissues. The interplay between LINC01857 level and clinical indexes and the prognosis of GCa patients was analyzed. Meanwhile, qRT-PCR was used to verify the expression level of LINC01857 in GCa cell lines. LINC01857 knockdown model was constructed by lentivirus transfection in GCa cell lines. Subsequently, the effect of LINC01857 on the biological function of GCa cells was analyzed by Cell Counting Kit 8 (CCK8), wound healing, and transwell assays. Furthermore, the in-depth relationship between LINC01857 and microRNA-200b was explored.

RESULTS: QRT-PCR results showed that LINC01857 level in GCa tissues was remarkably higher than that of adjacent tissues, and the difference was statistically significant ($p<0.05$). Compared with patients with a low level of LINC01857, the rate of lymph node and distant metastasis in patients with a high level of LINC01857 was remarkably higher, while the overall survival rate was lower ($p<0.05$). *In vitro* experiments showed that LINC01857 knockdown remarkably decreased the invasion, migration, and crawling ability of GCa cells ($p<0.05$). Subsequent qRT-PCR results demonstrated that the level of microRNA-200b was remarkably upregulated after the silence of LINC01857. In addition, the silence of microRNA-200b could reverse the biological function of GCa cells induced by the knockout of LINC01857.

CONCLUSIONS: LINC01857 was highly expressed in GCa, and was associated with lymph node metastasis, distant metastasis, and poor prognosis of patients with GCa. In addition, LINC01857 enhanced the metastatic ability of GCa cells by regulating microRNA-200b.

Key Words:
LINC01857, MicroRNA-200b, Gastric cancer (GCa), Development.

Introduction

Gastric cancer (GCa) is a common malignant tumor with the highest morbidity and mortality in China[1-3]. In recent years, with the advancement of comprehensive multidisciplinary treatment, the treatment of GCa has been greatly improved[4,5]. However, the 5-year survival rate of advanced GCa patients after radical resection remains between 30% and 50%. Meanwhile, the metastatic spread is the primary cause of poor prognosis[6-8]. Therefore, it is of great significance to explore the mechanism of the occurrence and metastasis of GCa, so as to find novel molecular markers for prediction and early diagnosis of high-risk individuals with metastasis, and to establish new therapeutic targets for improving the efficacy of GCa[8,9].

According to the traditional central law of genetics, the importance of RNA as a medium for the transmission of genetic information from DNA to proteins is evident[10]. In recent years, however, studies have found that less than 2% of genes in the human genome can be transcribed into proteins. The transcription products of genes that do not encode proteins are collectively referred to as non-coding RNA[11,12]. MiRNA and long non-coding RNA (lncRNA) can regulate each other[13,14]. LncRNA, a type of RNA with over than 200 nt in length, is located in the nucleus or cytoplasm without an evident open reading frame. With no protein-coding function, lncRNA regulates the gene expression in the form of RNA at transcriptional and post-transcriptional levels[15,16]. LncRNA has been found differentially expressed in some normal tissues, dysplasia tissues, and tumor tissues[16,17]. LINC01857 acts as a cancer-promoting gene in some human tumors[18,19]. However, its specific role in GCa still remains unknown.

Recent researches on the interaction between RNA transcripts have put forward a new model in

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regulating gene expression, namely the competitive model of endogenous RNA (ceRNA). Briefly, lncRNA, false gene transcription and miRNA transcription content can be a competitive combination of microRNAs response element (MRE) to influence the gene transcription regulation. This may eventually act on cell functions and provide communication between lncRNA and mRNA[13,14]. Currently, multiple studies have found that cytoplasmic lncRNAs specifically expressed during myoblast differentiation exert competitive endogenous RNA (ceRNA) activity. Meanwhile, they regulate the expression level of muscle-specific gene transcription regulators of MAMLl and MEF2C through competitive binding of miR-133 and miR-135[20]. Based on the above analysis, bioinformatics technology has been developed to predict the possible regulation of miRNA in LINC01857. In the present study, we explored the molecular mechanism of LINC01857 in regulating the invasion and metastasis of GCa mediated by microRNA-200b. Our findings might provide an microexperimental basis for its clinical application.

Patients and Methods

Patients and GCa Samples

In this study, 60 pairs of GCa tissues and adjacent tissues were collected from surgically treated GCa patients. The collected tissue samples were stored at -80°C for use. Informed consent was obtained from patients and their families before the study. The Declaration of Helsinki should be respected. This study was approved by the Ethics Monitoring Committee of Linyi Cancer Hospital.

