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LINC01605 regulates proliferation, migration and invasion of colorectal cancer cells *via* targeting miR-3960/SOX11

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Abstract. – OBJECTIVE: We aimed to determine the expression level of long intergenic non-coding ribonucleic acid 1605 (LINC01605) in colorectal cancer (CRC), and to explore the effects of the LINC01605/microRNA (miR)-3960/sex-determining region Y-box 11 (SOX11) regulatory axis on the biological behaviors of CRC cells and the molecular mechanism therein.

PATIENTS AND METHODS: Tissue specimens were collected from 38 patients with CRC, and the relative expression level of LINC01605 in the CRC tissues and CRC cells was measured using quantitative reverse transcription-polymerase chain reaction (qRT-PCR). Then, the effects of LINC01605 on the proliferation, apoptosis, invasion and metastasis of CRC cells were observed via in vitro assays [cell counting kit (CCK)-8 assay, flow cytometry and transwell assay]. Besides, the possible miRNAs binding to LINC01605 were predicted by the bioinformatics method, and they were screened and verified using qRT-PCR and Dual-Luciferase reporter gene assay. Finally, the downstream target genes of miR-3960 were predicted by means of bioinformatics, and they were also screened and confirmed via qRT-PCR and Dual-Luciferase reporter gene assay.

RESULTS: According to the results of qRT-PCR, the expression of LINC01605 was up-regulated in 31 out of 38 cases of CRC tissue specimens, and its expression in CRC cells was higher than that in normal colorectal cells. The results of in vitro assays revealed that the proliferation, migration and invasion abilities of CRC cells were weakened, with an increased apoptosis rate after interference with LINC01605 expression. Based on the results of qRT-PCR and Dual-Luciferase reporter gene assay, miR-3960 was the target of LINC01605, while SOX11 was the target of miR-3960. Moreover, the expression of miR-3960 rose, but that of SOX11 declined after interference with LINC01605 expression. It was found through Western blotting that the protein expression of SOX11 was lowered after interference with LINC01605 expression.

CONCLUSIONS: LINC01605 has an up-regulated expression in CRC, and accelerates the proliferation, migration and metastasis of CRC cells by the miR-3960/SOX11 regulatory axis.

Key Words:
Colorectal cancer, LINC01605, MiR-3960, SOX11, Biological behaviors.

Introduction

Colorectal cancer (CRC), one of the most common tumors worldwide, ranks third among definitely diagnosed malignancies in terms of the incidence rate[1]. Currently, the main treatments for CRC include surgery, chemotherapy, targeted therapy and immune therapy. However, the postoperative recurrence and metastasis rates remain as high as 40-50%[2,3], and the survival rate and quality of patients have to be improved. The development and progression of CRC involve the changes in multiple genes and signaling pathways, so in-depth research into the molecular mechanism of CRC has important implications for understanding tumor development and progression.

Long non-coding ribonucleic acids (lncRNAs) are a class of RNA molecules with a length of over 200 nt, but no protein-coding ability, whereas microRNAs (miRNAs) are a category of 21-25 nt-long and highly conservative non-coding RNA molecules. They both play a vital role in the differentiation, metastasis, proliferation and apoptosis of cells. In recent years, numerous studies[4-6] have confirmed that lncRNAs can regulate miRNAs in a targeted fashion, thereby participating in the development and progression of cancers.

Long intergenic non-coding RNA 1605 (LINC01605) is located on chromosome 8p11.23

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and 1,663 bp in full length, which has been rarely reported up to now. LINC01605 expression is up regulated in bladder cancer and indicates a poor prognosis of patients. LINC01605 modulates MMP9 to promote the development and progression of bladder cancer[7]. According to Feng et al[8], LINC01605 accelerates the proliferation of laryngeal squamous cell carcinoma cells by the targeted regulation of miR-493-3p. However, the expression and function of LINC01605 in CRC have not yet been reported. In the present study, it was found through *in vitro* assays that LINC01605 had a higher expression level in CRC, and interference with LINC01605 expression inhibited the proliferation, invasion and migration of CRC cells and induced their apoptosis.

