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MiR-130a regulating the biological function of colon cancer by targeting inhibition of PTEN

H.-L. LIU[1], H.-G. BAO[1], C.-L. ZHENG[1], C. TENG[2], M.-H. BAI[3]

[1]Surgical Oncology, The Second Affiliated Hospital of Qiqihar Medical University, Qiqihar, P.R. China
[2]Medical Oncology, The 2nd Affiliated Hospital of Harbin Medical University, Harbin, P.R. China
[3]Tumor Surgery Hepatobiliary Surgery, The Fourth Affiliated Hospital of Harbin Medical University, Harbin, P.R. China

Abstract. – OBJECTIVE: To investigate the expression of miR-130a in human colon cancer patients and its specific mechanism of regulating the biological function of colon cancer cells.

PATIENTS AND METHODS: Cancer tissues, paracancerous tissues, and serum samples of 40 colon cancer patients who underwent surgery in The Second Affiliated Hospital of Qiqihar Medical University from May 2018 to March 2019 were collected, and 40 healthy volunteers who received physical examination in The Second Affiliated Hospital of Qiqihar Medical University were collected. Real Time-quantitative Polymerase Chain Reaction (qRT-PCR) was used to detect the expression of miR-130a. Human colon cancer cell was divided into miR-130a mimic group, miR-130a inhibitor group, mimic NC (negative control), and inhibitor NC group. QRT-PCR was used to detect the expression of miR-130a, and MTT assay, colony formation assay, cell scratch assay, transwell assay were performed to detect cell viability, proliferation, migration, and invasion ability.

RESULTS: Compared with adjacent tissues, the expression of miR-130a was significantly increased in colon cancer tissues (p=0.0125); the expression of miR-130a in transfected miR-130a mimic group was higher than that in NC group, but the expression in transfected miR-130a inhibitor group was significantly lower than that in NC group; overexpression of miR-130a significantly increased cell viability, proliferation, migration, and invasion of colon cancer cells, while knockdown of miR-130a significantly inhibited colon cancer cell biological activity; target prediction, qRT-PCR, and Western blot assays showed that miR-130a participated in the development and progression of colon cancer by targeting inhibition of PTEN expression.

CONCLUSIONS: The expression of miR-130a in serum and cancer tissues of colon cancer patients is significantly increased, and it can regulate the biological function of colon cancer cells by inhibiting the expression of target gene PTEN. Knockdown of miR-130a may be used as a new clinical treatment for colon cancer.

Key Words:
MiR-130a, Colon cancer, Cell viability, Proliferation, Migration, Invasion.

Introduction

Colon cancer is one of the most common malignant tumors of the digestive tract. It has the characteristics of high incidence, high mortality, and low five-year survival rate[1,2]. According to statistics, China's colon cancer patients have an annual increase of 120,000 cases, and its incidence ranked third, patient mortality rate ranked fourth[3]. The cancer is difficult to cure, with high rates of recurrence metastasis. At present, the treatment for colon cancer mainly includes surgical resection, chemotherapy, and radiotherapy. Although it has certain curative effect, many patients still have unsatisfactory treatment effect and are difficult to heal[4,5]. Therefore, the treatment of colon cancer is challenging, and it is still a hot and difficult point in clinical and basic research.

In recent years, studies[6,7] have shown that the process of cancer development and progression is related to a small molecule, microRNA. MicroRNA (miRNA), a small molecule that is widely expressed in eukaryotes, is about 25 nucleotides in length and capable of regulating 1/3 of human genes at the post-transcriptional level. MiRNAs can complement or incompletely complement the binding site of the 3' untranslated region of the target gene, promote its mRNA degradation or inhibit

Corresponding Author: Hailong Liu, MD; e-mail: liuhailong0404@126.com

translation into many biological processes such as cell growth, proliferation, differentiation, apoptosis, thus participating in the regulation of human diseases such as diabetes mellitus, myocardial infarction, osteoporosis and cancer[8-10]. At present, the specific mechanism of miRNA expression in cancer tissues and serum of colon cancer patients and the biological functions of miRNAs regulating colon cancer cells need to be further explored. In previous studies, we examined the expressions of twelve human cancer-associated miRNAs in colon cancer, and the results indicated that miR-130a was highly expressed in human colon cancer, so we chose miR-130a to continue to explore its relationship with colon cancer.