Cell Lines and Reagents

Human GCa cell lines (AGS, BGC-823, SGC-7901, MKN28, and MKN45) and immortalized normal gastric mucosal epithelial cell line (GES-1) were purchased from American Type Culture Collection (ATCC; Manassas, VA, USA). All cells were cultured in DMEM (Dulbecco's Modified Eagle's Medium) high glucose medium (Gibco, Rockville, MD, USA) containing 10% fetal bovine serum (FBS; Gibco, Rockville, MD, USA), penicillin (100 U/mL), and streptomycin (100 μg/mL), and maintained in a 37°C incubator with 5% CO_2. Cell passage was performed with 1% trypsin + ethylene diamine tetraacetic acid (EDTA) for digestion when grown to 80%-90% of confluence.

Cell Transfection

Negative control (si-NC) and the lentivirus containing LINC01857 knockdown sequence (si-LINC01857) were purchased from Shanghai Jima Company (Shanghai, China). The cells were first seeded into 6-well plates and grown to a cell density of 30%-40%. Cell transfection was performed according to the manufacturer's instructions of Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA). 48h after transfection, the cells were collected for quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) analysis and cell function experiments.

Cell Counting Kit (CCK-8) Assay

48 h after transfection, the cells were harvested and plated into 96-well plates at a density of 2000 cells per well. After culture for 24, 48, 72, and 96 h, respectively. CCK-8 (Dojindo Laboratories, Kumamoto, Japan) reagent was added in each well, followed by incubation for 2 h in the dark. Optical density (OD) at the absorption wavelength of 490 nm was detected by a microplate reader.

Transwell Assay

48 h after transfection, the cells were digested, centrifuged, and resuspended in the serum-free medium. The density of cells was adjusted to 5 x 10^5 cells/mL. 200 μL of cell suspension (1 x 10^5 cells) was added to the upper chamber. Meanwhile, 700 μL of complete medium containing 20% FBS was added to the lower chamber. Then, the cells were put back into the incubator and cultured for a specific time. Subsequently, the cells were washed 3 times with 1 x phosphate-buffered saline (PBS) and fixed with methanol for 15 min. After staining with 0.2% crystal violet for 20 min, the cells on the upper surface of the chamber were carefully wiped off with a cotton swab. The perforated cells stained in the outer layer of the basement membrane of the chamber were observed under a microscope. 5 fields of view were randomly selected for each sample.

Wound Healing Assay

48 h after transfection, the cells were digested, centrifuged, and resuspended in the serum-free medium. Cell density was adjusted to 5 x 10^5 cells/mL. The density of plated cells was determined according to the size of cells (the majority of the number of cells plated was set to 50000 cells/well). On the next day, the confluency of cells reached 90% or more. After the stroke, the

cells were rinsed gently with PBS for 2-3 times and added with low-concentration serum medium (such as 1% FBS). Next, the cells were observed again after 24 hours. The difference in the cell healing ability was judged according to the migration area.

Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

1 ml of TRIzol (Invitrogen, Carlsbad, CA, USA) was used to extract the total RNA in tissues and cells. Subsequently, initially extracted RNA was treated with DNase I to remove genomic DNA and repurify the RNA. RNA reverse transcription was performed according to the instructions of Prime Script Reverse Transcription Kit (TaKaRa, Otsu, Shiga, Japan). Real Time-PCR was performed in accordance with SYBR® Premix Ex Taq™ (TaKaRa, Otsu, Shiga, Japan). PCR reaction was performed using the StepOne Plus Real-time PCR System (Applied Biosystems, Foster City, CA, USA). Three replicate wells were set for each sample, and the assay was repeated twice. Bio-Rad (Hercules, CA, USA) PCR instrument was used to analyze and process the data with the software iQ5 2.0. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and U6 were used as internal references for mRNA and miRNA, respectively. The gene expression level was calculated by the $2^{-\Delta\Delta Ct}$ method. The primer sequences used in this study were as follows: LINC01857, F: 5'-CAGGACTCCATTAAGGACTC-3', R: 5'-AACATCGATGTGTCCCAGGA-3'; miR-200b, F: 5'-GGCTAGGTGTGTACTCGACTG-3', R: 5'-AGGTTGCGTGTCGGAGTCG-3'; U6: F: 5'-CTCGCTTCGGCAGCACA-3', R: 5'-AACGCTTCACGAATTTGCGT-3'; GAPDH: F: 5'-CGCTCTCTGCTCCTCCTGTTC-3', R: 5'-ATCCGTTGACTCCGACCTTCAC-3'.