Patients and Methods

Tissue Specimens

The present study was conducted with the approval of the Medical Ethics Committee of Henan Provincial People's Hospital and the consent of patients. Tumor tissues and the corresponding paracancerous normal tissues were collected from 38 patients undergoing radical colectomy for CRC in our hospital from January 2018 to June 2019. All patients did not receive chemotherapy, radiotherapy, targeted therapy or immune therapy before surgery, and they were definitely diagnosed with CRC by pathology and had no cancer cells in the paracancerous tissues. The selection of patients was based on the guideline proposed by the Union for International Cancer Control (UICC). Upon surgical removal, the tissue specimens were preserved in liquid nitrogen at -180°C.

Cell Culture

Human CRC (HCT- 116, SW480, SW620, DLD-1, HT29) cell lines and normal colonic epithelial (CCD841) cell line were purchased from the Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences (Shanghai, China). The cells were cultured with Roswell Park Memorial Institute-1640 (RPMI-1640) medium or Dulbecco's Modified Eagle's Medium (DMEM) (Gibco, Rockville, MD, USA) containing 10% fetal bovine serum (FBS) (Gibco, Rockville, MD, USA) and 100 U/mL penicillin and 100 μg/mL streptomycin (Gibco, Rockville, MD, USA) in a thermostatic incubator with 5% CO_2 at 37°C, and the medium was changed every other day. When covering the whole bottom of the culture flask, all the cells were digested using 0.25% trypsin (Gibco, Rockville, MD, USA) and sub-cultured. Finally, the cells in the logarithmic growth phase were used for assays.

Cell Transfection

Cells were washed using phosphate-buffered saline (PBS) for 3 times, trypsinized for 2 min and cultured in a 6-well plate at 4×10^5 cells/well until the confluence rate reached about 60%. Prior to transfection, the transfection reagent Lip2000 (Invitrogen, Carlsbad, CA, USA) was diluted using serum-free medium at 3 μL/L and incubated at 37°C for 20 min. Besides, small interfering (si)-LINC01605 and si-negative control (NC) were separately diluted using serum-free medium to be 50 μmol/L, incubated at normal temperature for 5 min, and mixed well with an equal volume of the transfection reagent. Finally, the cells were transfected with the mixture and further cultured in the incubator at 37°C. At 6 h after transfection, the state of cells was observed, and the serum-free medium was replaced with complete medium, followed by further culture for 48 h. Subsequently, RNAs were extracted from the cells, and the efficiency of transfection was verified using quantitative reverse transcription-polymerase chain reaction (qRT-PCR).

QRT-PCR

Total RNAs were isolated from tissues and cell lines and purified according to the instructions of TRIzol reagent (GenePharm, Shanghai, China), and then complementary deoxyribonucleic acids (cDNAs) were synthesized using the RT kit (GenePharm, Shanghai, China) and amplified with a PCR instrument. Finally, the expressions of LINC01605 and miR-3960 were detected using SYBR Green PCR Master Mix kit (Toyobo, Osaka, Japan). The qRT-PCR conditions were as follows: pre-denaturation at 95°C for 10 min, 45 cycles of reaction at 95°C for 15 s and 60°C for 15 s and fluorescent signal acquisition at 60°C. With glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and U6 as the internal references, the relative expression levels of LINC01605, miR-3960 and SOX11 were calculated using $2^{-\Delta\Delta Ct}$ method. The following primers were designed and synthesized by Invitrogen (USA): GAPDH: F: 5'-TATGATGATATCAAGAGGGTAGT-3', R: 5'-TGTATCCAAACTCA GTCATAC-3'; U6: F: 5'-GCTTCGGCA GCACATATACTA-

AAAT-3', R: 5'-CGCTTCACGAATTTG CGTGTCAT-3'; LINC01605: F: 5′-CGTTACAAACAGCCGACCTT-3′, R: 5′- CCAGGGAGGGAC TCAAGAAT-3′; SOX11: F: 5'-GCCTCTTTTCTGCTGGGTCT-3', R: 5'-ACTGAAAACCTCCT CCGCTG-3'; MiR-3960: F: 5'-ATATATAGGCGGCGGCGGA-3'; R: 5'-GTGCAGGGTCCGAG GT-3'

Cell Counting Kit (CCK)-8 Assay

Cells were harvested in the logarithmic phase, prepared into suspension using 10% FBS and placed in medium. Each group of cells was incubated in a 96-well plate at 3×10^3 cells/well for 1, 2, 3 and 4 d. Then, each well was added with 10 μL of CCK-8 solution (Dojindo Molecular Technologies, Kumamoto, Japan) for 1 h of incubation at 37°C. Following further culture at 37°C for 2 h, the culture was terminated, and the optical density (OD) of each well was determined using a microplate reader at 450 nm, with a blank control well set for zeroing. Finally, the proliferation curves were drawn based on the relative OD ratio that represented the proliferation ability of cells.