Therefore, this study was to detect the expression of miR-130a in cancer tissues and serum samples of colon cancer patients, and to explore the effect of miR-130a on the viability, proliferation, migration, and invasion of human colon cancer cells.

Patients and Methods

Collection of Clinical Samples

A total of 40 colon cancer patients who underwent surgical resection in The Second Affiliated Hospital of Qiqihar Medical University from October 2017 to October 2018 were enrolled as subjects, and cancer tissues, paracancerous tissues, and serum samples were collected. Among them, there were 22 males and 18 females. They were 18 to 60 years old, with an average age of (42.43 ± 10.42) years. According to the pathological staging developed by the International Union Against Cancer (UICC), this study used the T staging in the TNM staging criteria, and there were 5 cases in T1, 17 cases in T2, 14 cases in T3, and 4 cases in T4. All patients were diagnosed by surgery and pathology, who had no other cancer history, and had not received radiotherapy or chemotherapy. Exclusion criteria: patients with tumors, chronic diseases, and organ dysfunction in other areas. When the patient underwent surgical resection, the colon cancer tissues and adjacent tissues were collected and immediately treated with RNALator (Vazyme, China) and stored in a liquid nitrogen tank (Thermo Fisher Scientific, Waltham, MA, USA) for later use. Normal human serum samples from The Second Affiliated Hospital of Qiqihar Medical University were collected for the same period of time, and a disposable vacuum blood collection tube was used to extract 5 mL of fasting venous blood, centrifuged at 4°C and 3000 r/min for 5 min, and the supernatant, i.e., the serum, was separated and stored in a refrigerator (Thermo Fisher Scientific, Waltham, MA, USA) at –80°C for later use. The investigation was approved by the Ethics Committee of The Second Affiliated Hospital of Qiqihar Medical University, and all patients signed informed consent forms and volunteered to participate in the study.

Cell Culture and Transfection

Human colon cancer cells HCT116, HT29, Caco-2 cell line, and human embryonic kidney epithelial cell 293T cells were purchased from Wuhan Procell Life Science Co., Ltd. (Wuhan, China). Colon cancer cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) containing 10% fetal bovine serum (FBS; Thermo Fisher Scientific, Waltham, MA, USA) and 1% penicillin and streptomycin, and cultured in a 5% CO_2 incubator (Thermo Fisher Scientific, Waltham, MA, USA).

Colon cancer cells were digested and inoculated into six-well plates (Nest, China) or 96-well plates (Nest, China). When the cell density reached 50% to 60%, the transfection reagent Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) and serum-free OPTI-MEM medium were used for transfection. MiR-130a mimic, miR-130a inhibitor, mimic NC, and inhibitor NC were transfected into colon cancer cells in logarithmic growth phase, and cells transfected with NC (negative control) were used as control group. The cells were grouped as miR-130a mimic group, miR-130a inhibitor group, mimic NC group, and inhibitor NC group. After 6 h of transfection, all cells were replaced with completely fresh culture medium for normal culture, and 24 h after transfection, subsequent experiments were performed.

RNA Extraction, Reverse Transcription and qRT-PCR Reaction

RNA extraction from cell tissue was performed using TRIzol (Thermo Fisher Scientific, Waltham, MA, USA) extraction method, and miRNA was extracted from the serum by kit method (RE-01113 Foregene, China). The reverse transcription system and reaction conditions were strictly in accordance with the instructions of the reverse transcription kit (4366596 ABI, Foster City, CA, USA). The reaction system included 2.0 μL total RNA, 3.0 μL stem loop reverse transcription primer (5×), 10 M dNTP mixture, and

1.5 μL reverse transcription buffer (10×), 1.0 μL reverse transcriptase, 0.19 μL RNase inhibitor, 7.16 μL DEPC water, and the reaction conditions were 16°C for 30 min, 42°C for 30 min, and 85°C for 5 min. The qRT-PCR experiment was carried out using cDNA as a template and strictly following the product manual of SYBR-Green Master Mix (413914001 Roche, Mannheim, Germany). The reaction conditions were as follows: 95°C for 2 min 1 cycle; 95°C for 15 s, renaturation temperature 20 s, 60°C for 40 s for amplification, for 45 cycles, and fluorescence signal was collected at 60°C after 40 s. Finally, U6 or GAPDH was used as an internal reference, and the relative expression amount was calculated by the $2^{-\Delta\Delta Ct}$ formula to detect the expression level of miR-130a or PTEN. All primer sequences in this research were purchased from Shanghai GenePharma Co., Ltd (Table I).

