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Long noncoding RNA LINC00858 promotes the proliferation, migration and invasion of gastric cancer cells *via* the miR-363-3p/FOXP4 axis

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Abstract. – OBJECTIVE: Long non-coding RNA (lncRNA) LINC00858 has been found to exert oncogenic activity in several types of cancers, except gastric cancer (GC). In the present study, we aimed to explore the potential role of LINC00858 in GC and the underlying molecular mechanism.

PATIENTS AND METHODS: The expression patterns of LINC00858 were determined using qRT-PCR in GC samples and cell lines. Cell proliferation was examined utilizing CCK-8 assay. Cell migration and invasion were evaluated using transwell assays. We used the bioinformatics software StarBase and TargetScan to predict lncRNA-miRNA and miRNA-mRNA interactions.

RESULTS: Our findings revealed that LINC00858 expression was markedly upregulated in GC tissues and cell lines. Loss-of-function experiments demonstrated that LINC00858 silencing inhibited the proliferation, migration and invasion of GC cells. Bioinformatics analysis showed that there were several complementary binding sites between LINC00858 and microRNA (miR)-363-3p, and further Luciferase reporter assay confirmed the interaction between LINC00858 and miR-363-3p. In addition, forkhead box P4 protein (FOXP4) was found to be a target gene of miR-363-3p in GC cells. FOXP4 overexpression reversed the inhibitory effects of miR-363-3p mimics on cell proliferation, migration and invasion of BGC-823 cells.

CONCLUSIONS: Collectively, LINC00858 acted as an oncogene in GC via regulating miR-363-3p/FOXP4 axis, which indicated that LINC00858 might be a novel therapeutic target for the treatment of GC.

Key Words:
Gastric cancer (GC), Long non-coding RNA (lncRNA), LINC00858, MiR-363-3p, FOXP4.

Introduction

Gastric cancer (GC) is one of the most common malignant tumors in digestive system over the world[1,2]. Although the medical and surgical therapies have been improved, the prognosis for advanced-stage GC is grim, which is mainly attributed to delayed diagnosis[3,4]. Therefore, it is important to explore appropriate diagnostic biomarkers and therapeutic targets for GC. Long non-coding RNAs (lncRNAs) are defined as transcripts longer than 200 nt and act as competing endogenous RNAs (ceRNAs) by competitively binding several miRNAs[5]. They are rarely involved in protein coding, however, lncRNAs have the ability to regulate gene expression through various mechanisms, such as chromatin modification/remodeling, gene suppression/activation, splicing modulation, miRNA sponges/translation[6]. Increasing data show that lncRNAs contribute to many biological processes, such as cell proliferation, differentiation, and migration, as well diverse signaling pathways. Therefore, lncRNAs are found to be implicated in the pathogenesis of various cancers, including GC[7,8].

Many lncRNAs are dysregulated in GC[9]. They are closely related to diagnosis, tumorigenesis, metastasis, or prognosis of GC patients[10]. Additionally, some of these lncRNAs are found to be upregulated in GC tissues and possess oncogenic activities, while some lncRNAs are downregulated and exhibit tumor suppressive activities[10]. These researches indicate diagnostic, prognostic, and even therapeutic values of lncRNAs in GC. LncRNA LINC00858 is a newly identified lncRNA that possesses oncogenic activity in several types of cancers, such as lung cancer[11], colorectal

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cancer[12], and osteosarcoma[13]. LINC00858 has been observed to be correlated with tumor progression and prognosis. However, the potential values of LINC00858 in GC have not been reported.

In the present study, we aimed to explore the potential role of LINC00858 in GC and the molecular mechanism. We found that LINC00858 expression was upregulated in GC tissues and cell lines. Further bioinformatics analysis and functional investigations demonstrated that LINC00858 acted as a sponge for microRNA (miR)-363-3p and thereby regulated the expression of forkhead box P4 protein (FOXP4), which is an identified oncogene in several cancers.

Patients and Methods

Clinical Tissues and Cell Culture

A total of 43 GC tissues and paired adjacent normal tissues were obtained from GC patients who were subjected to surgical resection at Huaihe Hospital of Henan University (Kaifeng, China). According to TNM staging system of the Union for International Cancer Control (UICC)/the American Joint Committee on Cancer (AJCC), a diagnosis of GC was confirmed, and these patients were pathologically diagnosed as GC by two experienced pathologists without any therapy. The collected fresh samples were placed into liquid nitrogen to protect RNA integrity, and then, stored at -80°C until further qRT-PCR analysis. This study was carried out with the approval of the Ethics Committee of Huaihe Hospital of Henan Universit. All participants enrolled in this study signed the informed consent.

To explore the biological roles of LINC00858 *in vitro*, a human gastric epithelial cell line (GES-1 cells) and five GC cell lines (AGS, BGC-823, HGC-27, MGC-803 and SGC-7901) were used. All cells obtained from American Type Culture Collection (ATCC; Manassas, VA, USA) were cultured at 37°C in Dulbecco's Modified Eagle's Medium (DMEM) containing 10% fetal bovine serum (FBS; HyClone, South Logan, UT, USA).