Measurement of Apoptosis Rate Using Flow Cytometry

CRC cells in the logarithmic growth phase were taken from each group, digested by 0.25% trypsin and harvested. Then, they were centrifuged at 1,000 rpm and a centrifugal radius of 6 cm for 6 min at room temperature, and the supernatant was discarded. The resulting cells were washed using pre-cooled PBS, added with 500 μL of binding buffer, mixed fully with 5 μL of Annexin V-FITC (fluorescein isothiocyanate), and incubated with 5 μL of Propidium Iodide (PI) at room temperature in the dark for 10 min. Finally, the apoptosis rate of cells was measured using a flow cytometer (FACSCalibur; BD Biosciences, Detroit, MI, USA).

Transwell Assay

At 48 h after transfection, the cells were collected from each group, digested and counted. At 1 d prior to inoculation, the upper surface of the transwell basal membrane was coated with Matrigel (BD, Detroit, MI, USA), which was not needed for migration assay. Then, the lower chamber was added with 10% FBS-containing RPMI-1640 medium, while the upper chamber was added with the suspension of cells from each group. Next, the transwell was placed in the 5% CO_2 incubator at 37°C, followed by culture for 24-48 h. After 24 h of incubation, the cells failing to migrate were removed from the upper chamber. The Matrigel and cells in the upper chamber were then swiped off using cotton swabs, whereas the cells in the lower chamber were fixed in 4% paraformaldehyde for 10 min and stained with 0.5% crystal violet.

Western Blotting

Each group of cells was harvested and added with protein lysis buffer to extract total proteins. The concentration of proteins was then determined using the bicinchoninic acid (BCA) method (Beyotime, Shanghai, China). After high-temperature denaturation, 30 μg of proteins were subjected to sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE). The isolated protein gels were transferred onto a polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA), blocked using 5% skim milk powder for 2 h and incubated with primary antibodies (1:1,000) in a shaking incubator overnight. After being washed by Tris-Buffered Saline with Tween-20 (TBST) for 3 times, the resulting proteins were incubated with secondary antibodies (1:2,000) in the shaking incubator for 1 h, washed by TBST for 3 times and exposed for image development.

Dual-Luciferase Reporter Gene Assay

Wild-type (WT) or mutant type (Mut) LINC01605 was first cloned into pGL3-Basic vector. Then, cells were seeded into a 24-well plate at 5×10^3 cells/well, and they were co-transfected with miR-3960 or control and WT or Mut reporter vectors. At 48 h after transfection, the activity of luciferases was determined using the Dual-Luciferase reporter assay system (Promega, Madison, WI, USA). The targeted binding between miR-3960 and sex determining region Y-box 11 (SOX11) was verified as above.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 21.0 (IBM, Armonk, NY, USA) was employed for statistical analysis. Differences between two groups were analyzed by using the Student's *t*-test. Comparison between multiple groups was done using One-way ANOVA test followed by Post-Hoc Test (Least Significant Difference). The differences were considered to be statistically significant at $p<0.05$.

Results

Expression of LINC01605 in CRC

Tissue specimens were firstly collected from 38 patients pathologically diagnosed with CRC, and RNAs were extracted from them and reversely transcribed into cDNAs. According to the results of qRT-PCR, the expression of LINC01605 was raised in CRC tissues (Figure 1A), and compared with that in the paracancerous tissues, the expression of LINC01605 was up-regulated in 31 cases (81.6%) (Figure 1B). To explore the biological function of LINC01605 in CRC, it was found through qRT-PCR that LINC01605 had an up-regulated expression in CRC cells (Figure 1C). Then, CRC cells were transiently transfected with the designed si-LINC01605, and the interference efficiency was measured 48 h later (Figure 1D).