MTT Assay

Cells were seeded in 96-well plates (Nest, China) at a density of 1×10^4 cells/mL. After transfection for 24 h, a volume of 20 μL of methyl thiazolyl tetrazolium (MTT) solution was added to each well and incubated for 4 h at 37°C. The supernatant was discarded, and 150 μL of dimethyl sulfoxide (DMSO) was added. The absorbance (OD) value of the cells was measured at a wavelength of 570 nm by a microplate reader (TECAN, Männedorf, Switzerland).

Cloning Formation

Cells were seeded in a six-well plate at a density of 1×10^5 cells/mL, and culture was continued for 2 weeks, and the fresh medium was changed every three days. After 2 weeks of culture, the cells were fixed with 4% paraformaldehyde for 30 min at room temperature, and the cells were washed with PBS. 500 μL of 10% crystal violet solution (Biosharp, Shanghai, China) was added to each well. After incubation for 30 min at room temperature, the cells were observed under a light microscope, and photographed, and the number of formed cell colonies was counted.

Scratch Test

Colon cancer cells were transfected with miR-130a mimic, miR-130a inhibitor, mimic NC and inhibitor NC for 24 h, and then an autoclaved sterile tip (10 μL) was scratched on a six-well plate. The cells were washed with PBS to remove the suspension cells, and the culture medium for normal culture was added, and was observed under an inverted optical microscope (Nikon, Tokyo, Japan) at 0 h, 24 h, and 48 h after the scratches, and photographed at random.

Transwell Assay

A polycarbonate microporous membrane-separated invasion chamber (Corning, Corning, NY, USA) was constructed, and 300 μL cell suspension with a density of 5×10^5 cells/mL after transfection was inoculated into the upper chamber with the Matrigel, and normal culture solution was added to the lower chamber. The chamber was placed in a 37°C incubator containing 5% CO_2. After 24 h, the lower surface of the PET membrane was soaked with 4% paraformaldehyde for 20 min, and then unbound hematoxylin was removed and incubated for 20 min. After staining, it was observed under a high-power microscope and counted.

Target Prediction

The downstream target gene of miR-130a was predicted by the TargetScanHuman 7.2 online website (http://www.targetscan.org/vert_72/).

Luciferase Reporter Gene Assay

Colon cancer cells were seeded in 6-well plates at 5×10^5. When the cell confluence reached 50%, miR-130a mimic and NC were co-transfected with PTEN-3'UTR-WT or PTEN-3'UTR-Mut plasmids into cells by Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). The subsequent steps were performed in strict accordance with the instructions of the Dual-Luciferase Reporter Assay Kit (Promega, Madison, WI, USA) and the Luciferase activity was detected by a Promega luminescence detector (Promega, Madison, WI, USA).

Table I. Primer sequences for qRT-PCR.

Gene	Forward (5'-3')	Reverse
miR-130a	TTGCGATTCTGTTTTGTGCT	GTGGGGTCCTCAGTGGG
PTEN	ACACGACGGGAAGACAAGTT	TCCTCTGGTCCTGGTATGAAG
U6	GCTTCGGCAGCACATA	ATGGAACGCTTCACGA
GAPDH	AACGGATTTGGTCGTATTG	GGAAGATGGTGATGGGATT

Western Blot

The culture medium in the well plate was removed, and the cells were washed three times with pre-cooled PBS, and 10 μL of RIPA lysate (Beyotime, Beijing, China) was added, and the total protein in the cells was extracted after 10 min. The protein concentration was measured by bicinchoninic acid (BCA) method. Then, 50 μg of protein was electrophoresed and transferred to a polyvinylidene difluoride (PVDF) membrane, blocked with 5% skim milk for 1 h, and incubated overnight on a 4°C shaker with primary anti-PTEN (CST, Danvers, MA, USA, 1:1000). The next day, the secondary antibody (CST, USA, 1:1000) was incubated for 1 h at room temperature in the dark. The band gray value was analyzed by Tanon software, with β-actin as the internal parameter, and the relative quantitative result was expressed as the gray value/optical density value.