Dual-Luciferase Reporter Assay

According to the instructions, GCa cells in the logarithmic growth phase were prepared by the Luciferase system. The transcription factor expression plasmid to be detected was co-transfected with the reporter gene plasmid into GCa cells. If the transcription factor could activate the target promoter, the Luciferase gene would be expressed. Meanwhile, the amount of Luciferase expression was directly proportional to the intensity of the transcription factor. A specific Luciferase substrate was added, and Luciferase reacted with the substrate to generate fluorescence. By measuring the intensity of the fluorescence, the activity of the Luciferase could be determined to determine whether the transcription factor interacted with the target promoter fragment.

Statistical Analysis

GraphPad Prism (La Jolla, CA, USA) 5 V5.01 software was used for all statistical analysis. The differences between the two groups were analyzed by the Student's *t*-test. One-way analysis of variance (ANOVA) was applied to compare the differences among different groups, followed by post-hoc test (Least Significant Difference). Independent experiments were repeated at least three times. Experimental data were expressed as mean ± standard deviation. There were three levels of $p<0.05$, $p<0.01$, and $p<0.001$ at the significance level. $p<0.05$ was considered statistically significant.

Results

LINC01857 Was Highly Expressed in GCa Tissues and Cell Lines

To clarify the role of LINC01857 in GCa, we first collected 60 pairs of GCa tissues and adjacent tissues. LINC01857 expression level in tissues was detected using qRT-PCR. The results showed that LINC01857 was remarkably higher in GCa tissues than that of adjacent tissues ($p<0.05$, Figure 1A). In addition, LINC01857 level in GCa cell lines was remarkably higher than that of normal gastric cell line GES-1 ($p<0.05$). These results suggested that LINC01857 might play a cancer-promoting role in GCa (Figure 1B).

LINC01857 Level Was Correlated With Lymph Node, Distance Metastasis and Overall Survival of GCa Patients

According to the mRNA expression level of LINC01857, GCa patients were divided into two groups, including: high LINC01857 expression group and low LINC01857 expression group. The relationship between LINC01857 level and age, gender, pathological stage, lymph node, or distant metastasis of GCa patients was analyzed. As shown in Table I, a high expression level of LINC01857 was positively correlated with lymph node metastasis and distant metastasis of GCa patients, rather than age, gender, and pathological stage. To further explore the relationship between LINC01857 expression and the prognosis of GCa patients, we collected relevant follow-up data. Kaplan-Meier survival curves showed that a high

