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Linc00707 promotes cell proliferation, invasion, and migration via the miR-30c/CTHRC1 regulatory loop in breast cancer

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Abstract. – OBJECTIVE: Breast cancer (BC) is the most common malignant tumor in women. We aimed at investigating the function of long non-coding RNA LINC00707 in BC and the potential mechanism.

PATIENTS AND METHODS: The expression level of linc00707 was determined using the quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) in BC tissues and cell lines. The Cell Counting Kit-8 (CCK-8) and colony formation assays were performed to detect the potential influence of LINC0070 on the proliferation ability of the BC cells. Also, the invasion and migration abilities were assessed by the transwell assay. Furthermore, with the bioinformatic analysis and the Dual-Luciferase Reporter Gene Assay, we analyzed the interaction in LINC00707/miR-30c/CTHRC1 regulatory loop. The regulatory effects of LINC00707/miR-30c/CTHRC1 on BC were finally determined.

RESULTS: LINC00707 was significantly upregulated in BC tissues and cell lines. The knockdown of LINC00707 inhibited proliferation, invasion, and migration in MDA-MB-231 cells, while the overexpression of LINC00707 achieved the opposite results in MDA-MB-468 cells. LINC00707, acting as a competing endogenous RNA (ceRNA), could sponge miR-30c to upregulate CTHRC1, thus promoting BC progression.

CONCLUSIONS: LINC00707 was highly expressed in BC tissues and cells. It promoted cell proliferation, invasion, and migration via miR-30c/CTHRC1 regulatory loop. This might provide a novel target for the diagnosis, treatment, and prognosis for BC.

Key Words:
Linc00707, Breast cancer, MiR-30c, CTHRC1, Metastasis.

Introduction

Breast cancer (BC) has become the second leading cause of cancer deaths among women worldwide. Death number of BC accounts for 14% of all female cancer deaths. There will be approximately 386,150 cases of BC in the United States in 2019[1,2]. Currently, remarkable results in surgical treatment, radiotherapy, chemotherapy, and endocrine therapy for BC have been achieved, but its 5-year survival rate still remains low[3]. Therefore, it is of great significance to find new targets for improving the prognosis of BC patients.

Long non-coding RNAs (LncRNAs), as a new class of non-coding RNAs, have been proved to be involved in a variety of cellular biological processes, including tumor development, proliferation, apoptosis, invasion, metastasis, and angiogenesis[4,5]. In particular, lncRNA LINC00337 promotes cell proliferation of gastric cancer by EZH2-mediated the downregulation of p21[6]. LINC00052 inhibits colorectal cancer metastasis *via* modulating CALCOCO1 expression by sponging miRNA-574-5p[7]. In hepatocellular carcinoma, lncRNA CCAT1 accelerates autophagy *via* sponging miR-181 to regulate ATG7[8]. In addition, lncRNA FOXO1 inhibits cell growth of lung cancer *via* inactivating the PI3K/AKT signaling axis[9]. Many lncRNAs are differentially expressed in BC tissues and normal tissues. LncRNAs could affect the tumorigenesis and progression of BC by affecting cell growth, apoptosis, and metastasis. LncRNA HCP5 functions as a ceRNA by sponging miR-219a-5p to regulate BIRC3 level, thereafter promoting the progression of triple-negative breast cancer[10]. LncRNA H19 regulates BC cell development and metastasis *via* sponging miR-138[11]. In triple-negative breast cancer, LINC01638, prevents SPOP-mediated c-Myc degradation and activates MTDH-Twist1 signaling[12]. In addition, the downregulation of lncRNA GAS5 activates miR-222 to confer tamoxifen resistance in BC[13]. LncRNA NKILA inhibits epithelial-mesenchymal transition (EMT) induced by TGF-β *via* suppressing the NF-κB signaling pathway in BC[14].

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LINC00707 is an intergenic non-coding RNA of 3087 nt, located on chromatin 10p17. It promotes the progression of several types of tumors, including colorectal cancer, gastric cancer, and hepatocellular carcinoma[15-18].

Here, we first measured the relative expression of LINC00707 in BC tissue samples compared to adjacent normal breast tissue samples. Also, LINC00707 expression in BC cells was detected using the quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). The regulatory effects of LINC00707 on proliferation, invasion, and migration in MDA-MB-231 and MDA-MB-468 cells were determined. The potential functions of LINC00707/miR-30c/CTHRC1 regulatory loop in BC, have been finally identified. Taken together, our current study might provide a viable new perspective for diagnosis and biotherapy of BC.

Patients and Methods

Tissue Specimens

A total of 79 cases of BC tissue specimens were collected from patients in the Shanxian Central Hospital from February 2015 to June 2017. The median age of enrolled patients was 54.2 years (31-77 years). No chemotherapy or radiotherapy was performed before surgery. Patients signed the informed consent, and the research protocol got the approval of the Ethics Committee of Shanxian Central Hospital.