Cell Transfection

Specific small interfering RNA (siRNA) targeting LINC00858 (si-LINC00858) and negative control siRNA (si-NC), miR-363-3p mimics, negative control mimics were all obtained from Annoron Biotech Co., Ltd. (Beijing, China). The complementary DNA (cDNA) encoding FOXP4 was PCR amplified and subcloned into pcDNA3.1 plasmid to construct FOXP4-overexpressing recombinant vector (pcDNA3.1-FOXP4). Cell transfections were conducted using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocols.

Cell Proliferation Assay

Cell Counting Kit-8 (CCK-8) assay was utilized to measure the proliferative ability of BGC-823 cells after transfection. In brief, BGC-823 cells were plated into 96-well plates and continued to culture for indicated times (24, 48, 72, 96 h). At the end period of the incubation, 10 μl CCK-8 reagent (Sangon Biotech, Shanghai, China) was added into the cells and incubated for 4 h, followed by analysis of absorbance using a microplate reader (BioTek Instruments, Winooski, VT, USA).

Cell Migration and Invasion Assays

The migrative and invasive abilities of BGC-823 cells were measured using transwell assay. BGC-823 cells were seeded into on the upper chamber with a Matrigel-coated or uncoated membrane (8 μm pore size; Corning Inc., Corning, NY, USA). The lower chambers were filled with 600 μl of DMEM medium supplemented with 10% FBS. Then, the cells were cultured for 24 h for free movement. After that, the cells moved to the lower surface of the membranes were fixed and stained with 0.1% crystal violet. Cell number in five random fields was counted under a microscope.

qRT-PCR Analysis

TRIzol reagent (Invitrogen, Carlsbad, CA, USA) was used for the extraction of total RNA from tissues and cell lines. The qRT-PCR analysis was performed using the PrimeScript RT Reagent Kit (TaKaRa, Otsu, Shiga, Japan) and SYBR Green Premix Ex Taq (TaKaRa, Otsu, Shiga, Japan) on an ABI 7500 Fast Real-time PCR machine (Applied Biosystem, Foster, CA, USA) according to the manufacturer's protocol. The miRcute miRNA First-Strand cDNA Synthesis Kit (Tiangen Biotech, Beijing, China) and miRcute miRNA qPCR detection kit (Tiangen Biotech, Beijing, China) were used to quantify the miR-363-3p expression. GAPDH and U6 were used as the internal controls. The primer sequences are as follows: LINC00858, CCCAGCTCCTTACACACGTT and TTCAGAGGC CTGCATCACTG; miR-363-3p, CGAATTGCACGGTATCCATCT and GTG CAGGGTCCGAGGT; GAPDH, 5'-CCTGGGCATGGAGTCCTGTG-3' and 5'-TCTTCATTGT-

GCTGGGTGCC-3'; U6, CTCGCTTCGGCAGCACATATACT and ACGCTTCACGAATTTGCGTGT C.

Western Blot

Total proteins from BGC-823 were isolated using 100 μl RIPA lysis buffer (Beyotime Biotechnology, Shanghai, China) and subjected to protein quantification using a BCA Protein Assay Kit (Beyotime Biotechnology, Shanghai, China). Next, the proteins were separated on 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) gel, and then, transferred onto polyvinylidene difluoride (PVDF) membrane by electro-transfection, followed by blockade in 5% dried skimmed milk for 1 h. Then, the membranes were incubated with primary antibodies diluted in 5% dried skimmed milk for 12 h at 4°C, and then, incubated with the following secondary antibody for 1 h. After that, the bands were visualized by enhanced chemiluminescence (ECL) Western blotting substrate (Invitrogen, Carlsbad, CA, USA).

Target Prediction

The StarBase (http://starbase.sysu.edu.cn/) and TargetScan (http://www.targetscan.org) were used to predict the molecular target binding sites of LINC00858 and miR-363-3p, respectively.

Luciferase Reporter Assay

The full-length sequences of LINC00858 or the mutant was embedded into psiCHECK-2 Dual-Luciferase expression vector (Promega, Madison, WI, USA) to construct psiCHECK-LINC00858-wt and psiCHECK-LINC00858-mut. A putative 3'-untranslated region (UTR) of FOXP4 or mutant 3'-UTR was cloned into the psiCHECK-2 vector to generate psiCHECK-FOXP4-wt and psiCHECK-FOXP4-mut. Then, the constructed vectors were co-transfected with miR-363-3p-3p mimics or negative control mimics into BGC-823 cells After 2 days of co-transfection, cells were collected for the determination of Luciferase activity using a Dual-luciferase Reporter Assay System (Promega, Madison, WI, USA).

