European Review for Medical and Pharmacological Sciences 2021; 25: 1379-1386

LINC00483 is regulated by IGF2BP1 and participates in the progression of breast cancer

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Abstract. – OBJECTIVE: To explore the role of long intergenic non-coding ribonucleic acid 483 (LINC00483) in the development of breast cancer (BC) and its possible mechanism of action.

PATIENTS AND METHODS: LINC00483 expression level in BC tissues and cell lines was detected *via* quantitative Reverse Transcription-Polymerase Chain Reaction (qRT-PCR). The association between LINC00483 expression and survival rate of BC patients was analyzed using Kaplan-Meier survival analysis. The binding relation between LINC00483 and insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) was verified *via* RNA immunoprecipitation (RIP) and RNA pull-down assays. The expression of IGF2BP1 in BC patients was determined using qRT-PCR. Moreover, the role of LINC00483 on the proliferative ability of BC cells was detected *via* cell counting kit-8 (CCK8) and 5-Ethynyl-2'-deoxyuridine (EdU) assays. Whether LINC00483 exerts its effects under the regulation of IGF2BP1 was verified *via* reversal assay.

RESULTS: The results of qRT-PCR showed that LINC00483 had a significantly high expression in BC tissues and corresponding cell lines, and it rose with the increase in tumor stage, which was higher in patients with metastasis. CCK8/EdU assay revealed that the proliferative ability of MDA-MB-231 and MCF-7 cell lines was enhanced by overexpression of LINC00483. It was confirmed by RIP and pull-down assays that IGF2BP1 could bind to LINC00483, and the expression of LINC00483 was significantly promoted after up-regulation of IGF2BP1. It was found *via* qRT-PCR that the expression of IGF2BP1 evidently rose in BC patients, which was positively related with the expression level of LINC00483. The results of reversal assay manifested that the function of LINC00483 on cell proliferation was regulated by IGF2BP1.

CONCLUSIONS: LINC00483 has a significantly higher expression in BC tissues than that in para-carcinoma tissues, and its effect of promoting proliferation of BC cells may be regulated by IGF2BP1.

Key Words:
Breast cancer, LINC00483, IGF2BP1, Proliferation.

Introduction

Breast cancer (BC) remains a worldwide public health problem. According to the Global Cancer Statistics 2018, there were about 2.1 million new cases (11.6% of total new cases of cancer) and 627 thousand deaths of BC (6.6% of total deaths of cancer) in 2018 around the world. BC is the most common cancer in females, accounting for 24.0% of female carcinoma, and also the most important cause of cancer death, which accounts for 15.0% of the total female cancer deaths[1]. With the development of BC screening and treatment, the survival time of about 80% of patients with localized lesions can be prolonged[2,3].

BC has an extremely complicated pathogenesis. It has been proved that BC is the result of the combination of various factors, such as personal lifestyle, environment, and genetic and reproductive factors[4]. According to follow-up studies, early screening and diagnosis of invasive BC can significantly improve the 5-year survival rate. In developing countries, however, the rates of early diagnosis and effective treatment are low, and the prognosis of cancer patients is generally poor. Therefore, it is of great importance to actively search for effective biomarkers and apply them to early diagnosis, molecular typing and individualized treatment of BC for the precise prevention and treatment.

Non-coding ribonucleic acids (ncRNAs), a new class of transcripts, are encoded by genomes, but most of them cannot be translated into protein. In spite of this, ncRNAs are important participants in various physiological functions[5]. Particularly, long ncRNAs (lncRNAs), with more than 200 nt in

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length, play a key role in regulating chromatin dynamics, gene expression, growth, differentiation and development[6]. It has been fully recognized that more than 80% of the human genome possesses biological functions and encodes lots of ncRNAs[7]. Thousands of lncRNAs have abnormal expressions or mutations and play a crucial role in the occurrence and development of various cancers[8]. Some researches have shown that they are related to the occurrence and development of BC[9]. It is reported that ITGA7 is down-regulated in BC tissues compared with that in normal ones. *In vitro* experiments indicated that the migration and invasion of BC MDA-MB-231 and BT-549 cell lines can be significantly inhibited by ITGA7 knockdown[10]. Moreover, the expression of long intergenic non-coding RNA 52 (LINC00052) is positively correlated with the HER3/ErbB3 level in BC cells. *In vitro* and *in vivo* assays have suggested that the overexpression of LINC00052 promotes growth of BC cells and enhances HER3-mediated downstream signal transduction[11].

