

Original Article

LncRNA LINC00473 promoted colorectal cancer cell proliferation and invasion by targeting miR-195 expression

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Abstract: Long noncoding RNAs (lncRNAs) have been shown to play crucial roles in cancer development. However, the role of LINC00473 in colorectal cancer has not been explored. In our study, we showed that LINC00473 expression was upregulated in colorectal cancer samples compared to nontumor samples. The expression of LINC00473 in colorectal cancer tissues from patients with distant metastasis was higher than that from cases without distant metastasis. The higher expression level of LINC00473 was positively correlated with advanced clinical stage. The elevated expression of LINC00473 accelerated colorectal cancer cell proliferation, cell cycle progression and invasion. Moreover, overexpression of LINC00473 induced epithelial to mesenchymal (EMT) progression in HT29 and SW480 cells. Ectopic expression of LINC00473 suppressed miR-195 expression in colorectal cancer cells. miR-195 expression was downregulated in colorectal cancer samples compared with nontumor samples. The expression of miR-195 in colorectal cancer tissues from patients with distant metastasis was lower than that from cases without distant metastasis. The lower expression level of miR-195 was positively correlated with advanced clinical stage. In addition, we showed that the expression of miR-195 was negatively correlated with the LINC00473 expression level in colorectal cancer tissues. LINC00473 accelerated colorectal cancer cell proliferation and cell cycle progression and regulated EMT progression by regulating miR-195 expression. These data suggested that LINC00473 induced cell proliferation, cell cycle progression and EMT progression by acting as a ceRNA for miR-195 in colorectal cancer.

Keywords: Colorectal cancer, LINC00473, miR-195, oncogene

Introduction

Colorectal cancer causes approximately 13% of all tumors and is the 2nd biggest cause of tumor-related death in western societies [1-5]. Disease metastases and progression are the major causes of death, and advanced cases occur in approximately 30% of patients at presentation [6-8]. Despite innovative cure strategies such as neoadjuvant chemotherapy, surgery and radiotherapy that have been applied to colorectal cancer treatment, the prognosis for colorectal cancer cases remains unsatisfactory [9-12]. Increasing evidence suggests that the carcinogenesis of colorectal cancer is a complicated process involving many complex signaling networks and genomic mutations [13-17]. Thus, it is better to study the molecular mechanisms underlying the progression and development of colorectal cancer and identify

a new method for colorectal cancer management.

Long noncoding RNAs (lncRNAs) are defined as noncoding RNA transcripts longer than two hundred nucleotides with limited or no protein coding capacity [18-21]. Emerging studies have demonstrated that lncRNAs are involved in a number of cellular functional processes, including cell differentiation, development, proliferation, cell cycle progression, invasion and autophagy [4, 22-25]. It has been shown that the expression of lncRNAs is deregulated in several tumors, such as osteosarcoma, hepatocellular carcinoma, lung cancer, bladder cancer, breast cancer, gastric cancer and colorectal cancer [4, 26-31]. LINC00473 is also known as C6orf176 and encodes intergenic lncRNA from chromosome 6q27 locus [32]. Previous studies have suggested that LINC00473 plays impor-

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tant roles in the development of different tumors and the progression of other diseases [32-35]. For example, Liang et al. [32] demonstrated that LINC00473 expression was upregulated in human endometrial stromal cells after decidual stimulation and that the cAMP-PKA pathway modulated LINC00473 expression via IL-11-induced STAT3 phosphorylation. Chen et al. [6] showed that LINC00473 expression was upregulated in the LKB1-inactivated non-small cell lung cancer (NSCLC) samples and cell lines. Zhu and colleagues indicated that LINC00473 expression was upregulated in Wilms tumors and that elevated expression of LINC00473 was correlated with unfavorable histology and higher tumor stage [35]. Knockdown of LINC00473 expression suppressed cell growth and induced apoptosis by regulating miR-195/IKK α expression. However, the role of LINC00473 in colorectal cancer has not been explored.

In our study, we found that LINC00473 expression was upregulated in colorectal cancer samples compared to nontumor samples. The expression of LINC00473 in colorectal cancer tissues from patients with distant metastasis was higher than that from cases without distant metastasis. The higher expression level of LINC00473 was positively correlated with advanced clinical stage. Elevated expression of LINC00473 accelerated colorectal cancer cell proliferation and cell cycle progression.