Statistical Analysis

Data were shown as mean±standard deviation (SD) and analyzed by Student's *t*-test or one-way ANOVA using GraphPad Prism software (GraphPad Software Inc., La Jolla, CA, USA). $p < 0.05$ was considered statistically significant.

Results

LINC00858 Is Highly Expressed in Human Gastric Tissue Specimens and Cells

In order to evaluate the expressions of LINC00858 in human gastric tissue specimens and cell lines, qRT-PCR analysis was performed. Data in Figure 1A revealed that LINC00858 expression in GC tissues was markedly upregulated compared with the adjacent non-tumor-

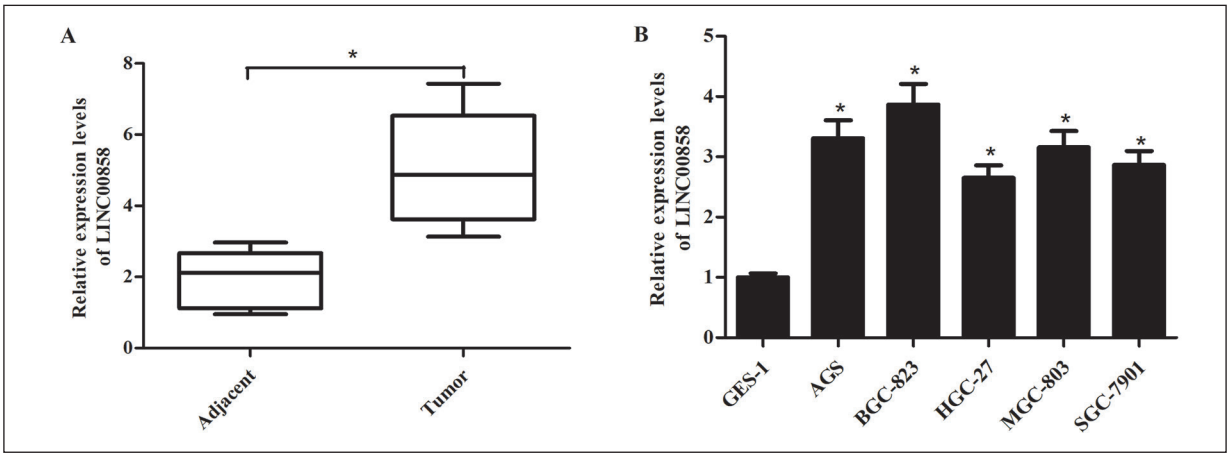

Figure 1. Expressions of LINC00858 in human gastric tissue specimens and cells. The expression levels of LINC00858 in clinical samples and cultured cells were determined using qRT-PCR analysis. **A,** LINC00858 expression was markedly upregulated in GC tissues. *p<0.05 *vs.* adjacent non-tumorous tissues. **B,** LINC00858 is highly expressed in human GC cell lines including AGS, BGC-823, HGC-27, MGC-803 and SGC-7901 cells. *p<0.05 *vs.* gastric epithelial cell line (GES-1 cells).

ous tissues. Besides, as shown in Figure 1B, LINC00858 expressions in GC cell lines (AGS, BGC-823, HGC-27, MGC-803 and SGC-7901) were also significantly higher than that in gastric epithelial cell line (GES-1 cells).

LINC00858 Silencing Inhibited the Proliferation and Invasion of GC Cells

Subsequently, loss-of-function experiments were performed after transfection with si-LINC00858 or si-NC. Si-LINC00858 markedly suppressed the expression of LINC00858 in BGC-823 cells (Figure 2A). Then, CCK-8 assay illustrated that cell proliferation was significantly decreased after transfection with si-LINC00858 (Figure 2B). Besides, transwell assays demonstrated that si-LINC00858 greatly repressed the migrative and invasive abilities of BGC-823 cells (Figure 2C and 2D).

LINC00858 Targeted MiR-363-3p in GC Cells

To investigate the functional mechanism of LINC00858, bioinformatics analysis was performed. The results showed that there were several complementary binding sites between LINC00858 and miR-363-3p (Figure 3A). To verify the interaction within LINC00858 and miR-363-3p, Luciferase reporter assay was carried out. The results revealed that LINC00858 directly combined with miR-363-3p, as evidenced by the decreased Luciferase activity in BGC-823 cells co-transfected with psiCHECK-LINC00858-wt and miR-363-3p mimics (Figure 3B). Furthermore, LINC00858 silencing caused a significant upregulation of miR-363-3p expression in BGC-823 cells (Figure 3C). In addition, we found that the expression of miR-363-3p was significantly decreased in GC cell lines (Figure 3D).