Statistical Analysis

Statistical analysis was performed using Graphpad Prism 5 software (La Jolla, CA, USA), and the results were expressed as mean ± standard deviation. The ΔCt values of miRNA expression between the two groups were compared using an independent sample *t*-test. $p<0.05$ for the difference was considered statistically significant.

Results

The Expression of MiR-130a in Colon Cancer Patients

QRT-PCR results showed that compared with adjacent tissues, the expression of miR-130a in cancer tissues of colon cancer patients was significantly increased, and the difference was statistically significant ($p=0.0125$; Figure 1A). The expression of miR-130a in serum of colon cancer patients was significantly higher ($p=0.002$), compared with healthy subjects (Figure 1B).

Expression and Transfection Efficiency of MiR-130a in Colon Cancer Cells

Compared with human embryonic kidney epithelial cells 293T cells, miR-130a expression was significantly increased in colon cancer cells, and the increase of expression was the most significant in human colon cancer cells Caco-2 (Figure 2A). The qRT-PCR results showed that the expression of miR-130a was significantly increased in the cells transfected with miR-130a mimic compared with the mimic NC group, and the difference was statistically significant ($p=0.001$; Figure 2B). Compared with inhibitor NC group, the expression of miR-130a was significantly decreased after transfected with miR-130a inhibitor, and the difference was statistically significant ($p=0.0204$; Figure 2C).

Comparison of Cell Viability and Proliferative Capacity of the Four Groups

The results are shown in Figure 3A. The activity of colon cancer cells in miR-130a mimic group was significantly higher than that in mimic NC group. The cells in the miR-130a inhibitor group were significantly lower than inhibitor NC group. Furthermore, as shown in Figure 3B, the colony of colon cancer cells in miR-130a mimic group was significantly higher than that in mimic NC

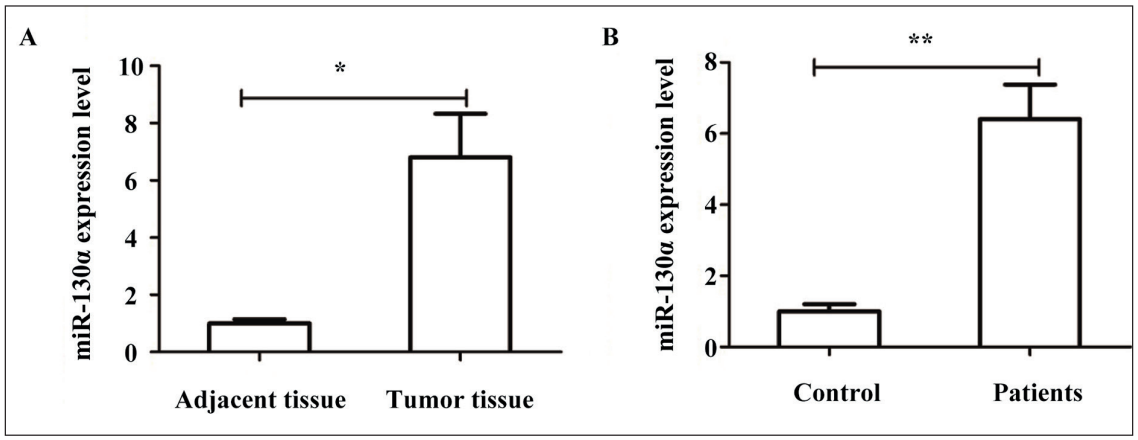

Figure 1. The expression of miR-130a in the tissues and serum samples from patients with colon cancer. **A,** Expression of miR-130a in adjacent tissues and tumor tissues of patients with colon cancer. **B,** Expression of miR-130a in the serum of controls and patients with colon cancer.