Cell Culture and Transfection

The human-derived BC cell lines SK-BR-3, MDA-MB-468, MDA-MB-415, Hs 362.T, and MDA-MB-231, and human breast epithelial cell line MCF10A were obtained from the Shanghai Institutes of Biological Sciences (Shanghai, China). The cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Grand Island, NY, USA) containing 1% penicillin-streptomycin (HyClone, South Logan, UT, USA) and 10% fetal bovine serum (FBS; Gibco, Grand Island, NY, USA). The cells were cultivated in 5% CO_2 humid air at 37°C. LINC00707 shRNA (shRNA-Linc00707), shRNA negative control (shRNA-NC), LV-Linc00707, LV-Control, miR-30c mimics, and mimics NC were all synthesized by Genomeditech (Shanghai, China). Cell transfection was done using Polybrene (Hanbio, Shanghai, China) following the manufacturer's protocols.

RNA Extraction and qRT-PCR

TRIzol reagent (Invitrogen, Carlsbad, CA, USA) was employed to isolate the total RNA of BC tissues and cells according to the manufacturer's protocol. A reverse transcription kit (TaKaRa, Otsu, Shiga, Japan) was bought to reverse transcribe RNA to complementary deoxyribose nucleic acid (cDNA). QRT-PCR was performed by using SYBR (TaKaRa, Otsu, Shiga, Japan) on ABI 7900 qRT-PCR system (Applied Biosystems, Foster City, CA, USA) in accordance with the manufacturer's instructions. The glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as an internal control for LINC00707, while U6 was used for miR-30c. The primer sequences used were: LINC00707: forward 5′-CCCAGACATGACCCGATGAC-3′ and reverse 5′-CTGGACTGTGAGTACCAGGC-3′; GAPDH: forward 5′-CTCACCGGATGCACCAATGTT-3′ and reverse 5′-CGCGTTGCTCACAATGTTCAT-3′. All primers were obtained by GeneWiz (Suzhou, China). The relative expressions were analyzed using the comparative cycle threshold (CT) ($2^{-\Delta\Delta CT}$) method. The reactions were measured in triplicates.

Cell Counting Kit-8 (CCK-8) Assay

The cells were inoculated in 96-well plates with 1000 cells per well. Cell proliferation ability was determined using the CCK-8 method (Dojindo Laboratories, Kumamoto, Japan). The detection time points were 24, 48, 72, and 96 hours after cell culture. Six parallel wells were set at each detection time. 10 μL of CCK-8 reagent was added into each well, and the absorbance at 470 nm was detected using a microplate reader after 2 h of incubation. The experiments were repeated for 3 times.

Colony Formation Assay

The cells were inoculated in 6 cm dishes with 1000 cells per well. They were cultured for 15 days. The cells were fixed with formaldehyde and stained with crystal violet. Under a microscope, the number of colonies containing more than 50 cells was counted and compared.

Transwell Assay

The 8-μm transwell well inserts (Millipore, Billerica, MA, USA) and Matrigel (BD Biosciences, San Jose, CA, USA) were prepared. For the migration assay, MDA-MB-231 and MDA-MB-468 cells suspended in the serum-free medium were seeded on the top of the transwell

chamber with 1×10^5 cells per well. The bottom chamber was filled with DMEM containing 10% FBS. After 48 h incubation, the non-penetrated cells were cleaned with a cotton swab from the upper filter. The cells on the bottom surface of the filter were incubated in methanol for 30-min fixation and crystal violet for 15-min staining. The migratory cell numbers were determined under a microscope (Olympus, Tokyo, Japan) in six randomly selected fields by counting the stained cells. For invasion assay, the upper chamber of the insert was covered with Matrigel. All assays were performed in triplicates.

Dual-Luciferase Reporter Gene Assay

We employed the Dual-Luciferase Reporter Gene Assay System (Promega, Madison, WI, USA) for the analysis. LINC00707 sequences containing the wild-type (WT) or mutant (MUT) miR-30c-binding sites were compounded by GenePharma (Shanghai, China) and inserted into the system. MDA-MB-468 cells were co-transfected with miR-30c mimics/negative control and WT/MUT Luciferase plasmids. Luciferase activities were measured after 48 h of co-transfection. The relative ratio of the Luciferase activity of firefly to that of Renilla was assessed. Also, the interaction between miR-30c and CTHRC1 was analyzed in the same way.