Biological Function of LINC01605 in CRC Cells

First, CRC cells were transiently transfected with si-LINC01605 or si-NC. CCK-8 assay results showed that the proliferation of CRC cells was inhibited after interference with LINC01605 expression (Figure 2A, 2B). Then, the effects of LINC01605 on the migration and invasion of CRC cells were investigated, and the transwell assay results showed that compared with those in si-NC group, the cells in si-LINC01605 group had weakened migration and invasion abilities (Figure 2C). The further flow cytometry results revealed that the apoptosis rate of CRC cells was raised after interference with LINC01605 expression (Figure 2D, 2E).

LINC01605 "Absorbed" MiR-3960 to Modulate SOX11

The possible miRNAs binding to LINC01605 were first predicted by the bioinformatics method (http://bioinfo.life.hust.edu.cn/lncRNASNP/#!/) to identify the molecular mechanism for the biological function of LINC01605 in CRC cells (Table I). According to qRT-PCR results, the expression of miR-3960 rose after interference with LINC01605 expression (Figure 3A). Moreover, a Dual-Luciferase reporter gene assay was conducted to verify whether LINC01605 can

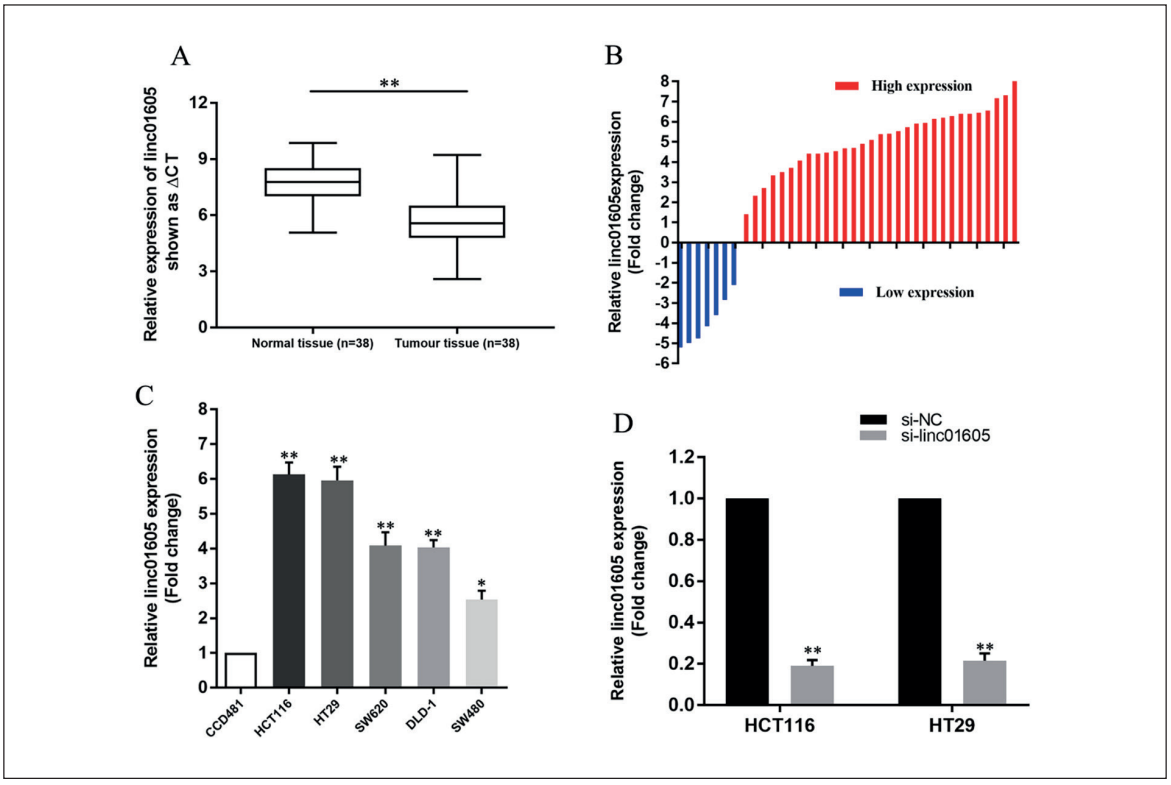

Figure 1. Expression of LINC01605 in CRC. **A,** QRT-PCR results showed that the expression of LINC01605 was up-regulated in CRC tissues, with GAPDH as an internal reference. **B,** The expression of LINC01605 was raised in 31 out of 38 cases of CRC tissues. **C,** Based on the qRT-PCR results, the relative expression level of LINC01605 was elevated in CRC cells. **D,** Interference efficiency measured using qRT-PCR at 48 h after CRC cells were transfected with si-LINC01605 or si-NC.