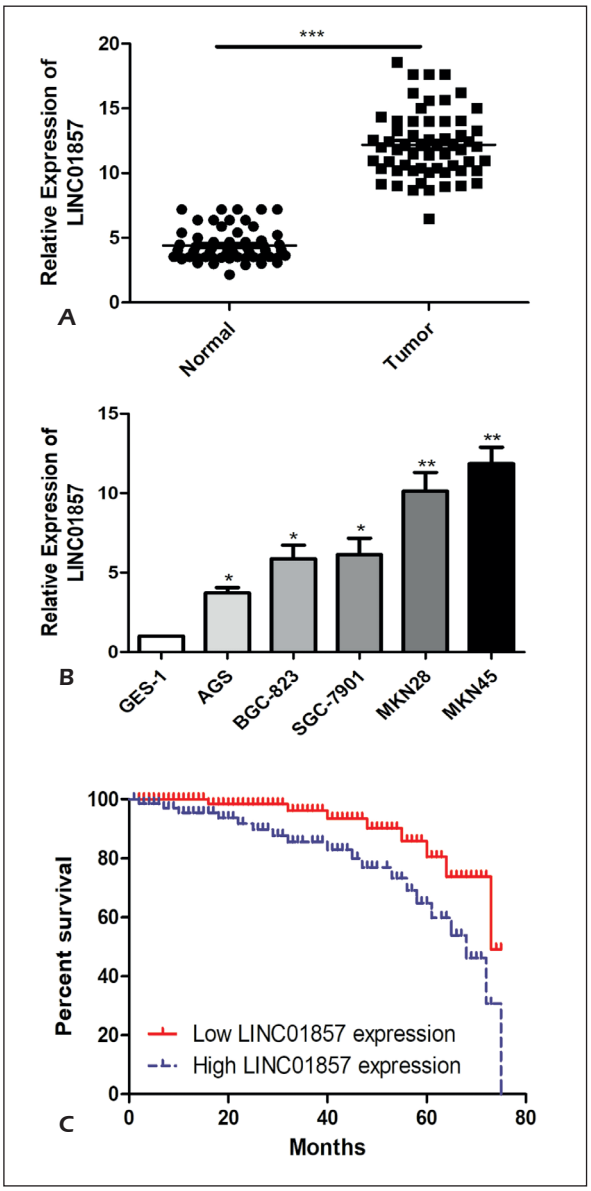

Figure 1. LINC01857 was highly expressed in GCa tissues and cell lines. **A**, QRT-PCR was used to detect the expression of LINC01857 in GCa tissues and adjacent tissues. **B**, QRT-PCR was used to detect the expression level of LINC01857 in GCa cell lines. **C**, Kaplan Meier survival curve of GCa patients based on LINC01857 expression; the prognosis of patients with high expression was significantly worse than that of patients in low expression group. Data were expressed as mean ± SD, *p<0.05, **p<0.01, ***p<0.001.

level of LINC01857 was remarkably associated with poor prognosis of GCa. Higher expression of LINC01857 indicated significantly worse prognosis (p<0.05; Figure 1C). These results demonstrated that LINC01857 level was correlated with lymph node, distance metastasis, and overall survival of GCa patients.

Knockdown of LINC01857 Inhibited GCa Cell Proliferation and Metastasis

To investigate the biological function of LINC01857 *in vitro*, we transfected si-LINC01857 lentiviral vector into MKN28 and MKN45 cell lines. The interference efficiency was verified by qRT-PCR (Figure 2A). CCK-8 results demonstrated that compared with the si-NC group, the proliferation of GCa cells in the si-LINC01857 group was remarkably inhibited, and the difference was statistically significant (p<0.05; Figure 2B). In addition, the transwell and wound healing assay demonstrated that the invasion, migration, and crawling abilities of GCa cells in the si-LINC01857 group were remarkably lower than those of si-NC group (Figures 2C, 2D). These findings suggested that the knockdown of LINC01857 inhibited GCa cell proliferation and metastasis.

MicroRNA-200b Was a Direct Target of LINC01857

To further validate the targeting of microRNA-200b to LINC01857, the Luciferase reporter gene assay was performed. The results indicated that microRNA-200b could bind to LINC01857 (Figure 3A). Subsequent qRT-PCR results demonstrated that the silence of LINC01857 remarkably upregulated the expression level of microRNA-200b (Figure 3B). Conversely, the silence of microRNA-200b significantly upregulated the expression level of LINC01857 (Figure 3C). In addition, microRNA-200b level remarkably decreased in GCa tissues when compared with para-cancerous tissues (Figure 3D). Further analysis indicated that there was a negative correlation between the expression levels of LINC01857 and microRNA-200b in GCa tissues (Figure 3E). In sum, microRNA-200b served as a direct target of LINC01857 in GCa.

LINC01857 Modulated MicroRNA-200b Level in Human GCa Cells

To further explore the interaction between LINC01857 and microRNA-200b in GCa cell lines, we silenced microRNA-200b in LINC01857 knockdown cell line. QRT-PCR was used to detect the expression level of LINC01857 in each transfection group (Figure 4A). Subsequent CCK-8, transwell migration, and cell scratch assays found that silencing microRNA-200b reversed the effect of LINC01857 on the proliferation, invasion, and migration of GCa cells (Figures 4B-4D). All these findings revealed that LINC01857 regulated GCa progression by modulating microRNA-200b level.

Table I. Association of miR-548c-5p expression with clinicopathologic characteristics of breast cancer.

Parameters	Number of cases	LINC01857 expression		*p*-value*
		Low (%)	High (%)	
Age (years)				0.190
<60	25	15	10	
≥60	35	15	20	
Gender				0.302
Male	30	17	13	
Female	30	13	17	
T stage				0.190
T1-T2	35	20	15	
T3-T4	25	10	15	
Lymph node metastasis				0.007
No	38	24	14	
Yes	22	6	16	
Distance metastasis				0.004
No	35	23	12	
Yes	25	7	18	

Discussion

In recent years, abnormal expression level of non-coding RNA has been found successively in GCa, lung cancer, breast cancer, liver cancer, pancreatic cancer, colorectal cancer, and other malignant tumors[11,12]. A single miRNA may regulate multiple target genes. Meanwhile, the expression level of a single gene may be regulated by multiple non-coding RNAs[13,14]. Recently, researchers[15,16] have found that multiple non-coding RNAs can promote or inhibit the proliferation, invasion, and metastasis of GCa cells by regulating single or multiple target genes.