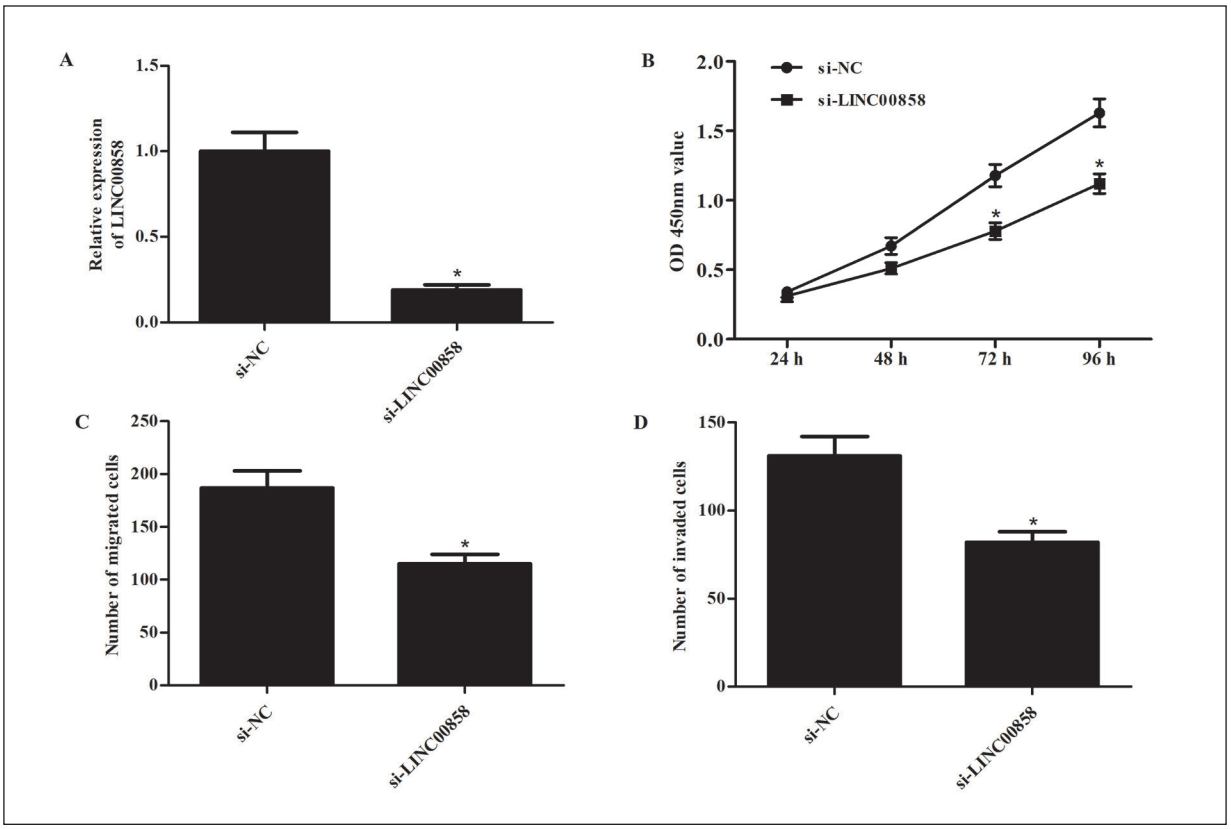

Figure 2. Effects of LINC00858 silencing on GC cells. BGC-823 cells were transfected with si-LINC00858 or si-NC, and then transfection efficiency was confirmed by qRT-PCR analysis. After 48 h post-transfection, CCK-8 assay and transwell assay were performed to determined cell proliferation and migration/invasion, respectively. **A,** Expression of LINC00858 in BGC-823 cells was markedly suppressed by si-LINC00858. **B,** LINC00858 silencing inhibited the cell proliferation of BGC-823 cells. **C,** and **D,** Si-LINC00858 repressed the migrative and invasive abilities of BGC-823 cells. *$p<0.05$ *vs.* si-NC.