LncRNAs are likely to play a crucial role in BC. In the present study, it was newly found that LINC00483 had a significantly high expression in BC tissues and cell lines, and it could greatly promote the proliferation of BC cells. This study aims to explore the role of LINC00483 in the development of BC and further explore its regulatory mechanism, which was correlated with insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1).

Patients and Methods

Clinical Samples

A total of 32 cases of BC tissues and corresponding para-carcinoma tissues were surgically resected from BC patients in Chifeng Municipal Hospital from May 2017 to June 2019. None of the patients underwent radiotherapy and chemotherapy before operation. The fresh tissue samples collected were immediately stored in liquid nitrogen for a long time. The pathological classification was made and graded by two independent experienced pathologists according to the World Health Organization Classification. Sample collection was reviewed and approved by the Ethics Committee of Chifeng Municipal Hospital, and all patients signed the informed consent.

Cell Culture

BC cell lines (MDA-MB-231, BT-549 and MCF-7) and normal breast cells (MCF-10A) were purchased from the American Type Culture Collection (ATCC; Manassas, VA, USA). They were maintained with Dulbecco's Modified Eagle's Medium (DMEM; Invitrogen, Carlsbad, CA, USA) containing 10% fetal bovine serum (FBS; Invitrogen, Carlsbad, CA, USA), 100 U/mL penicillin and 100 μg/mL streptomycin (Invitrogen, Carlsbad, CA, USA) with 5% CO_2 at 37°C.

Cell Transfection

The 3'-UTR sequence of insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) or a mutant sequence with the predicted target sites was inserted into the KpnI and SacI sites of pGL3 promoter vector. LINC00483, IGF2BP1 overexpression plasmids, IGF2BP1 small-interfering RNA and negative control sequences were synthesized by Shanghai GenePharma Co., Ltd. (Shanghai, China) based on the sequence issued by National Center for Biotechnology Information.. The cells were planted onto 6-well plates and were transfected with 100 ng of LINC00483 or IGF2BP1 overexpression plasmids, and IGF2BP1 small-interfering RNA (50nM) by using Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA). The differences in transfection efficiency were normalized by co-transfecting a Renilla luciferase vector pRLSV40 (5 ng).

Cell Counting Kit-8 (CCK8) Assay

CCK8 assay was performed using CCK8 proliferation assay kits (KeyGEN Biotech, Nanjing, China). After transfection, the cells were cultured in an incubator for 24 h. After the medium in the wells was discarded, the cells were washed once with phosphate-buffered saline (PBS), digested with trypsin and neutralized with complete medium. After centrifugation at 1000 rpm for 3 min, the cell precipitate was collected, resuspended with complete medium and counted. Then, they were inoculated into a 96-well plate (1000-4000 cells/well), with 3 replicates in each group. At 1, 2 and 3 d, the original medium was replaced with 100 μL of fresh complete medium in each well, and 10 μL of CCK8 reagent was added into each well, followed by culture in the incubator for 4 h. At last, the absorbance was measured at 450 nm using a microplate reader, and the tumor cell proliferation curves were plotted.

5-Ethynyl-2'-Deoxyuridine (EdU) Assay

The EdU incorporation assay was applied by using the Cell-LightTM EdU imaging detecting kit following the manufacturer's instructions (RiboBio). Cells in the logarithmic growth phase were seeded into a 96-well plate (4×10^4 cells/well) and cultured until normal growth. EdU solution was

diluted into the culture medium at 1000:1 (reagent A), and prepared into an appropriate amount of 50 μM EdU medium. According to the instructions of kits (RiboBio, Guangzhou, China), the cells were fixed and stained with Apollo and DNA dye. Eventually, representative photograph were taken by Zeiss Axiophot Photomicroscope (Carl Zeiss, Oberkochen, Germany).

