

MiR-374b reduces cell proliferation and cell invasion of cervical cancer through regulating FOXM1

N. XIA, W.-F. TAN, Q.-Z. PENG, H.-N. CAI

Department of Gynaecology, Maternal and Child Health Hospital of HuBei Province, Wuhan, China

Abstract. – OBJECTIVE: Deregulation of microRNAs (miRNAs) has been identified as critical event in tumor initiation and progression. We aimed to explore the role of miR-374b in cervical cancer progression.

PATIENTS AND METHODS: MiR-374b expression was detected using qRT-PCR in cervical cancer tissues compared with normal counterparts. Cell proliferation and invasion ability were detected using Cell Counting Kit-8 (CCK8) cell proliferation and transwell invasion assay. Dual luciferase reporter assay, qRT-PCR, and Western blot analysis were used to demonstrate that FOXM1 was a target of miR-374b.

RESULTS: We demonstrated that downregulation of miR-374b was frequently examined in cervical cancer tissues compared with normal counterparts. Furthermore, we showed the lower miR-374b expression associated with lymph node metastasis and advanced FIGO stage in patients with cervical cancer. Furthermore, ectopic expression of miR-374b could significantly decrease cell proliferation and invasion ability. However, inhibition of miR-374b had opposite effects. Dual luciferase reporter assay, qRT-PCR, and Western blot analysis revealed that miR-374b overexpression suppressed cell proliferation and invasion ability via affecting FOXM1 expression.

CONCLUSIONS: These results indicated that miR-374b acted as tumor suppressor and may serve as a potential target for cervical cancer treatment.

Key Words:

MicroRNAs, Cervical cancer, miR-374b, FOXM1, Cell proliferation.

Introduction

Cervical cancer is the one of the leading gynecological malignancies in female worldwide. More than 12,000 new cases of cervical cancer were diagnosed and 4,120 deaths occur in 2016 in the United States^{1,2}. The incidence of cervical cancer in China is about six times higher than in

developed countries³. Current treatments including surgery, chemotherapy and radiation present limited interventions for advanced disease. Cervical cancer patients with locally advanced or metastatic show a poor 5-year survival rate (about 30-50%), which causes major morbidity and mortality^{4,5}. Thus, to explore the underlying molecular mechanisms in cervical cancer development is still necessary. MicroRNAs (miRNAs) can degrade translation of their target mRNA by binding to the 3' untranslated region (UTR). Substantial evidence has revealed that deregulation of miRNAs affected cell proliferation, migration, invasion, metastasis and chemotherapy resistance^{6,7}. MiR-221 and miR-222 simultaneously target ARID1A and enhance proliferation and invasion of cervical cancer cells⁸. MiR-519d facilitates the progression and metastasis of cervical cancer through direct targeting Smad7⁹. MiR-125a promotes paclitaxel sensitivity in cervical cancer through altering STAT3 expression¹⁰. More and more microRNAs were identified as crucial regulators of cervical cancer. MicroRNA-374b has been suggested as a critical tumor suppressor in development and progression. MiR-374b suppresses proliferation and promotes apoptosis in T-cell lymphoblastic lymphoma by repressing AKT1 and Wnt-16¹¹. MicroRNA-374b reduces the proliferation and invasion of colon cancer cells by regulation of LRH-1/WNT signaling¹². However, the role of miR-374b in cervical cancer remains unknown. Thus, we hope to demonstrated the functional role of miR-374b and provide some value for cervical cancer treatment. In the study, we found that miR-374b expression was frequently downregulated in cervical cancer tissues. Ectopic expression of miR-374b could significantly decrease cell proliferation. Furthermore, we verified that miR-374b overexpression suppressed cell proliferation and invasion ability via affecting FOXM1 expression. Thus, these

results indicated that miR-374b acted as tumor suppressor and may serve as a potential target of cervical cancer treatment.

Patients and Methods

Patient Tissues Samples

The study was approved by the Ethics Committee of Maternal and Child Health Hospital of HuBei Province. Informed consent was obtained from all of patients. A total 48 pairs of cervical cancer tissues and adjacent non-tumor tissues were obtained from patients who had undergone surgical treatment at the Department of Gynecology, Maternal and Child Health Hospital of HuBei Province (Wuhan, China) between January 2014 and December 2015. The samples were stored at -80°C before RNA analyses. The clinical data were shown in Table I.