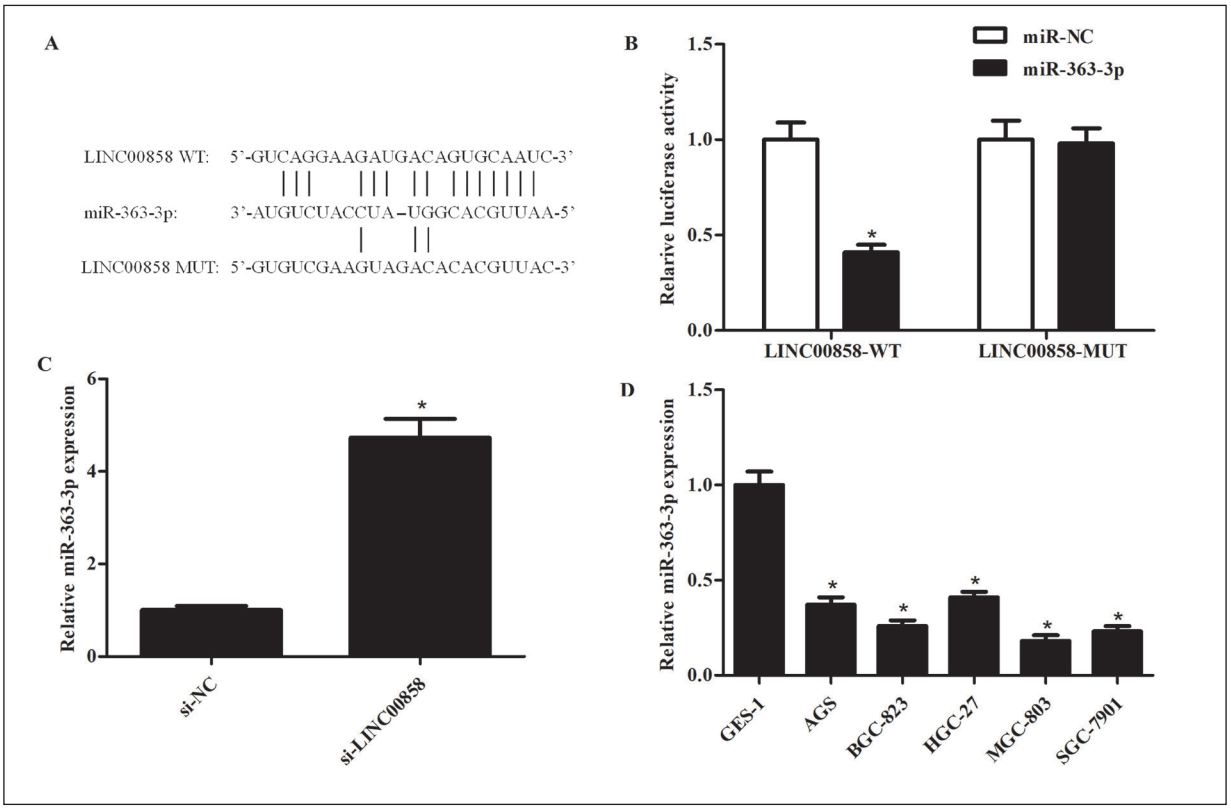

Figure 3. LINC00858 acted as a sponge of miR-363-3p in GC cells. **A,** Bioinformatics analysis showed that there were several complementary binding sites between LINC00858 and miR-363-3p. **B,** Luciferase reporter assay proved that LINC00858 directly combined with miR-363-3p. *$p<0.05$ *vs.* BGC-823 cells co-transfected with psiCHECK-LINC00858-mut and miR-363-3p mimics. **C,** Downregulation of LINC00858 resulted in significant up-regulation of the miR-363-3p expression in BGC-823 cells. **D,** The expression of miR-363-3p was detected using qRT-PCR in GC cell lines. *$p<0.05$.

Inhibition of MiR-363-3p Reversed the Inhibitory Effects of si-LINC00858 on Cell Proliferation and Migration

To determine whether LINC00858 promotes GC cell proliferation and invasion *via* inhibiting miR-363-3p, we performed rescue assays by transfection with miR-363-3p inhibitor. Adding miR-363-3p inhibitor abolished the upregulation of miR-363-3p induced by si-LINC00858 in BGC-823 cells (Figure 4A). Through the CCK-8 and transwell assays, we found that inhibition of miR-363-3p could significantly reverse the effects of si-LINC00858 on BGC-823 cell proliferation, migration and invasion (Figure 4B-D).

MiR-363-3p Targeted FOXP4 in GC Cells

Meanwhile, the bioinformatics tools were also used to predict the target gene of miR-363-3p. The results suggested that miR-363-3p possessed the potential binding sites with the 3'-UTR of FOXP4 (Figure 5A). Then, we used Luciferase reporter assay to confirm whether miR-363-3p could bind with FOXP4. As shown in Figure 5B, the Luciferase activity in BGC-823 cells was markedly reduced after co-transfection with psiCHECK-FOXP4-wt and miR-363-3p mimics. Furthermore, the expression of FOXP4 at both mRNA and protein levels in BGC-823 cells was manifestly decreased after transfection with miR-363-3p mimics (Figure 5C and 5D).

FOXP4 Reversed the Inhibitory Effects of MiR-363-3p Mimics on Cell Proliferation, Migration and Invasion

We examined the expression of FOXP4 and found that FOXP4 expression was significantly upregulated in GC tissues (Figure 6A). Furthermore, we explored the functions of miR-363-