Materials and methods

Clinical samples, cell culture and transfection

Forty colorectal cancer samples and adjacent colon samples were collected from colorectal cancer cases who underwent resection surgery at Rizhao People's Hospital (Shandong, China). None of these cases received any other treatment before the surgery. Our study was approved by the Rizhao People's Hospital (Shandong, China), and all cases provided written informed consent. Four colorectal cancer cell lines (HT29, SW620, DLD-1 and SW480) and one colon epithelium cell line (FHC) were obtained from the Chinese Academy of Sciences of Shanghai (Shanghai, China). These cells were cultured in DMEM (Dulbecco's modified Eagle's medium) supplemented with streptomycin/penicillin and FBS (fetal bovine serum). LINC00473-expressing pcDNA and pcDNA control vector, miR-195 scramble and control were

synthesized by GenePharma (Shanghai, China) and transfected by using the Lipofectamine 3000 kit (Invitrogen, Carlsbad, CA).

Quantitative RT-PCR

Cells or tissues were harvested using TRIzol Reagent, and total RNA was isolated following the manufacturer's instructions. Real-time RT-PCR assay was performed on a CFX96 System (Bio-Rad, Hercules, USA) with SYBR green qPCR kit (Takara, Dalian, China) to detect the mRNA or lncRNA and miRNA expression following the manufacturer's recommendations. GAPDH mRNA was used as the internal control. The relative expression level was determined according to the $2^{-\Delta\Delta Ct}$ method. The following primers were used: LINC00473, forward: 5'-AAACG CGAAC GTGAG CCCC-3' and 5'-CGCCA TGCTC TGGCG CAGTT-3'; miR-195, forward: 5'-ACACT CCAGC TGGGT AGCAG CAC-AG AAATA TT-3' and 5'-CTCAA CTGGT GTCGT GGA-3'; GAPDH forward: 5'-ACACC CACTC CTCCA CCTTT-3' and 5'-TTACT CCTTG GAGGC CATGT-3'.

Cell cycle, proliferation and invasion assays

For the cell cycle assay, cells were harvested by trypsinization and then fixed with ice-cold ethanol (70%) at -20°C overnight. After washing three times, the cells were resuspended in PI (propidium iodide, Sigma) and RNase A (Sigma) and then stained for half an hour. These cells were analyzed with a flow cytometer (BD, USA). For cell growth, a CCK-8 assay was performed. The cells were cultured in a 96-well plate (1×10^4 cells per well). CCK-8 solution (10 μ l) was added to each well and incubated for an additional 2 hours at the set time point. The absorbance at 450 nm was determined with a microplate reader (Bio-Rad, CA, USA). For the cell invasion assay, the cells were plated in the upper membrane of the Transwell insert precoated with Matrigel. Medium containing FBS (10%) was added to the lower membrane. After 48 hours, invasive cells were stained with crystal violet and counted.

Dual-luciferase assay

Fragments of LINC00473 containing mutated or putative miR-195 binding sites were amplified by RT-PCR. Following the manufacturer's recommendations, the PCR products were subcloned into the pmir-RB-REPORT vector (Ribio

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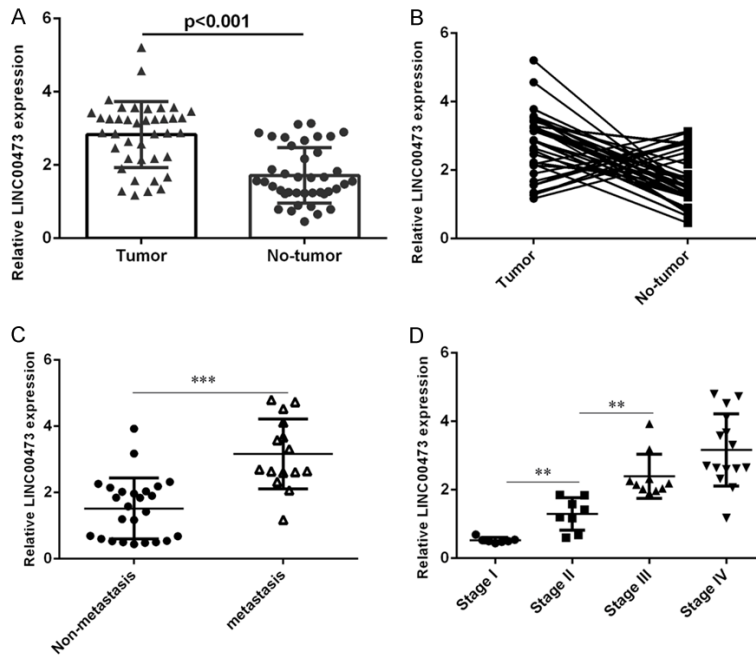


Figure 1. LINC00473 was overexpressed in colorectal cancer tissues. A. The expression level of LINC00473 in colorectal cancer tissues and adjacent colon samples was analyzed by qRT-PCR. B. LINC00473 was overexpressed in 31 colorectal cancer patients (31/40, 77.5%) compared to adjacent tissues. C. The expression of LINC00473 in colorectal cancer tissues from patients with distant metastasis was higher than that from cases without distant metastasis. D. The higher expression level of LINC00473 was positively correlated with advanced clinical stage. ** $P < 0.01$ and *** $P < 0.001$.