The rapid development of high-throughput chips and sequencing technology has made it easier for researchers at home and abroad to identify more functional lncRNAs. Meanwhile, researchers have gradually deepened their studies on important mechanisms[15,16]. Recent studies have shown that a total of 32,183 confirmed lncRNAs exist in humans. Most of them exert evident tissue specificity, revealing their potential importance in the process of biological development and differentiation[16]. LncRNAs have been observed to be involved in a variety of biological processes, including transcription, translation, cell differentiation, gene level regulation, and cell cycle regulation, etc[17]. In addition, lncRNAs participate in controlling chromatin condensation, regulating gene expression, promoting or inhibiting DNA transcription, regulating mRNA splicing and stabilization, promoting or inhibiting mRNA translation into proteins, and other important biological behaviors[16,17].

Abnormal levels of lncRNAs have been found in cardiovascular diseases, aging diseases, and other human diseases[11]. More importantly, lncRNAs play an important role in the occurrence, development, and prognosis of multiple tumors, such as ovarian cancer, lung cancer, breast cancer, GCa, and endometrial cancer[11-15]. The research group has conducted an in-depth review of the current research status of lncRNAs in GCa. They have found that their abnormal expression is involved in the regulation of apoptosis, tumor invasion and metastasis, and other important biological processes[16]. LINC01857 is a recently discovered lncRNA[18,19]. As an oncogene, LINC01857 regulates the activation of CREB1 by interacting with CREBBP in breast cancer. Meanwhile, its high expression level is related to poor prognosis of breast cancer patients[19]. In addition, LINC01857 promotes the growth, invasion, and migration of glioma by regulating miR-1281/TRIM65[18]. However, few studies have reported that LINC01857 is associated with malignant progression of GCa. In this study, bioinformatics was used to analyze differentially expressed lncRNAs in GCa tissues and adjacent tissues. LINC01857 was finally screened out as a candidate lncRNA related to the malignant progression of GCa. The relationship between LINC01857 and the occurrence and development of GCa was determined. The results demonstrated that LINC01857 expression was remarkably higher in GCa tissues than paracancerous tissues. Meanwhile, its expression level was positively correlated with lymph node metastasis, distant metastasis, and poor prognosis