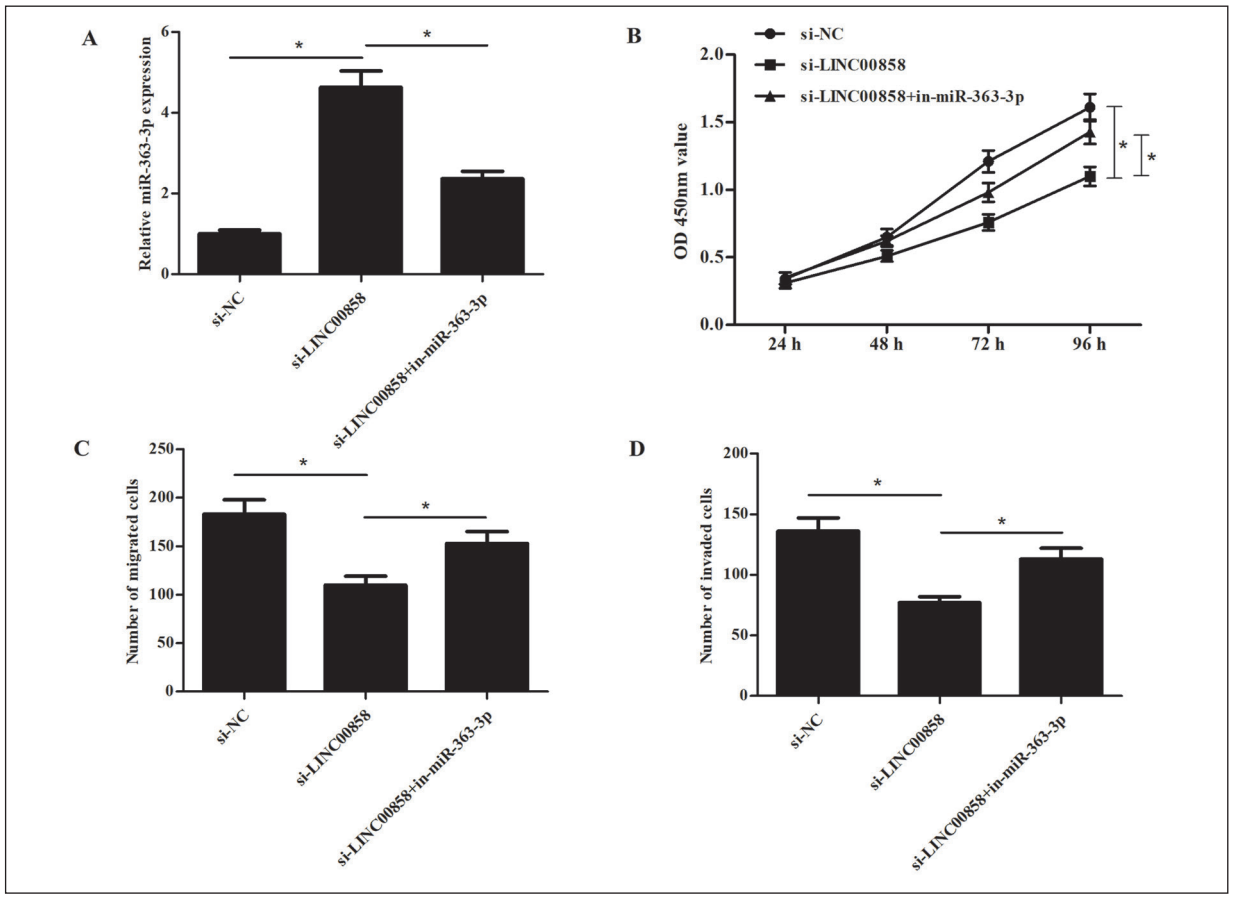

Figure 4. Inhibition of miR-363-3p reversed the inhibitory effects of si-LINC00858 on cell proliferation and migration. BGC-823 cells were transfected with si-LINC00858 and/or miR-363-3p inhibitor. **A,** The expression of miR-363-3p was detected using qRT-PCR analysis. **B,** Cell proliferation was evaluated using the CCK-8 assay. **C,** and **D,** Cell migration and invasion were examined by transwell assays. *p<0.05.