Western Blot Analysis

The cellular proteins were extracted using radioimmunoprecipitation assay (RIPA) reagent (Beyotime, Shanghai, China) supplemented with phenylmethylsulfonyl fluoride (PMSF) (Beyotime, Shanghai, China). A bicinchoninic acid (BCA) protein assay kit (Beyotime, Shanghai, China) was used to determine the protein concentration. A total of 20 μg proteins were separated with electrophoresis using 10% dodecyl sulfate, sodium salt-polyacrylamide gel electrophoresis (SDS-PAGE) gel and transferred onto polyvinylidene difluoride membranes (PVDF; Millipore, Billerica, MA, USA). After blockage in non-fat milk, the membranes were immersed at 4°C overnight in the primary antibodies. Next, these membranes were incubated with a horseradish peroxidase (HRP)-labeled secondary antibody (1:2000, CST, Danvers, MA, USA) for 2 h at room temperature after washing with Tris-Buffered Saline with Tween-20 (TBST). An enhanced chemiluminescence (ECL) kit (Millipore, Millipore, Billerica, MA, USA) was used to detect protein expressions using Bio-Rad (Hercules, CA, USA) imaging system. Each experiment was repeated for 3 times. The primary antibodies used were as follows: anti-CTHRC1 (1:1000, Cell Signaling Technology, Danvers, MA, USA) and anti-GAPDH (dilution 1:2000, CST, Danvers, MA, USA).

Statistical Analysis

The statistical analysis was conducted using the Statistical Product and Service Solutions (SPSS) 19.0 software (IBM Corp., Armonk, NY, USA) and GraphPad 5.0 software (La Jolla, CA, USA). The *t*-test was used for comparing the differences between the two groups. $p<0.05$ was considered to have a significant difference.

Results

Linc00707 Was Overexpressed in Breast Cancer Tissues and Cells

We employed qRT-PCR to measure the level of LINC00707 in 79 paired BC tissue samples comparing to adjacent normal breast tissue samples. Clearly shown in Figure 1A, LINC00707 level was highly expressed in BC tissues, indicating that LINC00707 might function as an oncogene in BC. Next, LINC00707 level in BC cell lines MDA-MB-468, SK-BR-3, MDA-MB-415, Hs 362.T, and MDA-MB-231, and human breast epithelial cell line MCF10A was determined. Similarly, LINC00707 was upregulated in BC cells (Figure 1B). These data suggested that LINC00707 was upregulated in BC tissues and cells, which could act as an oncogenic effect.

For further studying the function of LINC00707 in BC cells, LINC00707 expression was knocked down in MDA-MB-231 cells by transfection of shRNA-Linc00707 and it was overexpressed in MDA-MB-468 cells by transfection of LV-Linc00707 (Figures 1C, 1D).

Ectopic Expression of Linc00707 Influenced BC Cell Proliferation

To evaluate the influence of LINC00707 in cell proliferation, CCK-8 and colony formation assay were conducted. The knockdown of LINC00707 decreased the proliferation of MDA-MB-231 cells, while the overexpression of LINC00707 yielded the opposite result in MDA-MB-468 cells (Figures 2A, 2B). The colony formation assay obtained similar results (Figure 2C-2F). These results indicated that LINC00707 could promote the proliferation of BC cells.