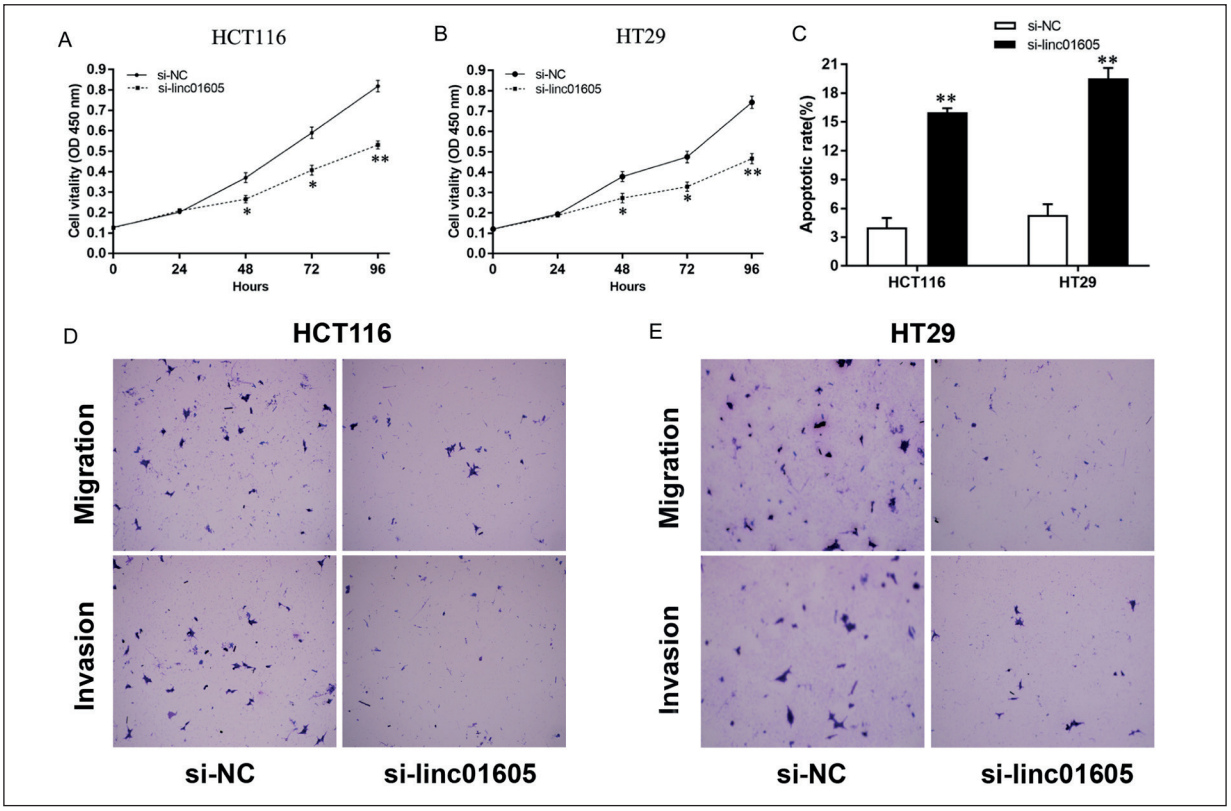

Figure 2. Biological function of LINC01605 in CRC cells. **A, B,** According to the CCK-8 results, the proliferation ability of CRC cells was weakened after interference with LINC01605 expression. **C,** The flow cytometry results revealed that the apoptosis rate of LINC01605 was raised after interference with LINC01605 expression. **D, E,** Based on the transwell assay results, the migration and invasion abilities of cells in si-LINC01605 group were poorer than those in si-NC group. (magnification: 40×).