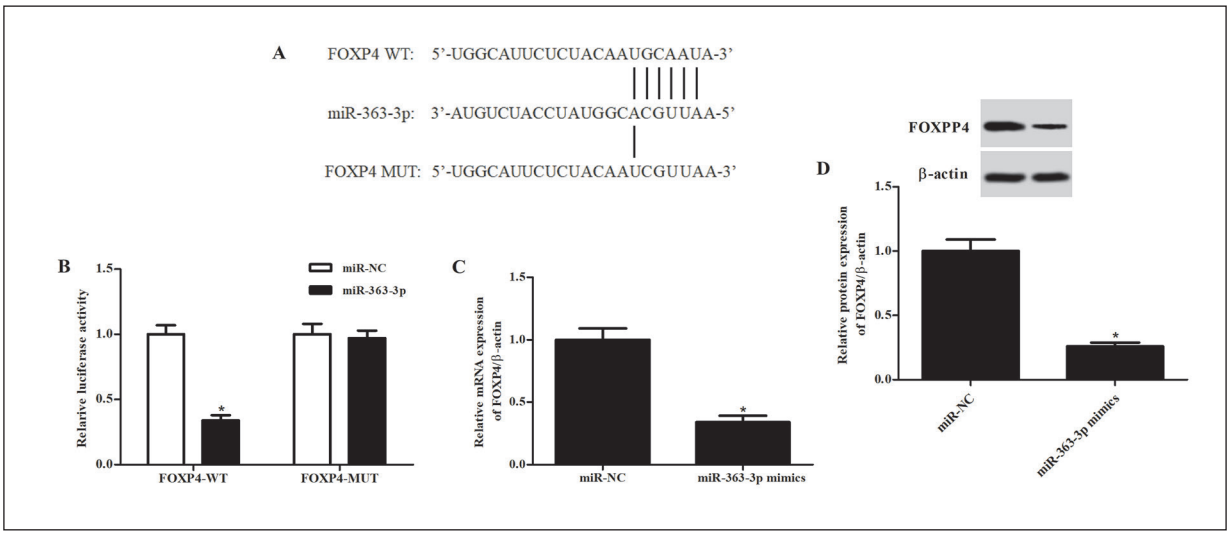

Figure 5. FOXP4 was a target of miR-363-3p in GC cells. **A,** Predicted results from bioinformatics tools suggested that miR-363-3p possessed potential binding sites with the 3'-UTR of FOXP4. B, Luciferase reporter assay showed that miR-363-3p could directly bind with the 3'-UTR of FOXP4. *p<0.05 *vs.* BGC-823 cells co-transfected with psiCHECK-FOXP4-mut and miR-363-3p mimics. **C,** and **D,** MiR-363-3p suppressed the expression of FOXP4 in BGC-823 cells. *p<0.05.

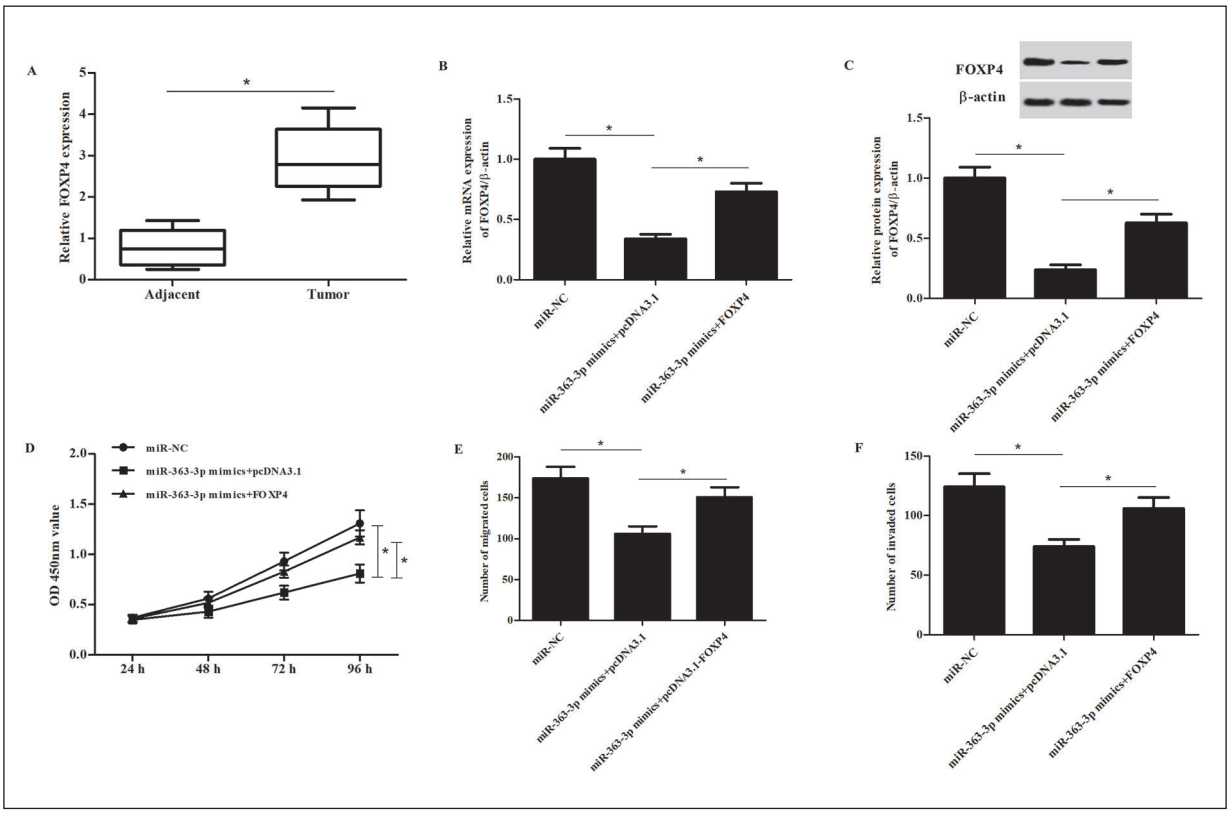

Figure 6. Effects of FOXP4 overexpression on the inhibitory effects of miR-363-3p mimics on GC cells. **A,** The expression of FOXP4 was detected using qRT-PCR in GC tissues. BGC-823 cells were transfected with pcDNA3.1-FOXP4/pcDNA3.1 and/or miR-363-3p mimics/control mimics. **B,** and **C,** The expression of FOXP4 was detected using qRT-PCR and Western blot. **D-F,** CCK-8 and transwell assays were performed to examined cell proliferation and migration/invasion. *$p<0.05$.