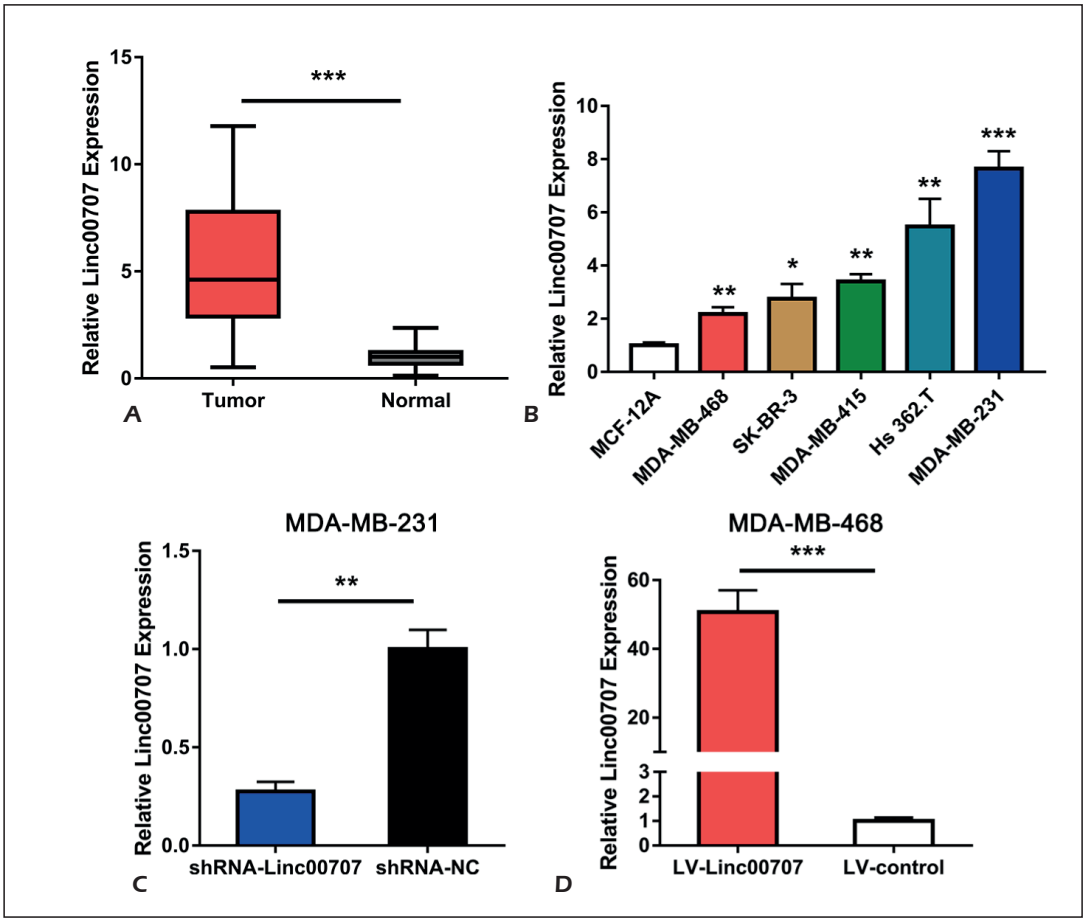

Figure 1. LINC00707 was highly expressed in breast cancer (BC) tissues and cells. **A**, QRT-PCR showed LINC00707 expression level in a total of 79 BC tissues and paired non-tumor tissues. **B**, LINC00339 expression level in BC cell lines (MDA-MB-468, SK-BR-3, MDA-MB-415, Hs 362.T, and MDA-MB-231) and human breast epithelial cell line MCF10A. **C**, ShRNA targeting LINC00707 (shRNA-LINC00339) or negative controls (shRNA-NC) was transfected into MDA-MB-231 cells. **D**, LV-Linc00707 or LV-control was transfected into MDA-MB-468 cells. ***p<0.001, **p<0.01, *p<0.05 compared to the control group.

LINC00707 Promoted Cell Invasion and Migration in BC

Next, the regulatory effects of LINC00707 on the metastatic abilities of BC were evaluated by the transwell assay. The invasion ability in MDA-MB-231 cells markedly decreased after transfection of shRNA-LINC00707 compared to the negative control cells (Figure 3A). By contrast, MDA-MB-468 cells overexpressing LINC00707 showed increased cell invasion ability compared to the LV-control group (Figure 3B). Similarly, the migration capability was stimulated by the overexpression of LINC00707, and it was attenuated after LINC00707 knockdown (Figures 3C, 3D). These experiments showed that LINC00707 could promote cell invasion and migration of BC cells.

MiR-30c Acted as a Direct Target of Linc00707 in BC

We next aimed to study the underlying mechanism of LINC00707 in BC. Several studies explained that lncRNAs exert as competing endogenous RNAs by binding to related miRNAs. Hence, we searched lncRNABase (http://starbase.sysu.edu.cn/agoClipRNA.php?source=lncRNA) and found that miR-30c acted as a potential target miRNA for LINC00707 (Figure 4A). Using Dual-Luciferase Reporter Gene Assay, we verified that miR-30c could directly bind to the specific sites in the promoter region of LINC00707 (Figures 4A, 4B). Further, we detected the expression of miR-30c in the transfected MDA-MB-231 cells and MDA-MB-468 cells using qRT-PCR. The level of miR-30c was negatively regulated by