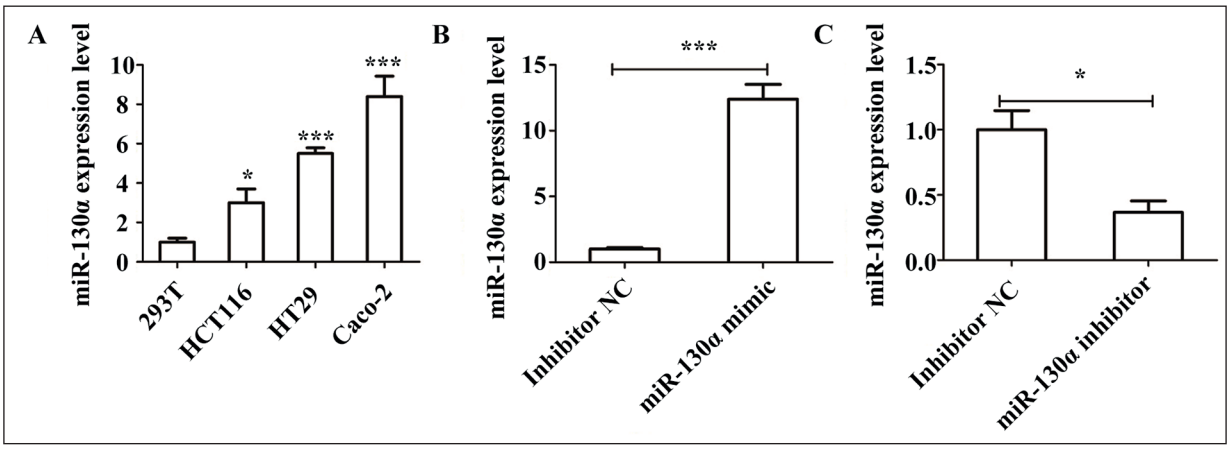

Figure 2. The expression of miR-130a in colon cancer cells. **A,** Expression of miR-130a in cells, including 293 T, HCT116, HT29 and Caco-2. **B,** and **C,** Expression of miR-130a in Caco-2 cells after transfection of miR-130a mimic or inhibitor.

group, while the number of cell clones in miR-130a inhibitor group was significantly lower than that in inhibitor NC group.

Comparison of Cell Migration and Invasion Ability of the Four Groups

As shown in Figure 4A, the cell scratch test showed that the migration ability of colon cancer cells in miR-130a mimic group was significantly higher than that in mimic NC group after 24 h of cell transfection. Compared with inhibitor NC group, the cell migration ability of miR-130a inhibitor group was significantly reduced. Transwell results indicated that the overexpression of miR-130a increased colon cancer cell invasion, while the knockdown of miR-130a significantly reduced colon cancer cell invasion (Figure 4B).

MiR-130a Targeted Regulation of PTEN

TargetScanHuman 7.2 results indicate that miR-130a and PTEN have binding sites, and their binding sites are shown in Figure 5A. qRT-PCR results showed that miR-130a mimic can significantly down-regulate the mRNA and tensin homologue deleted on chromosome ten (PTEN) mRNA levels, while miR-130a inhibi-