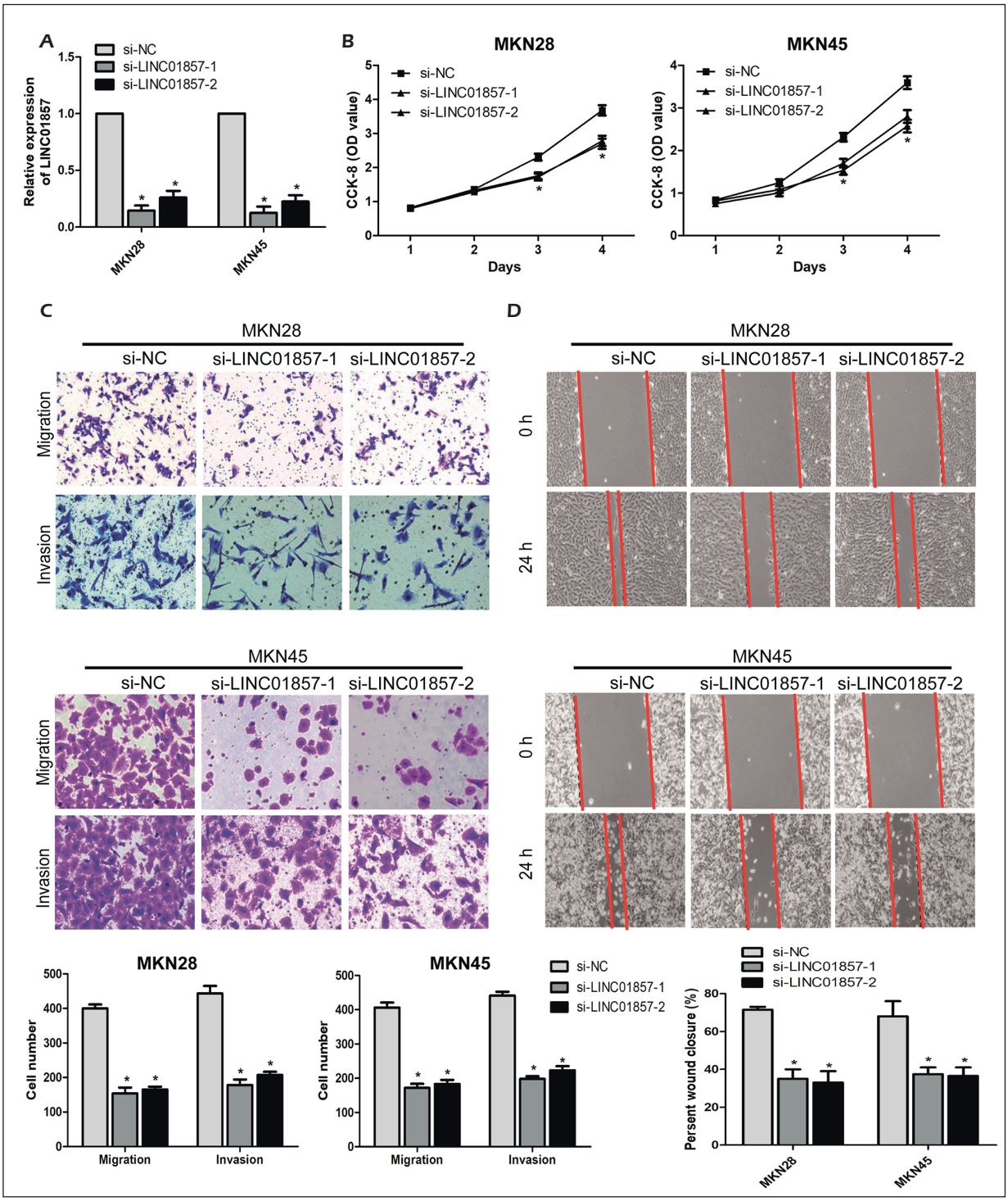

Figure 2. Silencing LINC01857 inhibited proliferation and metastasis of GCa cells. **A**, QRT-PCR verified the interference efficiency of transfection of LINC01857 knockdown vector in GCa cell lines (MKN28 and MKN45). **B**, CCK-8 assay detected the effect of si-LINC01857 on proliferation of MKN28 and MKN45 cells. **C**, Transwell migration assay detected the migration and invasion of MKN28 and MKN45 cells (magnification: 200×). **D**, Cell scratch assay detected the crawling ability of MKN28 and MKN45 cells (magnification: 200×). Data were expressed as mean ± SD, *$p<0.05$.