3p and FOXP4 in BGC-823 cells. The results showed that transfection with FOXP4 overexpressing plasmid greatly rescued miR-363-3p-decreased FOXP4 expression BGC-823 cells (Figure 6B and C). Moreover, transfection with miR-363-3p mimics resulted in a significant decrease in cell proliferation of BGC-823 cells. However, FOXP4 overexpression induced cell proliferation in miR-363-3p-overexpressing BGC-823 cells (Figure 6D). In addition, the inhibitory effects of miR-363-3p mimics on cell migration and invasion were blocked by FOXP4 overexpression (Figure 6E-F).

Discussion

The carcinogenesis of GC is complex and associated with multiple processing steps, such as numerous genetic and epigenetic alterations[14,15]. Deregulation of lncRNAs is involved in the tumorigenesis of GC[16]. It has been reported[11,13,17] that lncRNA LINC00858 could participate in the initiating and the progress of several cancers. Xue et al[11] detected that the expression of LINC00858 is significantly increased in lung cancer tissues compared with normal tissues, suggesting that LINC00858 may play an important role in lung cancer. Functional analysis proved that the overexpression of LINC00858 significantly promotes the proliferation, invasion and epithelial-mesenchymal transition (EMT) process in lung cancer cells[11]. Gu et al[13] demonstrated that LINC00858 expression is significantly upregulated in both clinical osteosarcoma tissues and culture cell lines, as compared to the adjacent non-cancer tissues and human osteoblastic cell line (hFOB), respectively. Mechanism assays presented that the knockdown of LINC00858 significantly repressed cell proliferation and invasion in osteosarcoma cells, and inhibits the tumor growth in a mice tumor xenograft model[13]. In addition, LINC00858 expression is significantly higher in colorectal cancer tissues than in adjacent tissues[12].

The higher expression of LINC00858 is significantly associated with histological grade, lymph nodes metastasis and TNM stage. Moreover, the 5-year overall survival of high-LINC00858 group is significantly lower than that of low-LINC00858 group. Taken together, LINC00858 may have potential to be a prognostic biomarker for colorectal cancer[12]. Our findings revealed that LINC00858 expression was markedly upregulated in GC tissues and cell lines. Loss-of-function experiments demonstrated that LINC00858 silencing inhibited the proliferation, migration and invasion of GC cells, implying that LINC00858 might be involved in the development of GC.

LINC00858 generally acts as a ceRNAs of miRNAs. In the present study, we used online software StarBase to predict the target miRNAs of LINC00858. The results showed that there were several complementary binding sites between LINC00858 and miR-363-3p. MiR-363-3p has been previously demonstrated to be downregulated in GC tissues and the miR-363-3p level is significantly associated with the degree of tumor differentiation[18,19]. In addition, Song et al[20] proved that miR-363-3p acts as a tumor suppressor in GC. MiR-363-3p mimics inhibits cell growth and migration in GC cells *via* targeting NOTCH1. Similarly, herein, our results also showed that miR-363-3p suppressed cell proliferation, migration and invasion of BGC-823 cells. Luciferase reporter assay revealed that LINC00858 directly combined with miR-363-3p. Furthermore, LINC00858 silencing significantly induced the miR-363-3p expression in BGC-823 cells. These findings suggested that LINC00858 functioned as miR-363-3p sponge in GC.

Family of forkhead box (FOX) transcription factors has been found to play an important role in oncogenesis[21,22]. FOXP4, a member of FOX family, is highly expressed in several types of cancers and acts as an oncogene[23-26]. FOXP4 is highly expressed in breast cancer tissues and cell lines[27]. High expression of FOXP4 is associated with bigger tumor size, pathological grade, lymph node metastasis, as well predicts a poor prognosis in breast cancer patients. Besides, the expression of FOXP4 is elevated in hepatocellular carcinoma (HCC) tissues and cell lines[28]. High expression of FOXP4 is closely associated with clinicopathological features of HCC patients, such as tumor size, TNM stage and metastasis, indicating that FOXP4 may play a key role in HCC development. Elevated expression of FOXP4 in HCC cells promotes cell proliferation, migration, invasion and EMT process[28]. In the present study, FOXP4 was found to be a target gene of miR-363-3p in GC cells. MiR-363-3p directly bound with FOXP4 and suppressed FOXP4 expression in BGC-823 cells. Additionally, FOXP4 overexpression reversed the inhibitory effects of miR-363-3p mimics on BGC-823 cells, implying that miR-363-3p exerted its roles *via* targeting FOXP4.

Conclusions

Our study demonstrated that LINC00858 acted as an oncogene *via* regulating miR-363-3p/FOXP4 axis in GC. Thus, LINC00858 might be a novel therapeutic target for the treatment of GC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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