RNA Immunoprecipitation (RIP)

Whether LINC00483 can interact with or bind to IGF2BP1 was detected *via* RIP. According to the protocol of EZ-Magna RIP kits (Millipore, Billerica, MA, USA), the cells were lysed with complete RIP lysis buffer, and the extracts were incubated with magnetic beads conjugated with antibodies that recognize IGF2BP1 or control IgG at 4°C for 6 h. Then the beads were washed and incubated with proteinase K to remove protein. Finally, the purified RNA was analyzed using quantitative Reverse Transcription-Polymerase Chain Reaction (qRT-PCR).

RNA Pull-Down Assay and Western blotting

RNA pull-down assay was processed according to the protocals of Pierce™ RNA 3' End Desthiobiotinylation Kit (Thermo Fisher Scientific, Waltham, MA, USA). Finally, the purified protein was analyzed *via* Western blotting. Total proteins were collected from cells via RIPA buffer and then quantified by using a protein assay (bicinchoninic acid method; Beyotime). The target proteins were removed to polyvinylidene fluoride (PVDF) membrane. Then they were incubated with rabbit anti-GAPDH (Cell Signaling Technology, CST, Danvers MA, USA) and rabbit anti-IGF2BP1 (Abcam Inc., Cambridge, MA, USA) were used for incubation of these membranes. The Pierce ECL was utilized for visualizing western Blotting Substrate Immunoreactive bands (Santa Cruz Biotechnology, Inc, Santa Cruz, CA, USA).

QRT-PCR

TRIzol reagent (Invitrogen, Carlsbad, CA, USA) was utilized to separate the total RNA. QRT-PCR was performed on the StepOnePlus fluorescence quantitative PCR instrument (ABI, Applied Biosystems, Foster City, CA, USA) using SYBR Green PCR Master Mix (Toyobo, Osaka, Japan), forward and reverse primers, RNase-free ddH_2O and complementary deoxyribose nucleic acid (cDNA) template. The data were analyzed using $2^{-\Delta\Delta Ct}$ method, so as to detect the difference in expression between the target group and the control group. The primer sequences are as follows: LINC00483 (F: 5'-GCTGAACCGGAACAGGACAT-3', R: 5'-CCAGTTCACAGCAACTCAC-3'). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (F: 5'-GAAGAGAGAGACCCTCACGCTG-3', R: 5'-ACTGTGAGGAGGGGAGATTCAGT-3'). IGF2BP1 (F: 5'-CAGGAGATGGTGCAGGTGTTT ATC C-3', R: 5'-GTTTGCCATAGATTCTTCCCT-GAG C-3').

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 17.0 software package (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The data were presented as mean ± standard error of mean. Analysis of variance followed by Post-Hoc Test (Bonferroni) and independent-samples *t*-test were performed to evaluate the intergroup difference. Kaplan-Meier method and log rank test were applied appropriately to compare intergroup differences in overall survival. $p<0.05$ was considered to be statistical difference.

Results

LINC00483 Expression Level Remarkably Rose in BC Tissues

First, the expression of LINC00483 was detected in BC tissues and corresponding para-carcinoma tissues. The correlation between patient's clinic pathological characteristics and the RNA level of LINC00483 was shown in Table I. The results indicated that the expression of LINC00483 markedly rose in cancer tissues (Figure 1A). Its expression was gradually increased with the increase in tumor stage (Figure 1B), and it was lower in patients without metastasis than that in those with metastasis (Figure 1C). According to further survival analysis, the survival of patients with a higher of LINC00483 was lower than that of patients with a lower of LINC00483 (Figure 1D). The receiver operating characteristic (ROC) curves revealed that the area under the curve (AUC) was 0.8472 and the cutoff value was 0.2482, indicating that LINC00483 has certain diagnostic potential (Figure 1E). These results showed that LINC00483 has good prognostic and diagnostic values in BC. Besides, it was found that the expression of LINC00483 was evidently higher in BC cell lines than that in normal breast cells, more evidently in MDA-MB-231 and MCF-7 cells (Figure 1F). Therefore, these two cells were selected for subsequent experiments.

Table I. Correlation between lncRNA LINC00483 expression and clinicopathological characteristics in TNBC patients.