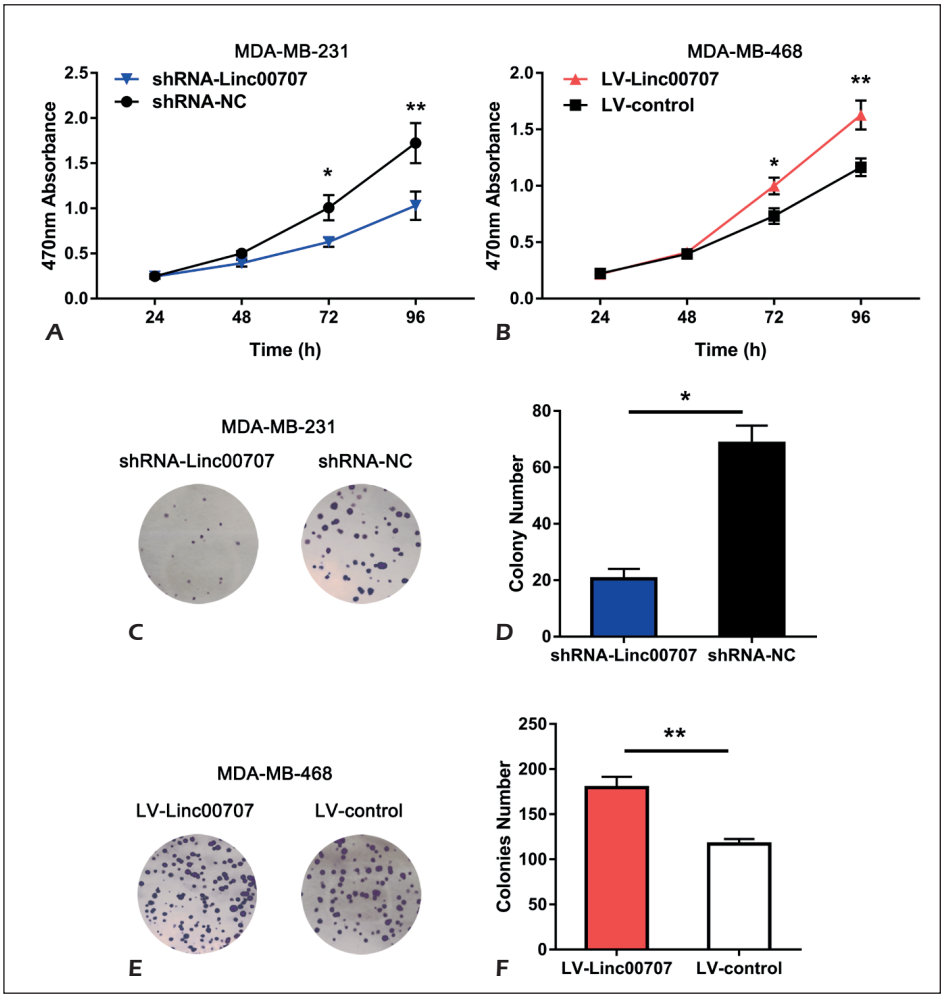

Figure 2. LINC00707 affected the proliferation of BC cells in vitro. **A-B**, CCK-8 assays showed the proliferation ability of MDA-MB-231 cells transfected with shRNA-Linc00707, or shRNA-NC, and MDA-MB-468 cells transfected with LV-Linc00707 or LV-control. **C-F**, Colony formation assay showed the proliferation ability of MDA-MB-231 cells transfected with shRNA-LINC00707 or shRNA-NC (**C-D**) and MDA-MB-468 cells transfected with LV-LINC00707 or LV-control (**E-F**) (magnification x 40). $^{**}p<0.01$, $^{*}p<0.05$ compared to the control group.

LINC00707 (Figures 4C, 4D). These results indicated that LINC00707 functioned as a ceRNA for miR-30c and negatively regulated its level.

Linc00707 Acted as an Oncogene Via Promoting CTHRC1 Expression Through Downregulating MiR-30c

As we claimed miR-30c as a target for LINC00707 in BC, we deeply explored the function of miR-30c in BC. We found that CTHRC1 was a direct target for miR-30c in BC by searching the databases, including miRBase, miRWalk, and TargetScan (Figure 5A). The binding relationship between miR-30c and CTHRC1 was further confirmed by Dual-Luciferase Reporter Gene Assay (Figure 5B). The protein and mRNA levels of CTHRC1 showed a positive correlation with LINC00707, but an evident negative correlation with miRNA-30c (Figure 5C-5G). These data demonstrated that LINC00707 could promote CTHRC1 expression *via* competitively sponging with miR-30c in BC.

Discussion

Breast cancer with high incidence is the second leading cause of cancer death in women and poses a serious threat to women's health[2,3]. The increasing survival rate of BC in recent years has