Biotech, China) downstream from the luciferase coding sequence. Cells were treated with mutant LINC00473 vector or wild-type LINC00473 vector and miR-195 mimic or scramble control. After 48 hours, luciferase activities were determined using a Dual-Luciferase Reporter Analysis Kit (Promega, Madison, WI, USA).

Statistical analysis

The results are listed as the mean \pm standard deviation (SD). Significant differences between different groups were measured with Student's t test (two-tailed). The significant correlation between LINC00473 and miR-195 was analyzed by Pearson correlation. $P < 0.05$ was set as statistically significant.

Results

LINC00473 overexpression in colorectal cancer tissues

The expression level of LINC00473 in colorectal cancer tissues and adjacent colon samples

was determined by qRT-PCR analysis. As shown in **Figure 1A**, LINC00473 expression was upregulated in colorectal cancer samples compared with nontumor samples. LINC00473 was overexpressed in 31 colorectal cancer patients (31/40, 77.5%) compared to adjacent tissues (**Figure 1B**). The expression of LINC00473 in colorectal cancer tissues from patients with distant metastasis was higher than that from cases without distant metastasis (**Figure 1C**). The higher expression level of LINC00473 was positively correlated with advanced clinical stage (**Figure 1D**).

Elevated expression of LINC00473 accelerated colorectal cancer cell proliferation and cell cycle progression

In line with a previous study, we found that LINC00473

was overexpressed in colorectal cancer cell lines (HT29, SW620, DLD-1 and SW480) compared to a colon epithelium cell line, FHC (**Figure 2A**). The expression of LINC00473 was significantly upregulated in HT29 (**Figure 2B**) and SW480 cells (**Figure 2C**) after transfection with the pcDNA-LINC00473 vector. Ectopic expression of LINC00473 accelerated the proliferation of HT29 (**Figure 2D**) and SW480 cells (**Figure 2E**), as demonstrated by CCK-8 analysis. Moreover, overexpression of LINC00473 increased the proportion of cells at G1/S phase in HT29 (**Figure 2F**) and SW480 cells (**Figure 2G**).

Overexpression of LINC00473 induced epithelial to mesenchymal (EMT) progression

Ectopic expression of LINC00473 decreased E-cadherin expression, which is an epithelial marker, in HT29 (**Figure 3A**) and SW480 cells (**Figure 3B**); however, enhanced N-cadherin and vimentin expression, which are mesenchymal markers, in HT29 (**Figure 3A**) and SW480 cells (**Figure 3B**), as determined by qRT-PCR analysis. Moreover, the results indicated that