Characteristics	Patients	Expression of lncRNA LINC00483		*p*-value
		Low-LINC00483	High-LINC00483	
Total	32	17	15	
Age (years)				0.491
≤50	17	10	7	
>50	15	7	8	
TNM stage				0.036
I-II	19	13	6	
III-IV	13	4	9	
Tumor size				0.304
<3cm	14	6	8	
>3cm	18	11	7	
Lymphatic metastasis				0.013
No	20	14	6	
Yes	12	3	9	

$p<0.05$ is considered as statistically significant.

LINC00483 Facilitated Proliferation of BC Cells

To further verify the effect of LINC00483 on the function of BC cells, the transfection efficiency of LINC00483 overexpression plasmids was first detected in MDA-MB-231 and MCF-7 cells. The data revealed that LINC00483 expression evidently rose after transfection compared with the control group (Figure 2A). The results of CCK8 assay manifested that the proliferative ability of MDA-MB-231 and MCF-7 cells was greatly enhanced after overexpression of LINC00483 (Figure 2B and 2C).

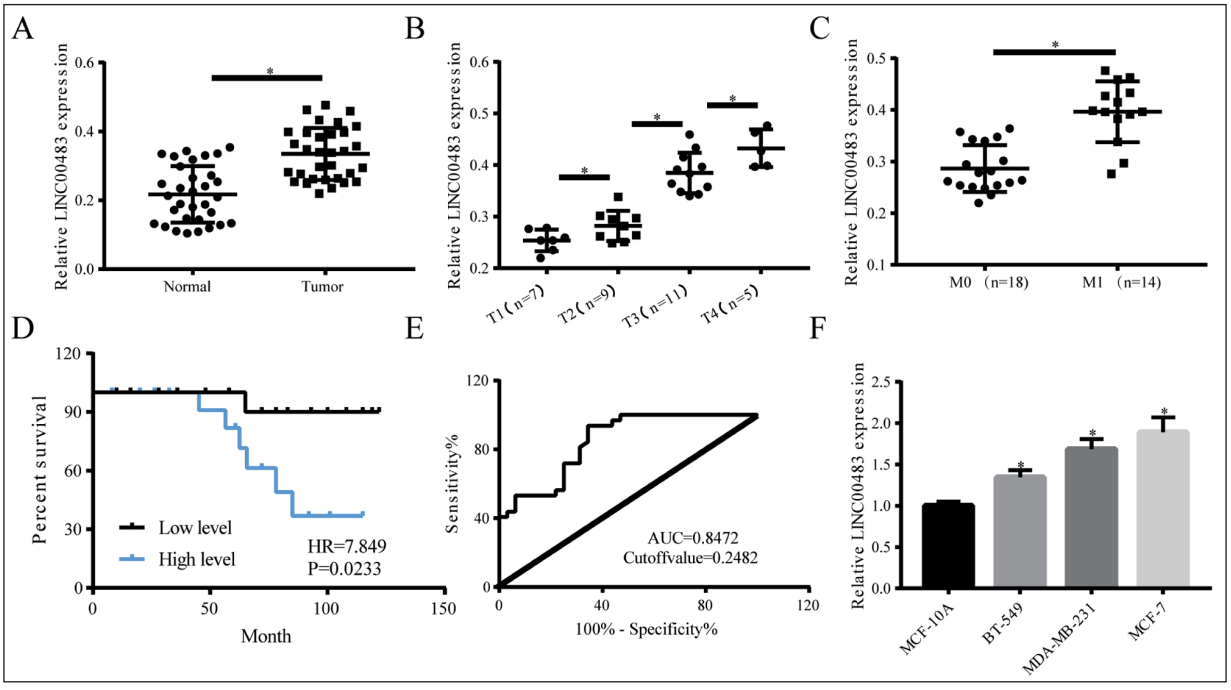

Figure 1. LINC00483 expression markedly rose in BC tissues. A, The expression of LINC00483 markedly rose in cancer tissues compared with that in control group. B, The expression of LINC00483 was gradually increased with the increase in tumor stage. C, The expression of LINC00483 was higher in patients with metastasis than that in those without metastasis. D, The survival rate of patients with a high expression of LINC00483 was lower than that of patients with a low expression of LINC00483. E, ROC curves revealed that the AUC was 0.8472 and the cutoff value was 0.2482. F, The expression of LINC00483 was evidently higher in BC cell lines than that in normal breast cells. (*$p<0.05$).