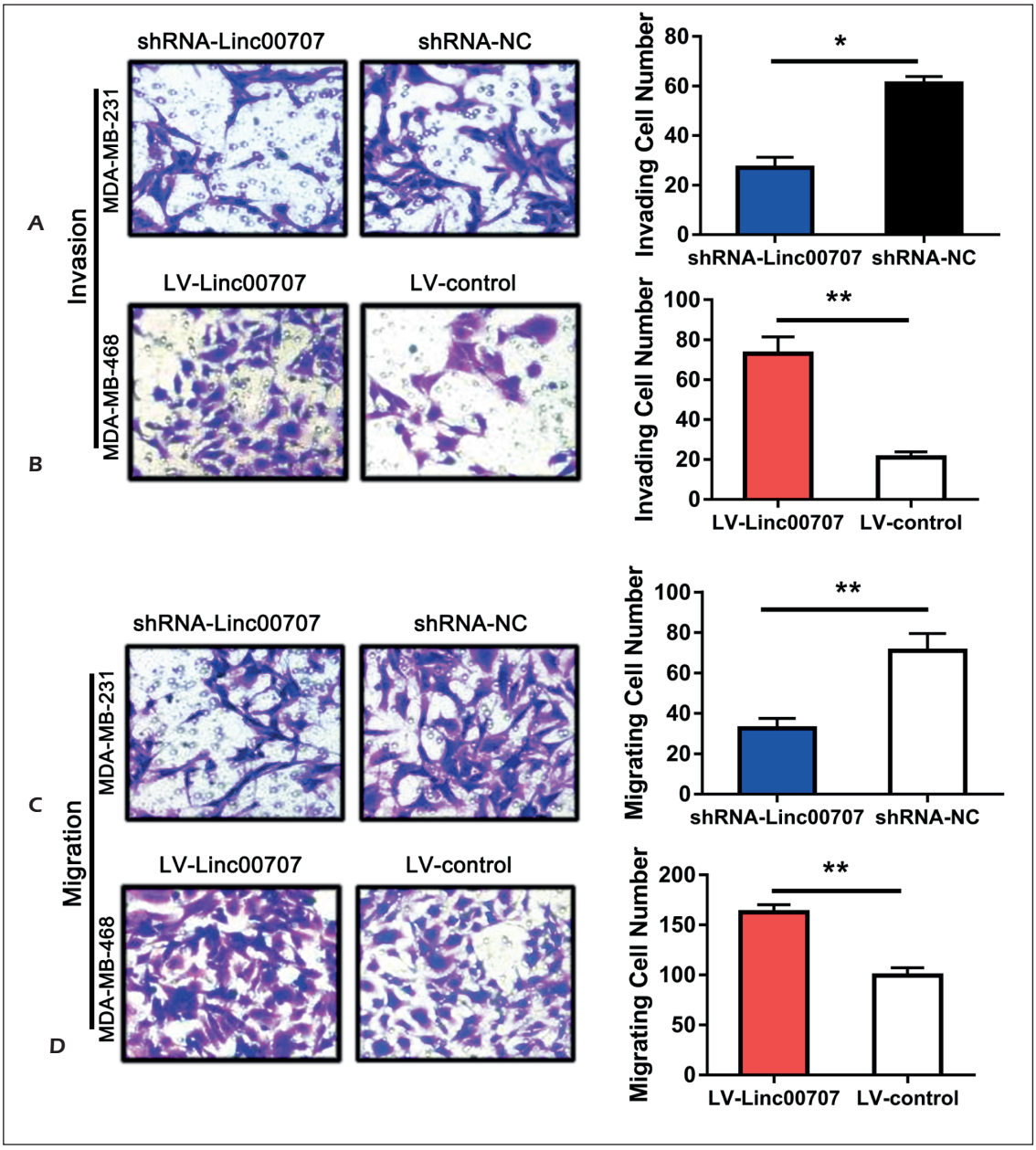

Figure 3. LINC00707 affected the invasion and migration of BC cells. **A-B**, The transwell invasion assay indicated the invasive cell number in established MDA-MB-231 cells and MDA-MB-468 cells. **C-D**, The transwell migration assay showed the migratory cell number in the established MDA-MB-231 cells and MDA-MB-468 cells (magnification ×100). $^{**}p<0.01$, $^{*}p<0.05$ compared to the control group.

mainly benefited from chemotherapy, radiotherapy, endocrine therapy, and bio-targeted therapy. The most promising treatment for improving tumor survival in the future should be targeted therapy[19-21]. Most of the therapeutic targets found in previous studies are protein-encoding genes. The discovery of lncRNAs has provided a new direction for finding new therapeutic targets. Therefore, in-depth researches on the biological properties of lncRNAs and their regulatory effects on tumor invasion and metastasis are expected to provide new targets for early diagnosis and prognosis monitoring of BC[22,23].

LINC00707 has been identified to participate in the development and progression of several types of cancers. It interacts with mRNA stabilizing protein HuR to promote growth and metastasis of gastric cancer[24]. In hepatocellular carcinoma, LINC00707