Table I. Prediction of possible binding miRNAs of linc01605.

miRNA ID	pita start	pita end	targetScan start	targetScan end	miRanda start	miRanda end	Score	Energy
hsa-miR-4786-5p	339	347	340	346	327	347	170	-28.32
hsa-miR-6884-3p	476	484	478	484	462	484	170	-21.42
hsa-miR-3690	878	886	880	887	863	886	167	-26.32
hsa-miR-1226-3p	104	112	105	111	91	112	164	-27.39
hsa-miR-6515-3p	73	81	83	89	71	90	164	-18.75
hsa-miR-3960	368	375	371	377	358	378	163	-41.69
hsa-miR-663a	366	373	366	372	353	373	162	-32.79
hsa-miR-643	822	830	824	831	809	830	161	-17.74
hsa-miR-8485	109	115	124	130	109	131	158	-19.51
hsa-miR-1908-5p	366	373	366	372	355	373	156	-33.76
hsa-miR-8072	364	372	371	377	355	375	156	-35.05
hsa-miR-219a-1-3p	490	497	491	498	476	497	155	-18.68
hsa-miR-4757-3p	1524	1532	1526	1532	1510	1532	155	-15.72
hsa-miR-671-5p	284	292	293	299	279	300	155	-23.86
hsa-miR-642b-5p	166	174	167	174	153	174	155	-23.19
hsa-miR-6757-5p	698	706	711	717	694	717	155	-26.96
hsa-miR-4330	97	104	97	103	83	104	155	-23.18
hsa-miR-4467	365	373	372	378	354	376	155	-32.27
hsa-miR-6807-5p	704	712	706	712	688	712	155	-25.7