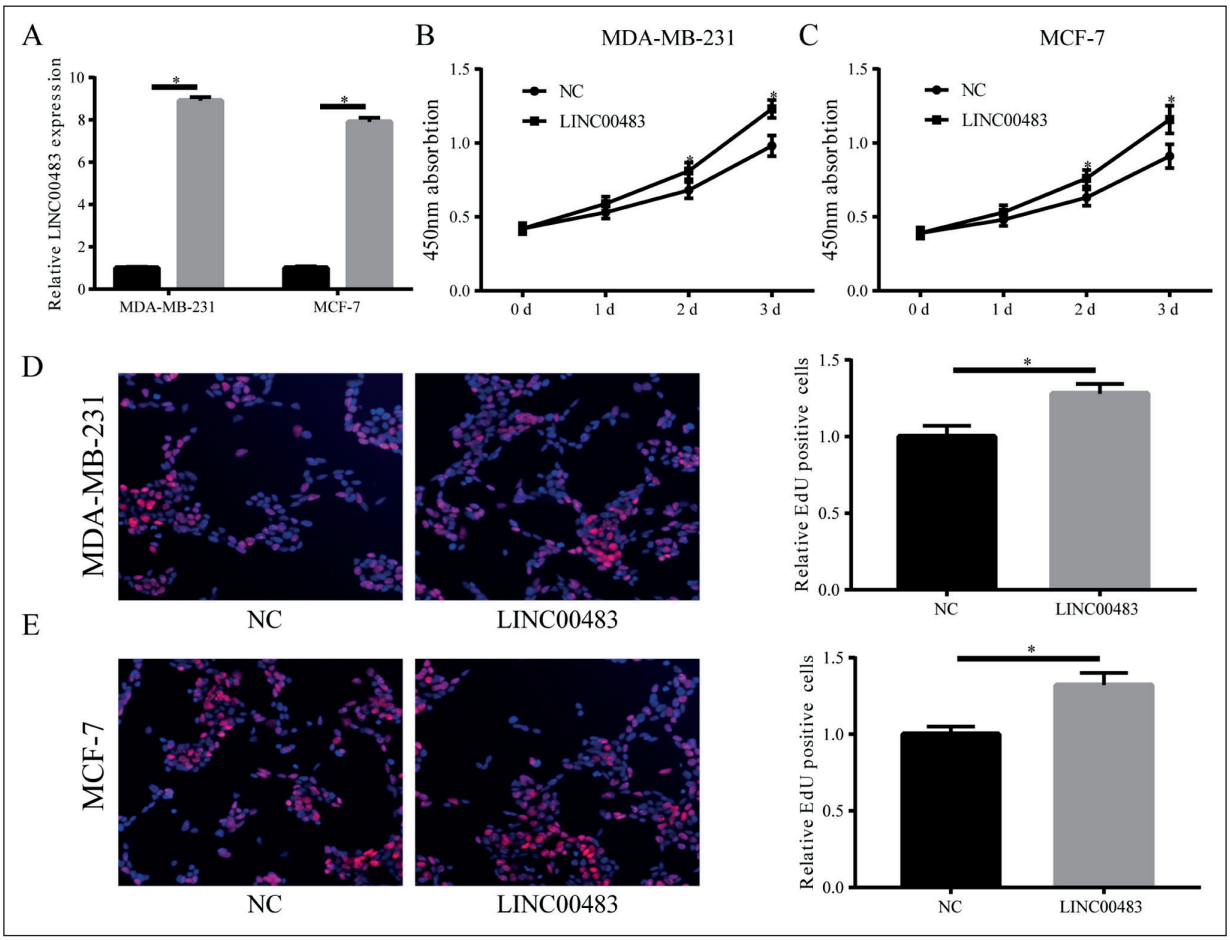

Figure 2. LINC00483 facilitated proliferation of BC cells. A, The expression of LINC00483 evidently rose after transfection of LINC00483 overexpression plasmids into MDA-MB-231 and MCF-7 cells. B-E, The proliferation of MDA-MB-231 and MCF-7 cells was greatly enhanced after overexpression of LINC00483. (*p<0.05) (magnification: 200×).

It was confirmed once again using EdU assay that LINC00483 facilitated the proliferation of BC cells (Figure 2D and 2E).