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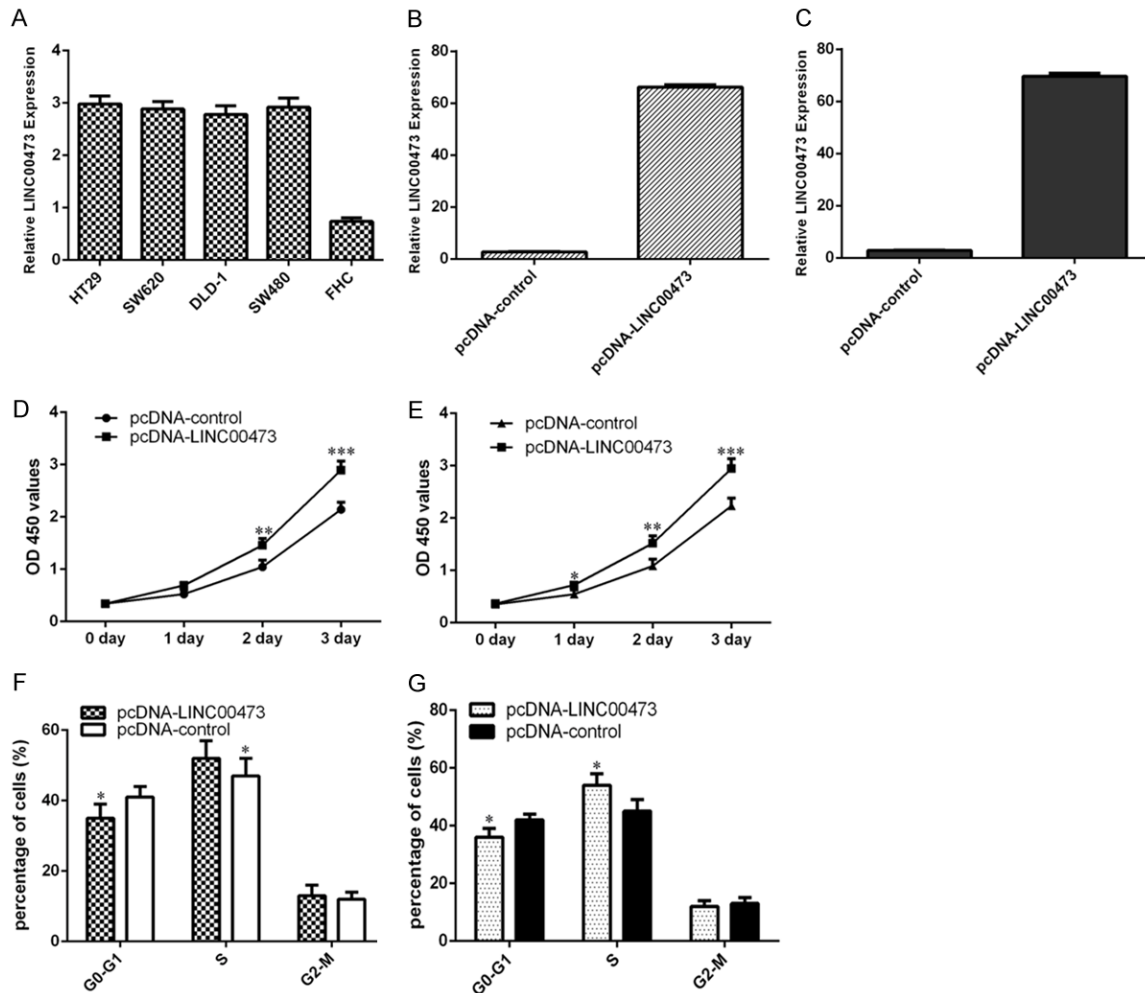


Figure 2. Elevated expression of LINC00473 accelerated colorectal cancer cell proliferation and cell cycle progression. A. The expression of LINC00473 in four colorectal cancer cell lines (HT29, SW620, DLD-1 and SW480) and one colon epithelium cell line, FHC, was determined by qRT-PCR. B. The expression of LINC00473 was significantly upregulated in HT29 cells after transfection with the pcDNA-LINC00473 vector. C. The expression of LINC00473 in SW480 cells was measured by qRT-PCR. D. Ectopic expression of LINC00473 accelerated the proliferation of the colorectal cancer cell line HT29, as shown by CCK-8 analysis. E. CCK-8 analysis was performed to detect cell proliferation. F. Overexpression of LINC00473 increased the proportion of HT29 cells at G1/S phase. G. Elevated expression of LINC00473 increased the proportion of SW480 cells at G1/S phase. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$.

elevated LINC00473 expression induced cell invasion in HT29 cells (Figure 3C and 3D). Overexpression of LINC00473 increased cell invasion in SW480 cells (Figure 3E and 3F).

Ectopic expression of LINC00473 suppressed miR-195 expression in colorectal cancer cells

Bioinformatic analysis indicated that there is a putative complementary sequence for miR-195 in LINC00473, and the predicted miR-195 binding site is shown in Figure 4A. The expression of miR-195 was significantly upregulated in HT29 cells after transfection with the miR-195 mimic (Figure 4B). To study the direct binding relationship between miR-195 and LINC00473,

we performed luciferase reporter analysis. We demonstrated that overexpression of miR-195 markedly decreased the luciferase activity of WT LINC00473 3'UTR; however, the luciferase activity of mut LINC00473 3'UTR was not changed (Figure 4C). Moreover, elevated expression of LINC00473 suppressed miR-195 expression in HT29 (Figure 4D) and SW480 cells (Figure 4E).

miR-195 expression was downregulated in colorectal cancer tissues

The expression level of miR-195 in colorectal cancer samples and adjacent colon tissues was measured with qRT-PCR analysis. As sh-