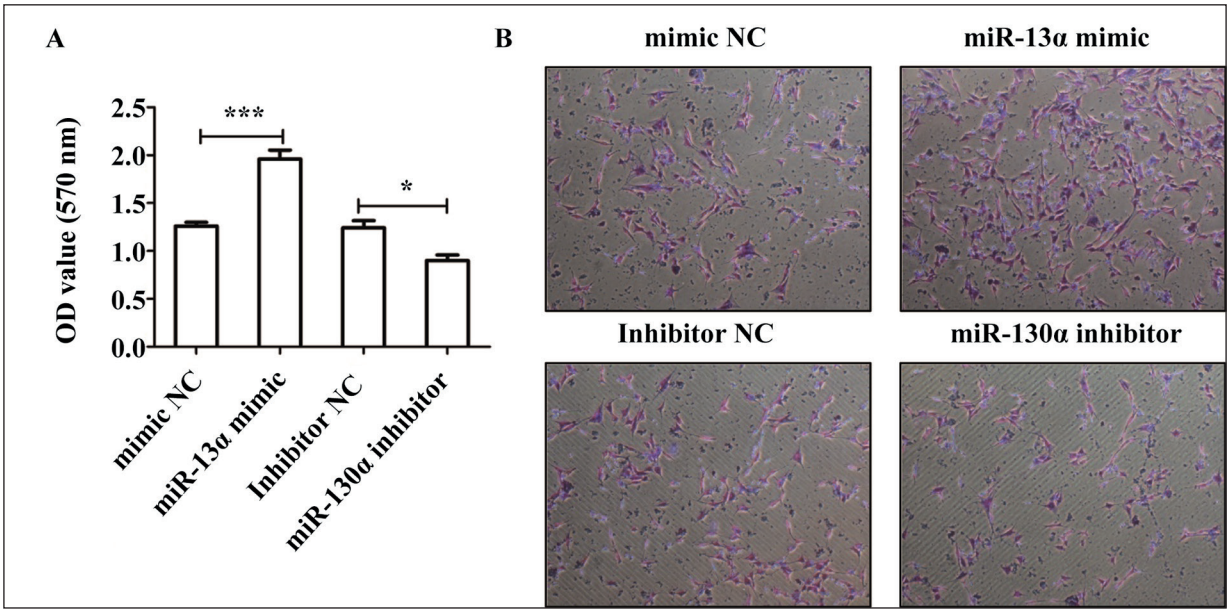

Figure 3. The effect of miR-130a on the cell viability and proliferation of colon cancer cells. **A,** MTT assay. **B,** Colony formation assay (magnification 40×).