IGF2BP1 Regulated LINC00483 Expression

RIP assay identified that IGF2BP1 and LINC00483 were significantly enriched in anti-IGF2BP1 beads compared to IgG group (Figure 3A). Using RNA pull-down assays it was found that there was a binding relation between IGF2BP1 and LINC00483 in BC cells (Figure 3B). To further determine the regulatory effect of IGF2BP1 on LINC00483, MDA-MB-231 and MCF-7 were transfected with IGF2BP1 overexpression plasmids, and its transfection efficiency was detected (Figure 3C). Then the expression of LINC00483 was determined using qRT-PCR, and it showed that IGF2BP1 markedly promoted the expression of LINC00483 (Figure 3D and 3E).

LINC00483 Exerted its Effects Under the Regulation of IGF2BP1

IGF2BP1 expression was determined in BC tissues, and its high expression was detected, which had a significant positive correlation with the expression of LINC00483 (Figure 4A and 4B). To verify whether LINC00483 exerts its effects under the regulation of IGF2BP1, reversal assay was performed. First, MDA-MB-231 and MCF-7 were transfected with LINC00483 overexpression plasmids and si-IGF2BP1. It was found that the expression of LINC00483 declined in cells compared with that in cells transfected with LINC00483 overexpression plasmids alone (Figure 4C). The results of CCK8 and EdU assays showed that down-regulation of IGF2BP1 could partially reverse the promoting effect of LINC00483 on the proliferative ability of MDA-MB-231 and MCF-7 (Figure 4D and 4E). To sum up, LINC00483 exerts its effects under the regulation of IGF2BP1.