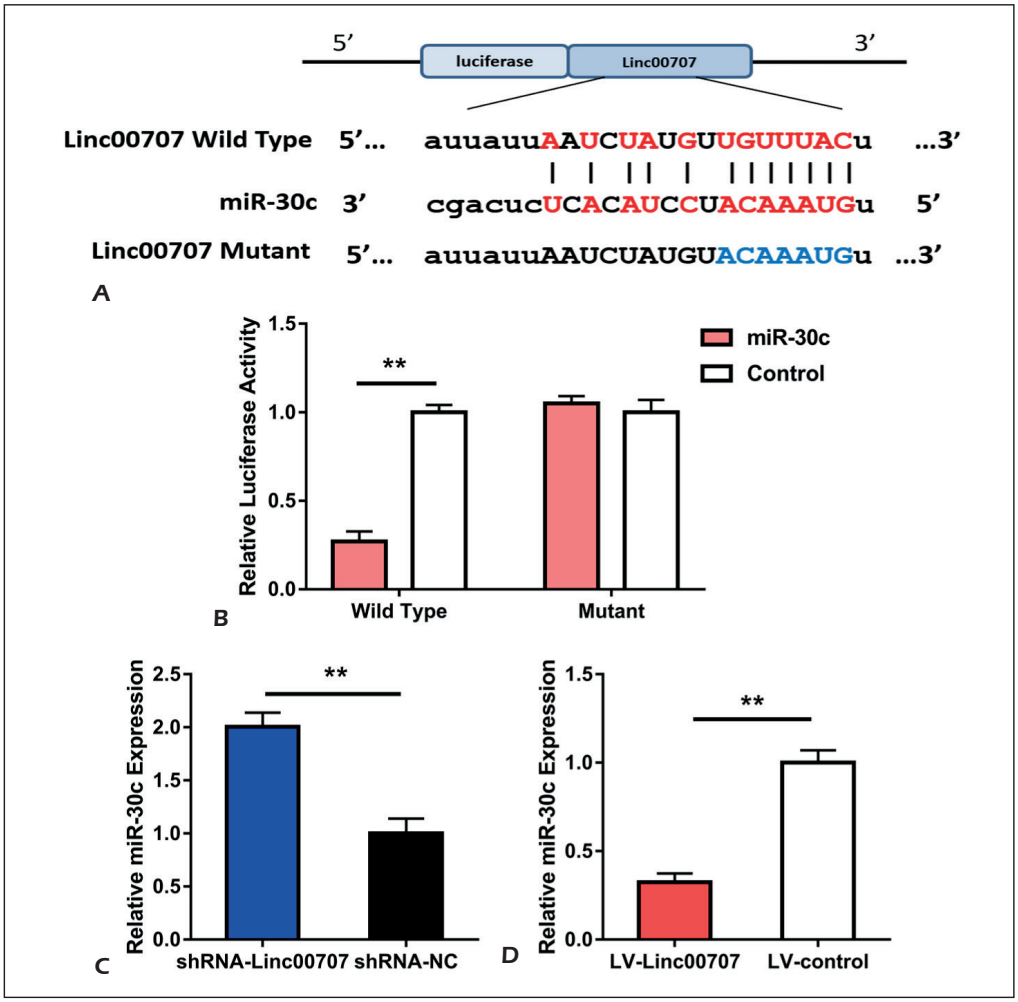

Figure 4. LINC00707 functioned as a sponge of miR-30c. **A**, The sequences of LINC00707 binding miR-30c, including the wild-type and mutant-type one. **B**, Dual-Luciferase Reporter Gene Assay verified the molecular binding between LINC00707 and miR-30c. **C-D**, QRT-PCR showed the miR-30c expression level in MDA-MB-231 or MDA-MB-468 cells transfected with shRNA-LINC00707 or LV-LINC00707. $^{**}p<0.01$, $^{*}p<0.05$ compared to the control group.

contributes to tumor progression by upregulating CDK4 *via* sponging miR-206[17]. In colorectal cancer, LINC00707 accelerates cell proliferation and migration by miR-206/FMNL2 axis[15]. Furthermore, it accelerates osteogenesis of human bone marrow-derived mesenchymal stem cells *via* sponging miR-370-3p[25]. Here, for the first time, we detected the expression of LINC00707 in BC tissues and cell lines. Our results indicated LINC00707 was upregulated in BC. Functional experiments revealed that LINC00707 could promote proliferation, invasion, and migration of BC cells, suggesting that LINC00707 acted as an oncogene in BC.

LncRNAs exert its biological effects by inhibiting the expressions of their target genes through ceRNA theory. We searched several databases and found that miR-30c acted as a potential target for LINC00707 in BC. MiR-30c has been identified as a tumor-suppressor gene[26-28]. It could inhibit the proliferation and metastasis of BC cells *via* SOX9 and indicate poor prognosis of BC[29]. Also, in triple-negative breast cancer, miR-30c might act as a prognostic and predictive factor[30,31]. Here, Dual-Luciferase Reporter Gene Assay verified that LINC00707 directly bound miR-30c and inhibited the function of miR-30c. Next, we found that CTHRC1 acted as a downstream molecule for miR-30c by searching different databases, including miRBase, miRWalk, Starbase, and TargetScan. CTHRC1 (Collagen triple helix repeat containing 1 protein) has been verified as an oncogene in cervical carcinoma, hepatocellular carcinoma, and colorectal cancer to promote tumor development and metastasis[32-37]. In BC, an immu-