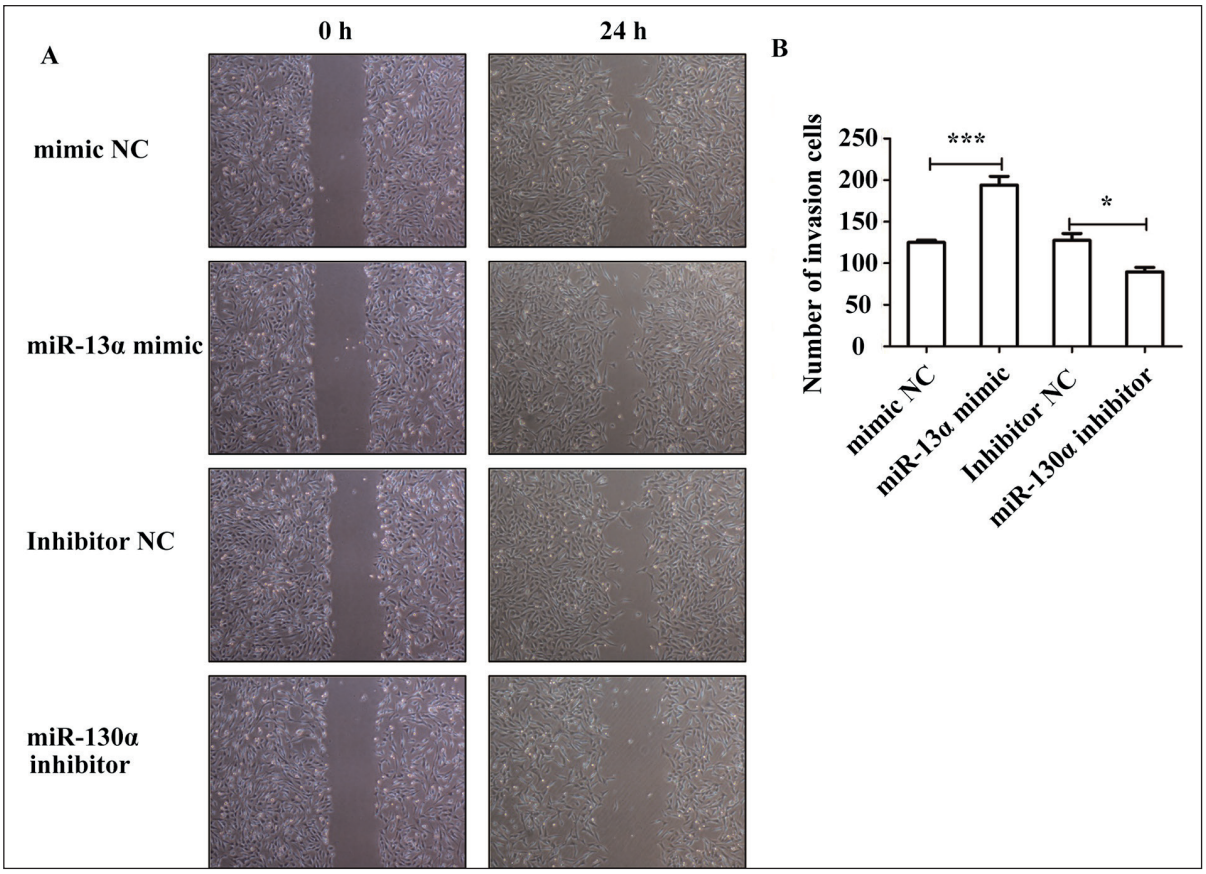

Figure 4. The role of miR-130a in the migration and invasion of colon cancer cells. **A,** Migration of colon cancer cells (magnification 40×). **B,** Number of invasion cells of colon cancer cells, 40×.

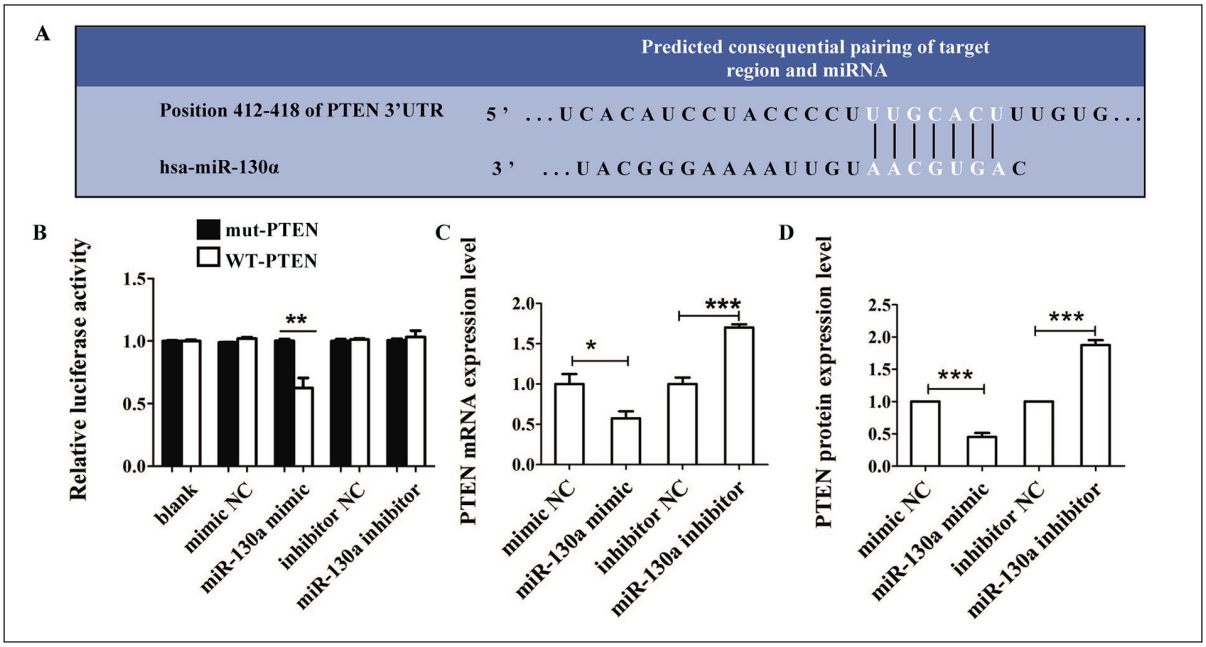

Figure 5. MiR-130a directly targeting PTEN. **A,** Binding sites between miR-130a and PTEN. **B,** Luciferase reporter assay. **C,** MRNA expression of PTEN. **D,** Protein expression of PTEN.

tor can up-regulate its mRNA level (Figure 5B). Western blot analysis showed that the overexpression of miR-130a reduced PTEN protein levels compared with NC group, while knockdown of miR-130a increased PTEN protein levels.