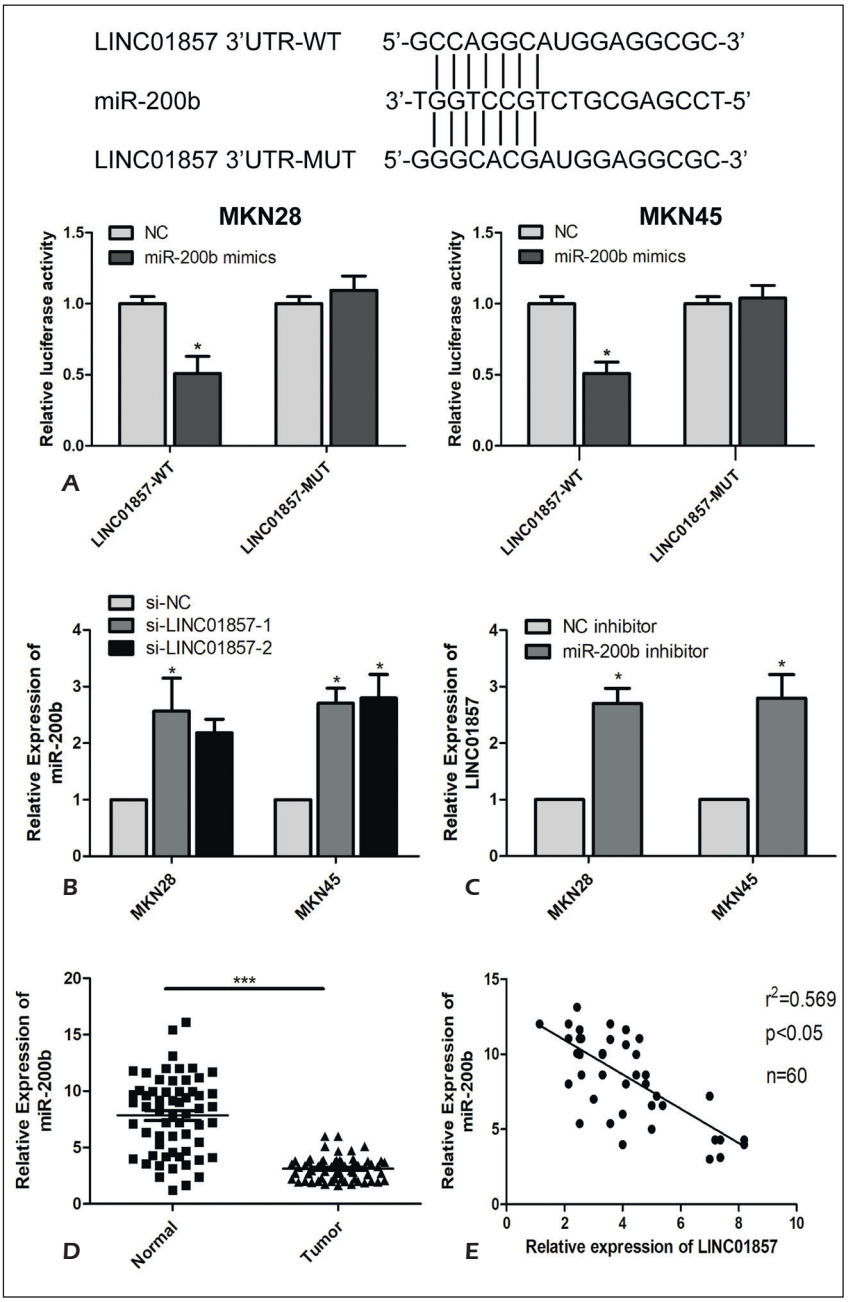

Figure 3. LINC01857 direct targeting of miR-200b. **A**, Dual-Luciferase reporter gene assay verified the direct targeting of LINC01857 and miR-200b. Luciferase reporter gene assay in MKN28 and MKN45 cell lines showed that the overexpression of miR-200b significantly attenuated the Luciferase activity of wild-type LINC01857 vector ($p<0.001$) without attenuating the vector containing the mutant (Luciferase activity ($p>0.05$) $p>0.05$). **B**, QRT-PCR was used to detect the expression of miR-200b after silencing LINC01857. **C**, QRT-PCR was used to detect the expression of LINC01857 after silencing miR-200b. **D**, QRT-PCR was used to detect the expression of miR-200b in GCa tissues and adjacent tissues. **E**, There was a significant negative correlation between the expression levels of LINC01857 and miR-200b in GCa tissues. Data were expressed as mean ± SD, *$p<0.05$, ***$p<0.001$.

of GCa. These findings suggested that LINC01857 might play an important role in promoting GCa development.

To investigate the effect of LINC01857 on GCa cell proliferation and migration, we performed CCK8 and transwell migration experiments. The results showed that compared with the si-NC group, the proliferation and migration abilities of GCa cells in the si-LINC01857 group significantly decreased. These findings provided a theoretical basis for revealing the occurrence and development mechanism of GCa. However, the specific molecular mechanism of signal transduction remained to be clarified.

In recent years, the competitive endogenous RNA (ceRNAs) hypothesis has become a new gene level model. Certain specific lncRNAs can regulate gene expression by competitively binding miRNAs, thereby resulting in gene silencing[13,14]. Biological information analysis revealed that LINC01857 could bind to microRNA-200b to regulate the malignant progression of GCa.