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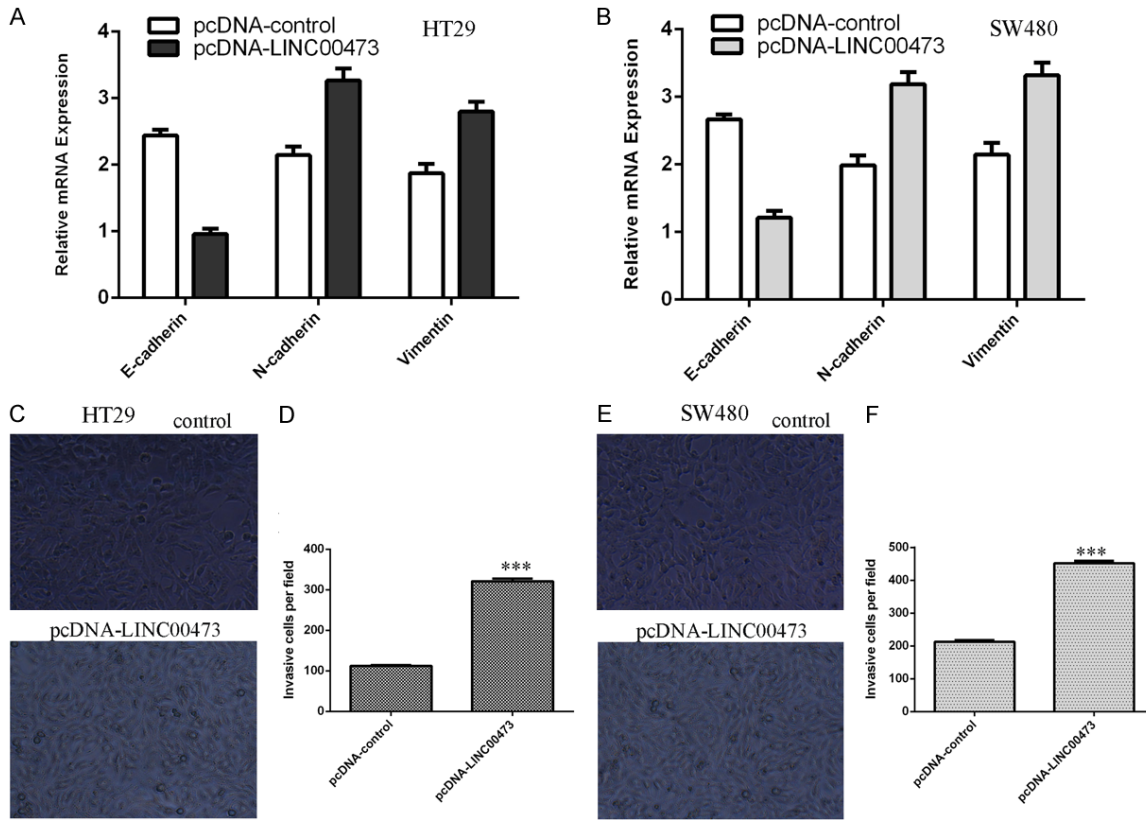
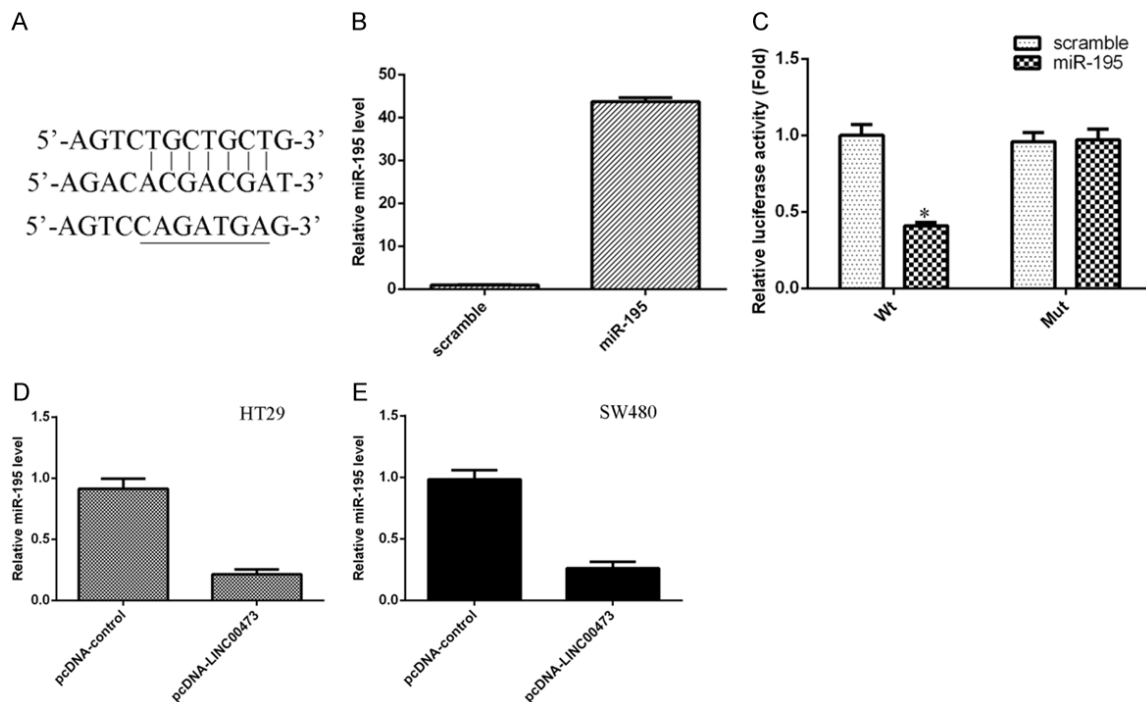