Discussion

MicroRNAs (miRNAs), a class of highly conserved, endogenous, non-coding RNAs that are widely present in viruses and higher organisms, are approximately 22 nucleotides in length[11]. MiRNA regulates intracellular signaling pathways through exosomes or connexins, acting on cell receptors to exert anti-cancer or cancer gene effects[9]. Therefore, abnormal miRNAs are detected in a variety of tumor cells[12-14]. Moreover, miRNA has a small molecular weight and high specificity, and it is expected to become a new method in clinical work[15]. In the present study, we found that miR-130a is significantly elevated in cancer tissues, and serum of colon cancer patients, and miR-130a was significantly upregulated in human colon cancer cells HCT116, HT29, Caco-2 cell lines compared to human embryonic kidney epithelial 293T cells. Increased expression of miR-130a in cancer tissues, serum and colon cancer cells of colon cancer patients suggests that miR-130a can be used as a potential colon cancer marker. Using miR-130a as a marker may be an important method for early diagnosis and treatment of colon cancer.

Studies have reported that abnormal expression of miRNA is closely related to the incidence and development of colon cancer. Ullmann et al[16] found that the tumor suppressor miR-215 was involved in the regulation of colon cancer stem cell activity by regulating hypoxia/miR-125/LGR5 axis and was expected to become a new method for the treatment of colon cancer. In this study, we analyzed the expression level of miR-130a in colon cancer patients and colon cancer cells, and further confirmed that miR-130a abnormal expression was closely related to the occurrence and development of colon cancer. The vitality, proliferative capacity, migration ability, and invasive ability of colon cancer cells are important biological functions. In this study, MTT assay, colony formation assay, cell scratch assay, and transwell assay were used to detect the effects of miR-130a on cell biological activity such as cell viability, proliferation ability, migration ability, and invasive ability. The results showed that the overexpression of miR-130a significantly increased colon cancer cell viability, proliferation, migration and invasion. Knockdown of miR-130a significantly reduced colon cancer cell viability, proliferation, migration, and invasion. However, in the process of tumor cell proliferation, migration and invasion, there are often multiple gene networks or signaling pathways involved. Notably, miR-223 promotes oral squamous cell proliferation and migration by regulating its target gene FBXW7[17]. MiR-500 promotes prostate cancer cell proliferation by directly targeting inhibition of LRP1B[18]. Therefore, we continued to study the gene regulatory network of miR-130a in regulating the biological function of colon cancer, which had important theoretical and practical value. In this work, we performed target prediction, qRT-PCR, Western blot, and luciferase experiments, and the results showed that miR-130a can targetedly inhibit the expression of gene of phosphates and tensin homologue deleted on chromosome ten (PTEN). PTEN has phosphatase activity and is a tumor suppressor essential for maintaining normal cell survival and plays an important regulatory role in the occurrence and development of cancer. He et al[19] found that miR-20b can inhibit the expression of PTEN and promote the proliferation of hepatoma cell line H22. miR-182-3p promotes the growth of non-small cell lung cancer cells by targeting inhibition of PTEN[20]. Therefore, this study indicated that miR-130a increased the viability, proliferation, migration, and invasion ability of human colon cancer cells by targeting inhibition of PTEN. However, the sample size of this subject is small, and only the effect of miR-130a on colon cancer cell Caco-2 is explored. In the future, the sample size and cell line need to be expanded for further exploration.

Conclusions

Altogether, the expression of miR-130a in cancer tissues and serum samples of colon cancer patients is significantly increased, and miR-130a increases the viability, proliferation, migration, and invasion ability of human colon cancer cells by targetedly inhibiting PTEN, which provides new biomarkers for early clinical prediction and diagnosis of colon cancer, and new methods and targets for the treatment of colon cancer.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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