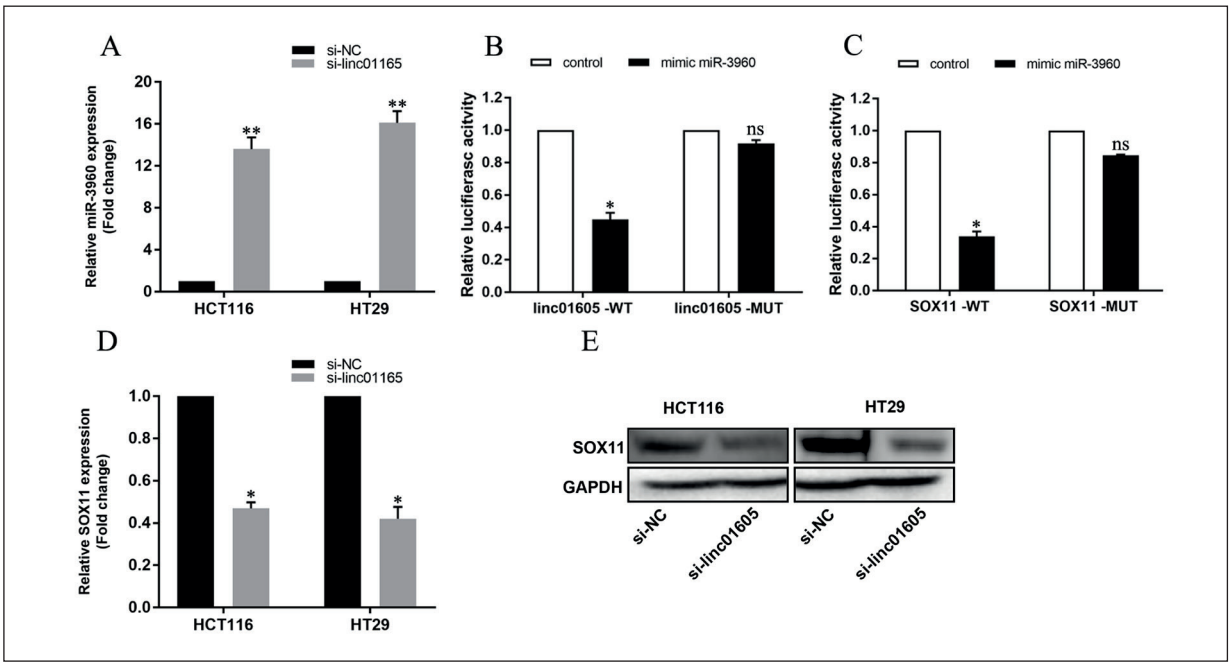

Figure 3. LINC01605 ''absorbed'' miR-3960 to modulate SOX11. **A,** The qRT-PCR results showed that with U6 as an internal reference, the expression of miR-3960 was elevated after interference with LINC01605 expression. **B,** The Dual-Luciferase reporter gene assay results manifested that LINC01605 directly bound to miR-3960. **C,** It was found through the Dual-Luciferase reporter assay that miR-3960 directly bound to SOX11. **D,** It was discovered through the qRT-PCR that the mRNA expression of SOX11 declined after interference with LINC01605 expression. **E,** According to the Western blotting results, the protein expression of SOX11 dropped after interference with LINC01605 expression.

bind to miR-3960 in a targeted manner, and it was discovered that miR-3960 mimic notably weakened the Luciferase activity of LINC01605-Mut, without a significant influence on that of LINC01605-WT (Figure 3B). According to the bioinformatics prediction (http://www.targetscan.org/vert_71/ and http://www.mirdb.org/), SOX11 was likely to be the target gene of miR-3960. It was confirmed by Dual-Luciferase reporter gene assay that miR-3960 directly bound to SOX11 (Figure 3C). Furthermore, whether LINC01605 regulates the expression of SOX11 was determined by *in vitro* assays, and it was found that the messenger RNA (mRNA) and protein expression levels of SOX11 fell following interference with LINC01605 expression (Figure 3D, 3E).

Discussion

The incidence and case fatality rates of CRC, a common malignancy, decline in Western countries, but substantially rise in Asian countries, especially China[8]. Moreover, due to inconspicuous symptoms of CRC in the early stage, about 20% of patients have metastatic CRC when definitely diagnosed and lose the opportunity for surgery[9]. Therefore, it is vital to explore the molecular pathogenesis of CRC and search for feasible molecular treatment targets for improving patients' survival rate.

LncRNAs play a pivotal role in regulating such biological processes as gene imprinting, cell differentiation, immune response, cell cycle and apoptosis as well as human diseases, including various cancers[10,11]. LncRNAs are competing endogenous RNAs (ceRNAs) containing miRNA response elements (MERs), which can inhibit the regulation of miRNAs on downstream genes by competitively binding miRNA sites[12,13]. There are many reports[14,15] showing that lncRNAs may have a carcinogenic or anti-cancer effect in CRC. Notably, lncRNA CCAL activates the Wnt/β-catenin signaling pathway by inhibiting activator protein 2a[16], thereby promoting the development and progression of CRC. LINC01133 interacts with SRSF6 to suppress the epithelial-mesenchymal transition and metastasis of CRC cells[17]. LncRNAs serve as the sponges of miRNAs or competitive endogenous RNAs to restrain the bind-

ing of miRNAs to mRNAs[18]. Besides, lncRNA CASC9 absorbs miR-193a-5p to up-regulate the expression of ERBB2, thus driving the development and progression of CRC[19]. In the present study, it was detected through bioinformatics and *in vitro* assays that LINC01605 directly bound to miR-3960.

SOX11, a nuclear transcription factor belonging to the SOX-C family[20], is located on chromosome 2p25.2, and its encoded protein is composed of 441 amino acids. Petrakis et al[21] uncovered that SOX11 can promote the progression of mantle cell lymphoma, while modulating the development and progression of melanoma and breast cancer[22,23]. Besides, SOX11 is differentially expressed in small cell lung cancer and Burkett's lymphoma tissues to exert an anti-cancer or carcinogenic effect[24,25]. In this study, it was discovered that miR-3960 directly bound to SOX11, and the mRNA and protein expression levels of SOX11 declined after interference with LINC01605 expression. However, the biological functions of miR-3960 and SOX11 in CRC failed to be further explored. Therefore, the correlations among the expressions of LINC01605, miR-365 and SOX11 in CRC and the biological functions of miR-3960 and SOX11 in CRC will be investigated deeply in the subsequent study.

Conclusions

Concisely, the present study firstly found that LINC01605 has an up-regulated expression in CRC and functions like an oncogene by the potential molecular mechanism that SOX11 expression is modulated through the targeted absorption of miR-3960. Thus, this work provides a theoretical basis for the search of novel targets for the clinical treatment of CRC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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