Figure 3. Overexpression of LINC00473 induced epithelial to mesenchymal (EMT) progression. A. The expression of E-cadherin, N-cadherin and vimentin was measured by qRT-PCR in HT29 cells. B. The expression of E-cadherin, N-cadherin and vimentin was measured by qRT-PCR in SW480 cells. C. Elevated LINC00473 expression promoted cell invasion in HT29 cells. D. The relative number of invasive cells is shown. E. Elevated LINC00473 expression promoted cell invasion in SW480 cells. F. The relative number of invasive cells is shown. *** $P < 0.001$.



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Figure 4. Ectopic expression of LINC00473 suppressed miR-195 expression in colorectal cancer cells. A. Bioinformatic analysis indicated that there is a putative complementary sequence for miR-195 in LINC00473 and predicted the miR-195 binding site. B. The expression of miR-195 was significantly upregulated in HT29 cells after transfection with the miR-195 mimic. C. Overexpression of miR-195 markedly decreased the luciferase activity of WT LINC00473 3'UTR; however, the luciferase activity of mut LINC00473 3'UTR was not changed. D. Elevated expression of LINC00473 suppressed miR-195 expression in HT29 cells. E. Ectopic expression of LINC00473 suppressed miR-195 expression in SW480 cells. * $P < 0.05$.