Cell Culture and Transfection

An immortalized cervical epithelial cell line (Hacat) and three cervical cancer cell lines (Si-Ha, Hela and CaSki) were obtained from the Shanghai Institute of Biochemistry and Cell Biology (Shanghai, China). Cells were grown in Dulbecco's Modified Eagle Medium (DMEM; Thermo Fisher Scientific, Inc., Waltham, MA, USA) medium supplemented with 10% fetal bo-

vine serum (FBS, Thermo Fisher Scientific, Inc., Waltham, MA, USA) and maintained at 37°C and 5% CO₂ in an atmosphere. Human miR-374b mimic, miR-374b inhibitor and miR negative control (NC) were purchased from Guangzhou RiboBio Co., Ltd. (Guangzhou, China). Cells were transfected using Lipofectamine 2000 reagent (Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA) according to the manufacturer's protocol.

RNA Extraction and Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

Total RNA of tissues or cells was extracted using TRIzol Reagent (Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA), according to the manufacturer's instructions. RNA was reversed transcribed to cDNAs using the Primer-Script one step RT-PCR kit (TaKaRa, Dalian, China). QRT-PCR assays were carried out with SYBR Green I Mix (TaKaRa, Dalian, China) on the Real-Time PCR Detection System (Bio-Rad Laboratories, Inc., Hercules, CA, USA). The primers for miR-374b and FOXM1 were designed and synthesized by Guangzhou RiboBio Co., Ltd. (Guangzhou, China). The sequences for primers were as follow: GAPDH-forward primer: 5'-TGTGGGCATCAATGGATTGG-3', GAPDH-reverse primer: 5'-ACACCATGTAT-

Table I. The association between miR-374b expression and clinicopathological factors.

Clinicopathological features	Patients (n = 48)	MiR-374b expression		p-value
		Higher (n = 25)	Lower (n = 23)	
Age				0.990
≤ 45	25	13	12	
> 45	23	12	11	
HPV 16/18 infection				0.307
Positive	32	15	17	
Negative	16	10	6	
Tumor size (cm)				0.087
≤ 4	19	7	12	
> 4	29	18	11	
Differentiation				0.853
Higher and moderately	34	18	16	
Lower	14	7	7	
Lymph node metastasis				0.041*
Negative	32	20	12	
Positive	16	5	11	
FIGO stage				0.044*
I	30	19	11	
II	18	6	12	

**p* < 0.05.

TCCGGGTCAAT-3'. FOXM1-forward primer: 5'-TGCAGCTAGGGATGTGAATCTTC-3', FOXM1-reverse primer: 5'-GGAGCCCAGTC-CATCAGAACT-3'. U6 or GAPDH mRNA expression was normalized to miR-374b or FOXM1. The $2^{-\Delta\Delta C_t}$ methods were used for quantization.

Cell Counting Kit -8 Assay

Cells (2000 cells/ well) were seeded in the 96 well plates and then were transfected with 100 nM miR-NC, miR-374b mimic or miR-374b inhibitor according to the manufacturer's protocol. Cells were incubated at 37°C in 5% CO₂ for 0 h, 24 h, 48 h and 72 h. Cells were added with 10 μ L of cell counting kit (CKK)-8 solutions (CKK8, Beyotime, Jiangsu, China) and incubated for 2 h according to the manufacturer's protocol. A microplate reader (Bio-Rad, Hercules, CA, USA) was applied to examine the cell viability and the optical density was at 450 nm.

Transwell Invasion Assay

Cell invasion assay was performed using 24-well transwell plates with polycarbonate membrane and 8.0 μ m pores (Corning Inc., Corning, NY, USA) pre-coated with Matrigel (BD Falcon, Franklin Lakes, USA). Cells were seeded into the upper chambers with serum-free DMEM at a density of 1×10^5 cells / per well. The lower chambers were added with DMEM and were supplemented with 10% FBS. After cells transfection for 48 h, invasive cells on the lower chambers were fixed, stained with violet crystalline. Cell numbers were calculated in five random fields with a wide-field microscope (Eclipse TS100; Nikon, Melville, NY, USA).