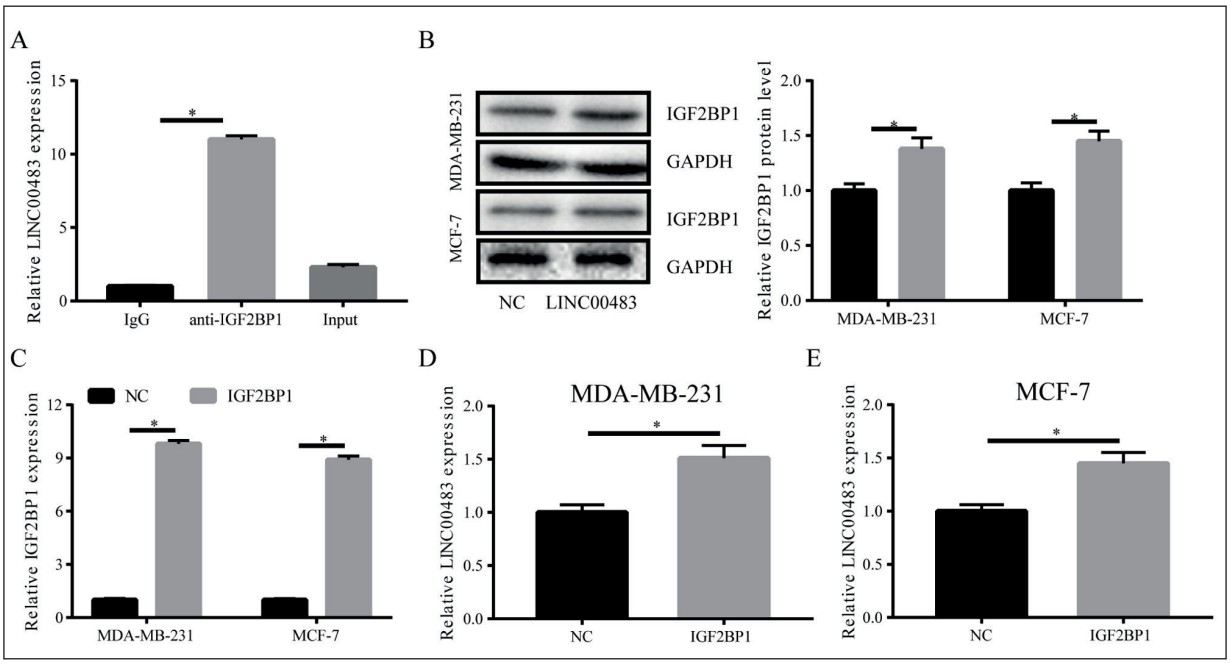

Figure 3. IGF2BP1 regulated LINC00483 expression. A, RIP assay identified that IGF2BP1 and LINC00483 were significantly enriched in anti-IGF2BP1 beads compared to IgG group B, It was found using RNA pull-down assays that there was a binding relation between IGF2BP1 and LINC00483. C, After transfection of IGF2BP1 overexpression plasmids into MDA-MB-231 and MCF-7 cells, the expression of IGF2BP1 markedly rose. D, E, After upregulation of IGF2BP1 in MDA-MB-231 and MCF-7 cells, the expression of LINC00483 rose. (*$p<0.05$).

Discussion

Recent studies have demonstrated that lncRNAs may be a new class of important regulatory factors during tumor metastasis, and they play a crucial role in the occurrence of BC. For example, Liao et al[12] systematically studied lncRNAs related to epithelial-mesenchymal transition (EMT) in BC cells, and found that a large number of lncRNAs may regulate the metastasis of BC *via* regulating EMT. LINC00483, located on human chromosome 17q21.33, has a total of 825 bases in length. It has been proved that LINC00483 is closely related to the occurrence and development of tumors. There is a study showing that LINC00483 has an increased expression in gastric cancer tissues and cell lines, and it can raise the expression of downstream target genes and promote the proliferation, invasion and metastasis of gastric cancer cells through absorbing the endogenous tumor suppressor gene miR-30a-3p[13]. Moreover, LINC00483 promotes the proliferation and invasion of kidney cancer cells by regulating FMN12[14]. However, there have been no reports on LINC00483 in BC. In this study, it was found that LINC00483 had a significantly high expression in BC tissues and cells, and it was related to the poor prognosis of BC, indicating that LINC00483 has the potential as a diagnostic marker. At the same time, the proliferation of BC cells could be promoted by the up-regulation of LINC00483. The above results suggest that LINC00483 may play a crucial role in the occurrence and development of BC.

Then, the regulatory mechanism of LINC00483 in BC was further explored in this study. It is speculated that LINC00483 may be regulated by RNA-binding protein, and the IGF2BP family has attracted our attention. At present, there are increasingly more studies on the IGF2BP family involved in post-transcriptional regulation. IGF2BP family members can promote the expression of the target gene through directly binding to mRNA of the target gene. There are 3 members (IGF2BP1-3) in this family, with the same functional domains, including 2 RNA recognition motif (RRM) domains at the C-terminus and 4 K homology (KH) domains at the N-terminus, all of which can bind to mRNAs[15].

As an important member of IGF2BP family, IGF2BP1 was abnormally regulated in various tumor tissues[16,17]. For example, IGF2BP1 is a known oncofetal protein linked to several human malignant