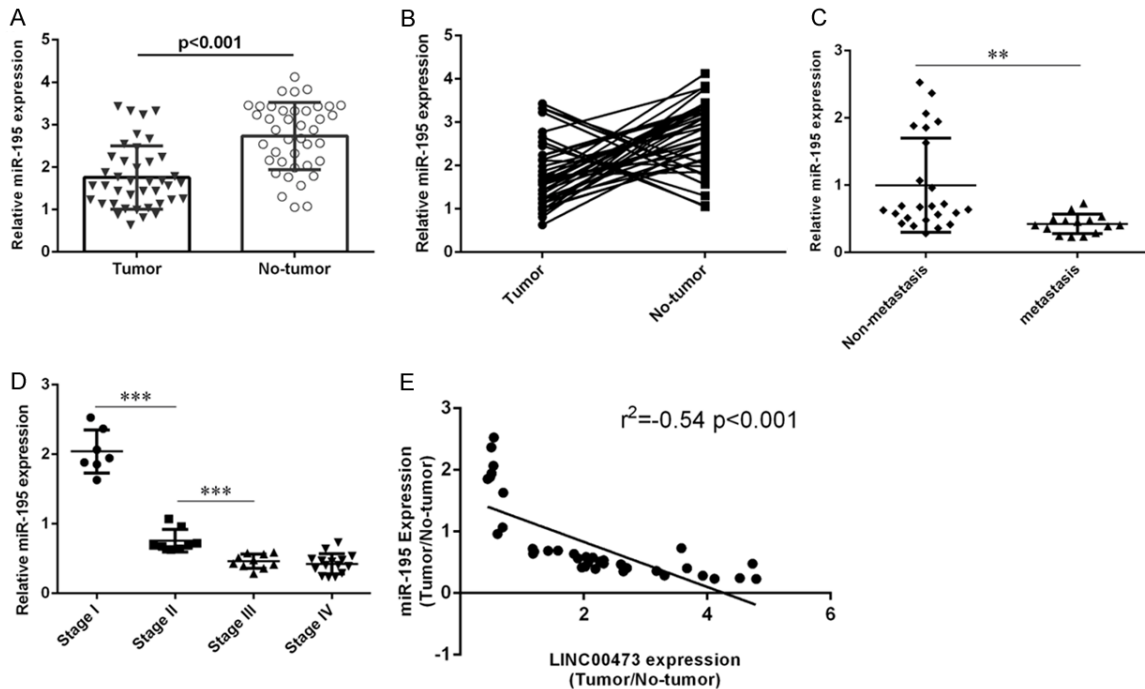


Figure 5. miR-195 expression was downregulated in colorectal cancer tissues. A. The expression level of miR-195 in colorectal cancer tissues and adjacent colon samples was determined by qRT-PCR analysis. B. The expression of miR-195 was downregulated in 30 colorectal cancer patients (30/40, 75%) compared to adjacent tissues. C. The expression of miR-195 in colorectal cancer tissues from patients with distant metastasis was lower than that from cases without distant metastasis. D. The lower expression level of miR-195 was positively correlated with advanced clinical stage. E. The expression of miR-195 was negatively correlated with the LINC00473 expression level in colorectal cancer tissues. ** $P < 0.01$ and *** $P < 0.001$.

own in **Figure 5A**, miR-195 expression was downregulated in colorectal cancer samples compared with nontumor samples. The expression of miR-195 was downregulated in 30 colorectal cancer patients (30/40, 75%) compared to adjacent tissues (**Figure 5B**). The expression of miR-195 in colorectal cancer tissues from patients with distant metastasis was lower than that from cases without distant metastasis (**Figure 5C**). The lower expression level of miR-195 was positively correlated with advanced clinical stage (**Figure 5D**). In addition, we showed that the expression of miR-195 was negatively correlated with the LINC00473 expression level in colorectal cancer tissues (**Figure 5E**).

LINC00473 accelerated colorectal cancer cell proliferation and cell cycle progression and regulated EMT progression by regulating miR-195 expression

Next, we investigated whether overexpression of LINC00473 promoted colorectal cancer cell proliferation and cell cycle progression and induced EMT progression by inhibiting miR-195 expression. We transfected the miR-195 mimic into LINC00473-overexpressing HT29 cells. We found that ectopic expression of miR-195 decreased the proliferation of LINC00473-overexpressing HT29 cells (**Figure 6A**). Moreover, overexpression of miR-195 decreased the proportion of cells at G1/S phase, which was induced by pcDNA-LINC00473 (**Figure 6B**).

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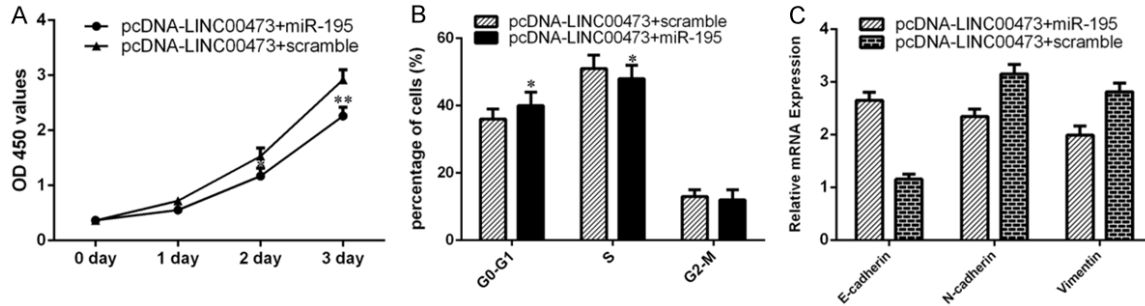


Figure 6. LINC00473 accelerated colorectal cancer cell proliferation and cell cycle progression and regulated EMT progression by regulating miR-195 expression. A. Cell proliferation was measured by using CCK-8 analysis. B. Overexpression of miR-195 decreased the proportion of cells at G1/S phase, which was induced by pcDNA-LINC00473. C. Elevated expression of miR-195 increased E-cadherin expression and decreased N-cadherin and vimentin expression in HT29 cells as shown by qRT-PCR analysis. * $P < 0.05$ and ** $P < 0.01$.

Elevated expression of miR-195 increased E-cadherin expression and decreased N-cadherin and vimentin expression in HT29 cells, as shown by qRT-PCR analysis (Figure 6C).

Discussion

In our study, we showed that LINC00473 expression was upregulated in colorectal cancer samples compared to nontumor samples. The expression of LINC00473 in colorectal cancer tissues from patients with distant metastasis was higher than that from cases without distant metastasis. The higher expression level of LINC00473 was positively correlated with advanced clinical stage. Elevated expression of LINC00473 accelerated colorectal cancer cell proliferation, cell cycle progression and invasion. Moreover, overexpression of LINC00473 induced epithelial to mesenchymal (EMT) progression in HT29 and SW480 cells. Ectopic expression of LINC00473 suppressed miR-195 expression in colorectal cancer cells. miR-195 expression was downregulated in colorectal cancer samples compared with nontumor samples. The expression of miR-195 in colorectal cancer tissues from patients with distant metastasis was lower than that from cases without distant metastasis. The lower expression level of miR-195 was positively correlated with advanced clinical stage. In addition, we showed that the expression of miR-195 was negatively correlated with the LINC00473 expression level in colorectal cancer tissues. LINC00473 accelerated colorectal cancer cell proliferation and cell cycle progression and regulated EMT progression by regulating miR-195 expression. These data suggested that LINC-

00473 induced cell proliferation, cell cycle progression and EMT progression by acting as a ceRNA for miR-195 in colorectal cancer.