Luciferase Reporter Assay

The wild type fragment of FOXM1 3'-UTR (WT) containing the miR-374b predicted binding site or mutant type fragment of FOXM1 3'-UTR (MUT) was synthesized by Guangzhou RiboBio Co., Ltd. (Guangzhou, China). Then the two fragments were sub-cloned into the luciferase reporter pMIR-Reporter (Promega Corporation, Madison, WI, USA). The SiHa cells were plated in 6-well plates and maintained at 37°C and 5% CO₂ in an atmosphere. When cells reached 80-90% confluency, cells were co-transfected with 3'UTR-FOXM1-WT, 3'UTR-FOXM1-MUT plasmid (100 ng), miR-NC or miR-374b (50 nM) using Lipofectamine 2000 reagent (Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA) according to the manufacturer's protocol. After

cell transfection at 48 h, luciferase activity was detected using the Dual-Luciferase® Reporter Assay System (Promega Corporation, Madison, WI, USA) according to the manufacturer's protocols. Firefly luciferase activity was normalized to the corresponding Renilla luciferase activity.

Western Blot Assay

Proteins were extracted using RIPA lysis buffer (Beyotime Institute of Biotechnology, Jiangsu, China), according to the manufactures' protocol. The concentration was quantified using a BCA Protein Assay kit (Beyotime Institute of Biotechnology, Jiangsu, China). Proteins (45 μ g) were separated on 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and were transferred onto nitrocellulose membranes (PVDF) (Millipore, Billerica, MA, USA). The membranes were cultured with following antibodies were at 4°C overnight: FOXM1 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) and GAPDH (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA). Western blots were visualized by a chemiluminescent detection system (Pierce ECL Substrate Western blot detection system, Waltham, MA, USA) and protein expression was normalized to GAPDH.

Statistical Analysis

All results from experiments are shown as the mean $\pm$ standard deviation. All statistical analyses were performed with SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA). A two-sided Student's *t*-test or one-way ANOVA with Tukey-Kramer post-hoc test was used to analyze the differences among two groups or more than two groups, respectively. A *p*-value < 0.05 was considered to be statistically significant.

Results

MiR-374b Expression is Reduced in Cervical Cancer Tissues and Cells

To investigate the expression of miR-374b in cervical cancer, we analyzed miR-374b expression in 48 paired of cervical cancer tissues and adjacent normal tissues by qRT-PCR analysis. Compared with their adjacent normal tissues, downregulation of miR-374b expression was present in cervical cancer tissue samples (Figure 1A, *p* < 0.05). Furthermore, we analyzed the association between miR-374b expression and clinicopathological fac-

tors. According to the median expression of miR-374b, we divided the patients into two groups (higher expression group and lower expression groups). The results indicated that lower miR-374b expression associated with lymph node metastasis and advanced FIGO grade (all of $p < 0.05$, Table I). These results indicated that lower miR-374b expression was frequent events during the progression of cervical cancer. Moreover, we also found that miR-374b expression was downregulated in three cervical cancer cells including HeLa, SiHa, and Caski cells, compared to one normal epithelial cell line (Hacat) ($p < 0.05$, Figure 1B).

MiR-374b Reduces Cervical Cancer Cell Proliferation and Invasion Ability

Furthermore, we detected the effects of miR-374b expression on cell proliferation and inva-

sion ability. We performed gain-function and loss-function using miR-374b mimic or miR-374b inhibitor in SiHa and CaSki cells (Figure 1C-1D). CCK8 cell proliferation assays in SiHa cells revealed that transfection of miR-374b mimic significantly reduced cell proliferation ability compared to miR-NC group (Figure 2A). However, transfection of miR-374b inhibitor in CaSki cells enhanced cell proliferation compared to miR-NC group (Figure 2B). By performed cell invasion assay, we observed that cell invasion was impaired when miR-374b mimic was transfected into SiHa cells (Figure 2C). On the contrary, a converse result was observed when miR-374b inhibitor was transfected into CaSki cells (Figure 2D). These results indicated that miR-374b reduced cell proliferation and invasion ability of cervical cancer.