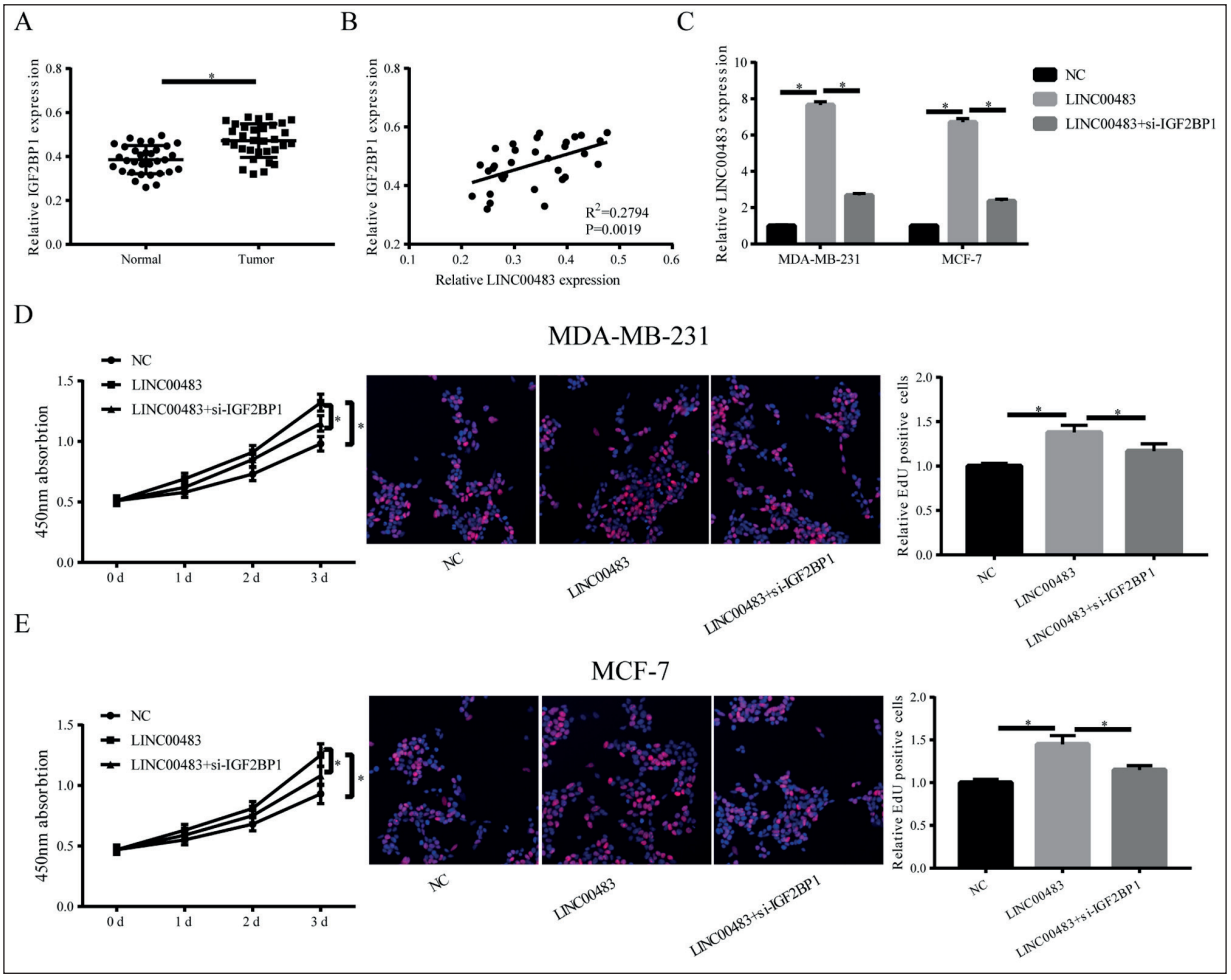

Figure 4. LINC00483 exerted its effects under the regulation of IGF2BP1. A, IGF2BP1 had a significantly high expression in BC patients. B, There was a significant positive correlation between the expressions of IGF2BP1 and LINC00483 in BC tissues. C, The expression of LINC00483 declined in MDA-MB-231 and MCF-7 cells transfected with LINC00483 overexpression plasmids and si-IGF2BP1 compared with that in cells transfected with LINC00483 overexpression plasmids alone. D-E, Downregulation of IGF2BP1 could partially reverse the promoting effect of LINC00483 on the proliferation of MDA-MB-231 and MCF-7 cells. (*p<0.05) (magnification: 200×)

diseases, and its expression is induced in human malignant melanomas or colorectal carcinomas with activated WNT/β-Catenin/TCF[18,19]. Xie et al[20] suggest that LIN28B-AS1, binding to IGF2BP1, is required for LPS-induced NF-κB activation and pro-inflammatory responses in human macrophages. In this study, the binding relation between IGF2BP1 and LINC00483 was verified using RIP and RNA pull-down assays, and the expression of LINC00483 evidently rose after upregulation of IGF2BP1 in BC cells, indicating that IGF2BP1 can bind to LINC00483 to regulate its expression. Finally, the results of reversal assay manifested that the promoting effect of LINC00483 on BC cell proliferation was regulated by IGF2BP1.

Conclusions

The above results demonstrate that LINC00483 is highly expressed in BC and can promote the proliferation of BC cells, whose mechanism of action may be regulated by IGF2BP1. This study is the first to find the pro-cancer effect of LINC00483 in breast cancer, which provides a new perspective for the mechanism research on occurrence and development of BC, and a new possibility for targeted therapy of BC.

Conflict of Interests

The authors declare that they have no conflict of interest.

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