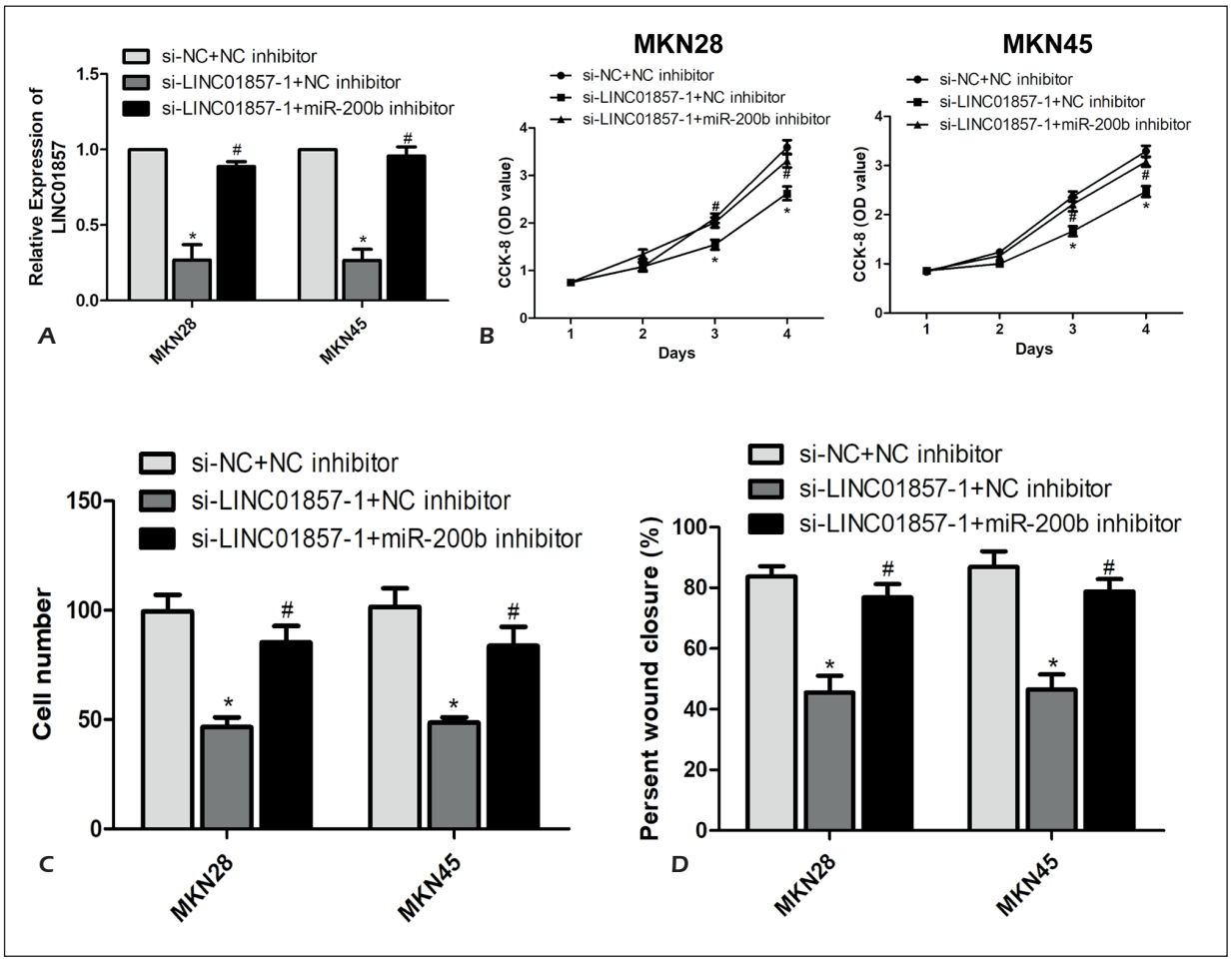

Figure 4. LINC01857 regulated the expression of miR-200b in GCa tissues and cell lines. **A**, The expression level of LINC01857 after co-transfection with LINC01857 and miR-200b was detected by qRT-PCR. **B**, CCK-8 assay detected the proliferation ability of MKN28 and MKN45 cells after co-transfection of LINC01857 and miR-200b. **C**, The transwell migration assay was performed to detect the migration and invasion abilities of MKN28 and MKN45 cells after co-transfection of LINC01857 and miR-200b. **D**, Cell scratch assay was performed to detect the crawling ability of MKN28 and MKN45 cells after co-transfection of LINC01857 and miR-200b. Data were expressed as mean ± SD, $*^{\#}p<0.05$.

However, the mechanism of LINC01857 and microRNA-200b in the occurrence and development of GCa have not been fully explored. To further explore the regulatory role of LINC01857 and microRNA-200b in GCa cell lines, we detected the level of microRNA-200b after silencing LINC01857. The results indicated that LINC01857 knockdown remarkably increased the expression level of microRNA-200b, thus promoting the occurrence and development of GCa. Silencing microRNA-200b could synergistically reverse the effect of LINC01857 knockout in GCa cell lines. These investigations suggested that the transcriptional activity of the gene locus of LINC01857 might be regulated by microRNA-200b. All our findings suggested that LINC01857 promoted the proliferation, invasion, and migration of GCa cells by modulating microRNA-200b level.

Conclusions

We first confirmed that LINC01857 was highly expressed in GCa, and was closely associated with lymph node metastasis, distant metastasis, and poor prognosis of GCa. In addition, LINC01857 promoted the proliferation, invasion, and migration of GCa by regulating microRNA-200b.

Conflict of Interests

The authors declared that they have no conflict of interests.

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