LINC00473 (also known as C6orf176) encodes intergenic lncRNA from chromosome 6q27 locus [35]. Previous studies have suggested that LINC00473 plays crucial roles in the development of different tumors and the progression of other diseases [6, 18, 35]. For instance, Liang et al. [18] demonstrated that LINC00473 expression was upregulated in human endometrial stromal cells after decidual stimulus. The authors further demonstrated that the cAMP-PKA pathway modulated LINC00473 expression via IL-11-induced STAT3 phosphorylation. Chen et al. [6] showed that LINC00473 expression was upregulated in LKB1-inactivated non-small cell lung cancer (NSCLC) samples and cell lines. Zhu and colleagues indicated that the LINC00473 expression level was upregulated in Wilms tumors and that elevated expression of LINC00473 was correlated with unfavorable histology and higher tumor stage [35]. Knockdown of LINC00473 expression suppressed cell growth and induced apoptosis by regulating miR-195/IKK α expression. Shi and colleagues found that ectopic expression of LINC00473 induced cervical cancer cell growth and suppressed cell apoptosis by regulating miR-34a/ILF2 expression. However, the role of LINC00473 in colorectal cancer has not been explored. In our study, we demonstrated that LINC00473 expression was upregulated in colorectal cancer samples and cell lines. The expression of LINC00473 in colorectal cancer tissues from patients with distant metastasis was higher than that from cases without dis-

tant metastasis. The higher expression level of LINC00473 was positively correlated with advanced clinical stage. Elevated expression of LINC00473 promoted colorectal cancer cell proliferation and cell cycle progression. Moreover, overexpression of LINC00473 induced epithelial to mesenchymal (EMT) progression in HT29 and SW480 cells.

Interactions between miRNAs and lncRNAs have been shown recently [36, 37]. For instance, Cai et al. [38] showed that lncRNA TP73-AS1 sponged microRNA-194 to induce colorectal cancer cell growth, invasion and migration by enhancing TGF α expression. Zhou et al. [39] demonstrated that lncRNA HAND2-AS1 plays a suppressive role in colorectal cancer by sponging miR-1275 and regulating KLF14 expression. He and colleagues indicated that lncRNA PVT1-214 enhanced the invasion and proliferation of colorectal cancer by interacting with miR-128 and stabilizing Lin28 [40]. In our study, we used bioinformatic analysis to find a putative complementary sequence for miR-195 in LINC00473 and predicted the miR-195 binding site. To study the direct binding relationship between miR-195 and LINC00473, we performed a luciferase reporter assay. We demonstrated that overexpression of miR-195 markedly decreased the luciferase activity of WT LINC00473 3'UTR; however, the luciferase activity of mut LINC00473 3'UTR was not changed. Moreover, elevated expression of LINC00473 suppressed miR-195 expression in colorectal cancer cells. Previous studies have indicated that miR-195 expression is downregulated in colorectal cancer tissues and that ectopic expression of miR-195 suppresses cell proliferation and cell cycle progression partly through regulating fibroblast growth factor 2 (FGF2) expression and suppressing the Wnt/ β -catenin pathway. In line with this, we also found that the miR-195 expression level was downregulated in colorectal cancer samples and that the expression of miR-195 in colorectal cancer tissues from patients with distant metastasis was lower than that from cases without distant metastasis. The lower expression level of miR-195 was positively correlated with advanced clinical stage. In addition, we showed that the expression of miR-195 was negatively correlated with the LINC00473 expression level in colorectal cancer tissues. LINC00473 accelerated colorectal cancer cell

proliferation and cell cycle progression and regulated EMT progression by regulating miR-195 expression.

In summary, we discovered that LINC00473 expression was upregulated in colorectal cancer samples and cell lines and that overexpression of LINC00473 accelerated colorectal cancer cell proliferation, cell cycle progression, and invasion and regulated EMT progression by sponging miR-195. These data suggest an effective therapeutic target for colorectal cancer treatment.

Disclosure of conflict of interest

None.

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