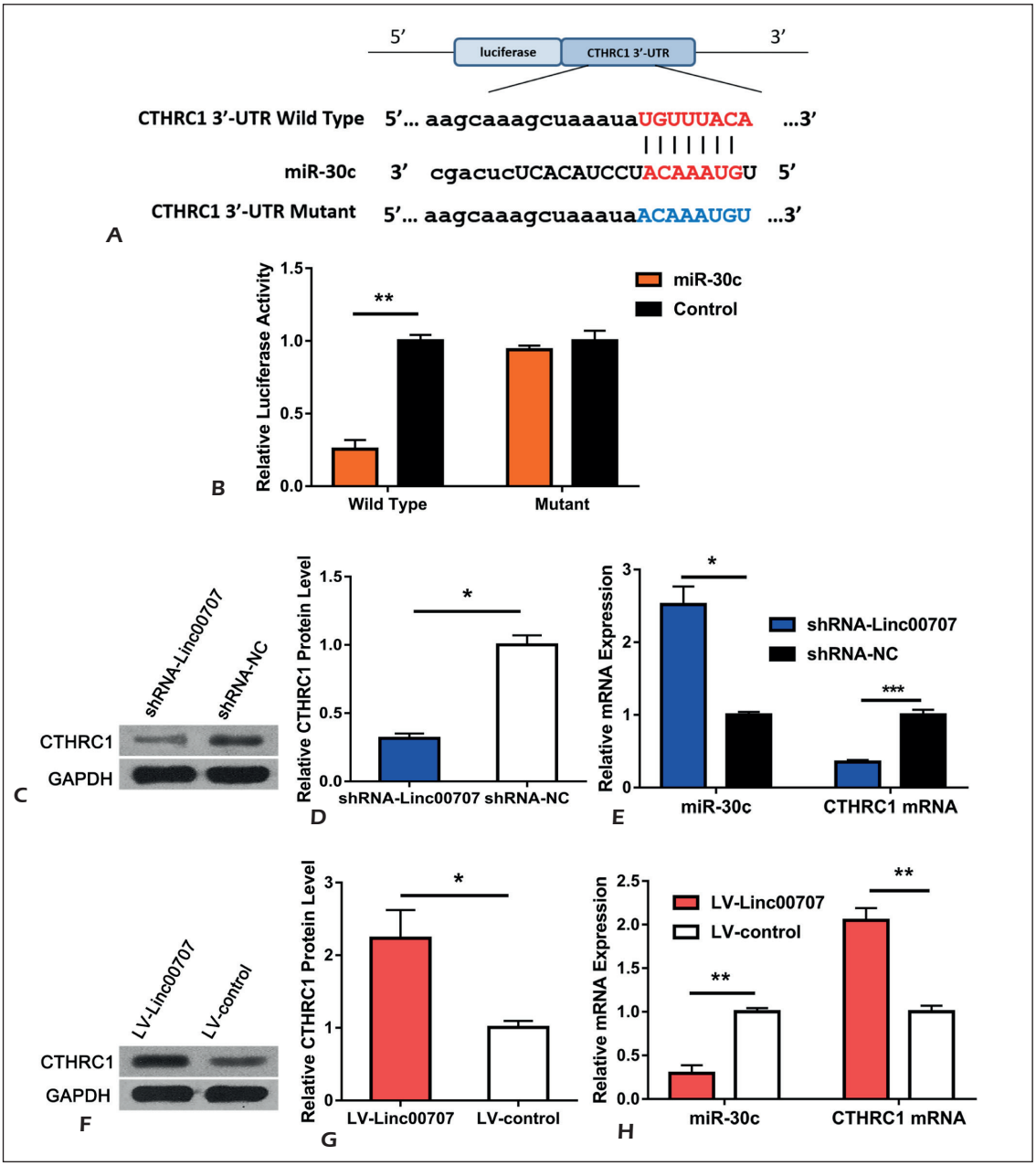

Figure 5. CTHRC1 was identified as the target protein of miR-30c. **A**, The sequences of CTHRC1 mRNA 3'-UTR and miR-30c, including the wild-type and mutant-type one. **B**, Dual-Luciferase Reporter Gene Assay indicated the molecular binding between CTHRC1 and miR-30c. **C**-**G**, Western blot assay indicated that the CTHRC1 protein expression in the established MDA-MB-231 cells (**C**-**D**) and MDA-MB-468 cells (**F**-**G**). **E**-**H**, QRT-PCR showed the mRNA expressions of miR-30c and CTHRC1 in MDA-MB-231 cells transfected with shRNA-LINC0339 or shRNA-NC (**E**) and MDA-MB-468 cells transfected with LV-LINC00707 or LV-control (**H**) $^{**}p<0.01$ $^{*}p<0.05$ compared to the control group.

nohistochemical study showed increased positive expression of CTHRC1. In our study, LINC00707 could sponge miR-30c to upregulate CTHRC1, thus promoting cell growth and metastasis in BC. In the future, *in vivo* functions of LINC00707 are required to be investigated.

Conclusions

We demonstrated that LINC00707 was significantly upregulated in BC tissues and cells. It could promote cell proliferation, invasion, and migration *via* sponging miR-30c to upregulate

the expression of CTHRC1. These findings could provide a novel sight for biological diagnosis and therapy of BC.

Conflict of Interests

The authors declare that they have no conflict of interests.

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