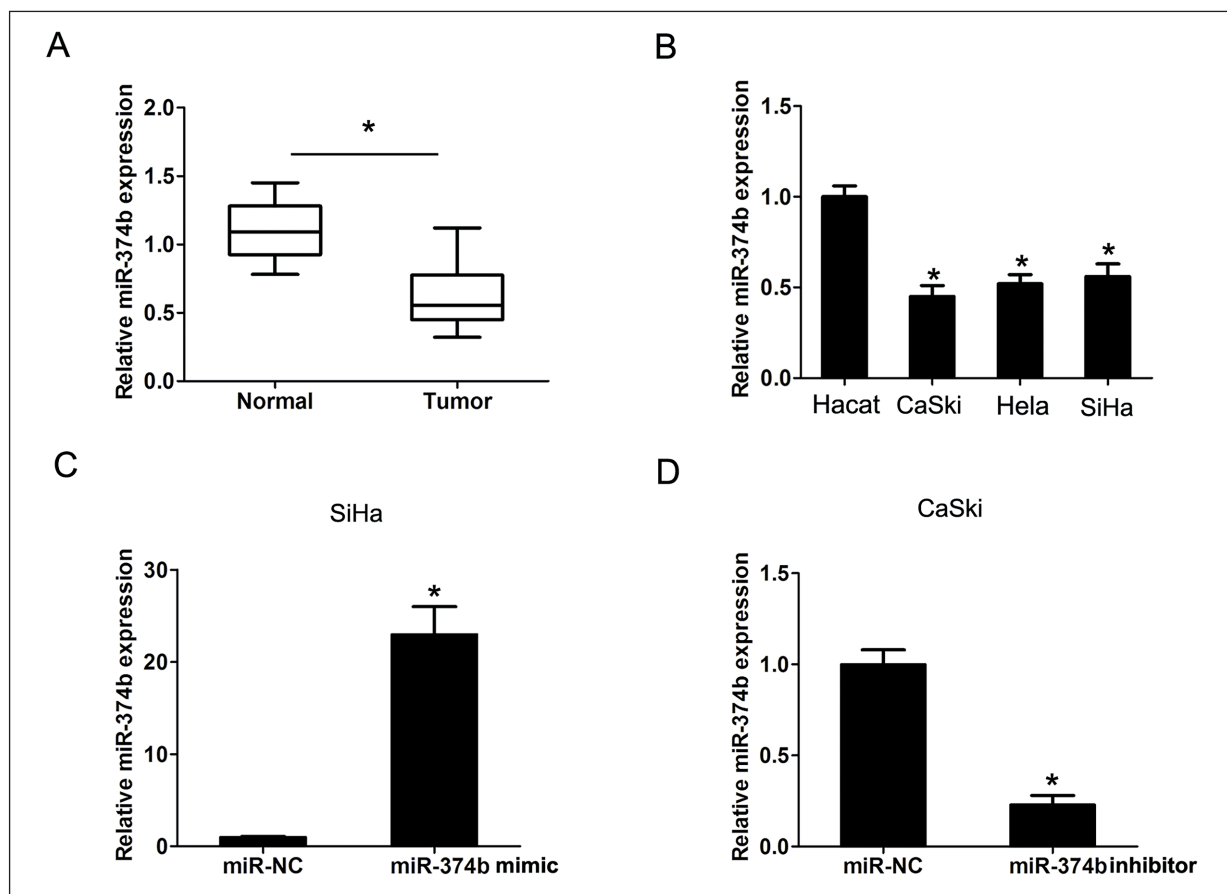


Figure 1. MiR-374b expression is reduced in cervical cancer tissues and cells. **(A)** QRT-PCR analysis of the miR-374b expression in 48 pairs of cervical cancer tissues and adjacent normal tissues. **(B)** QRT-PCR analysis of the miR-374b expression in immortalized cervical epithelial cell line and three cervical cancer cell lines. **(C)** QRT-PCR analysis of the miR-374b expression after miR-NC or miR-374b mimic was transfected into SiHa cells. **(D)** QRT-PCR analysis of the miR-374b expression after miR-NC or miR-374b inhibitor was transfected into Caski cells. * $p < 0.05$.

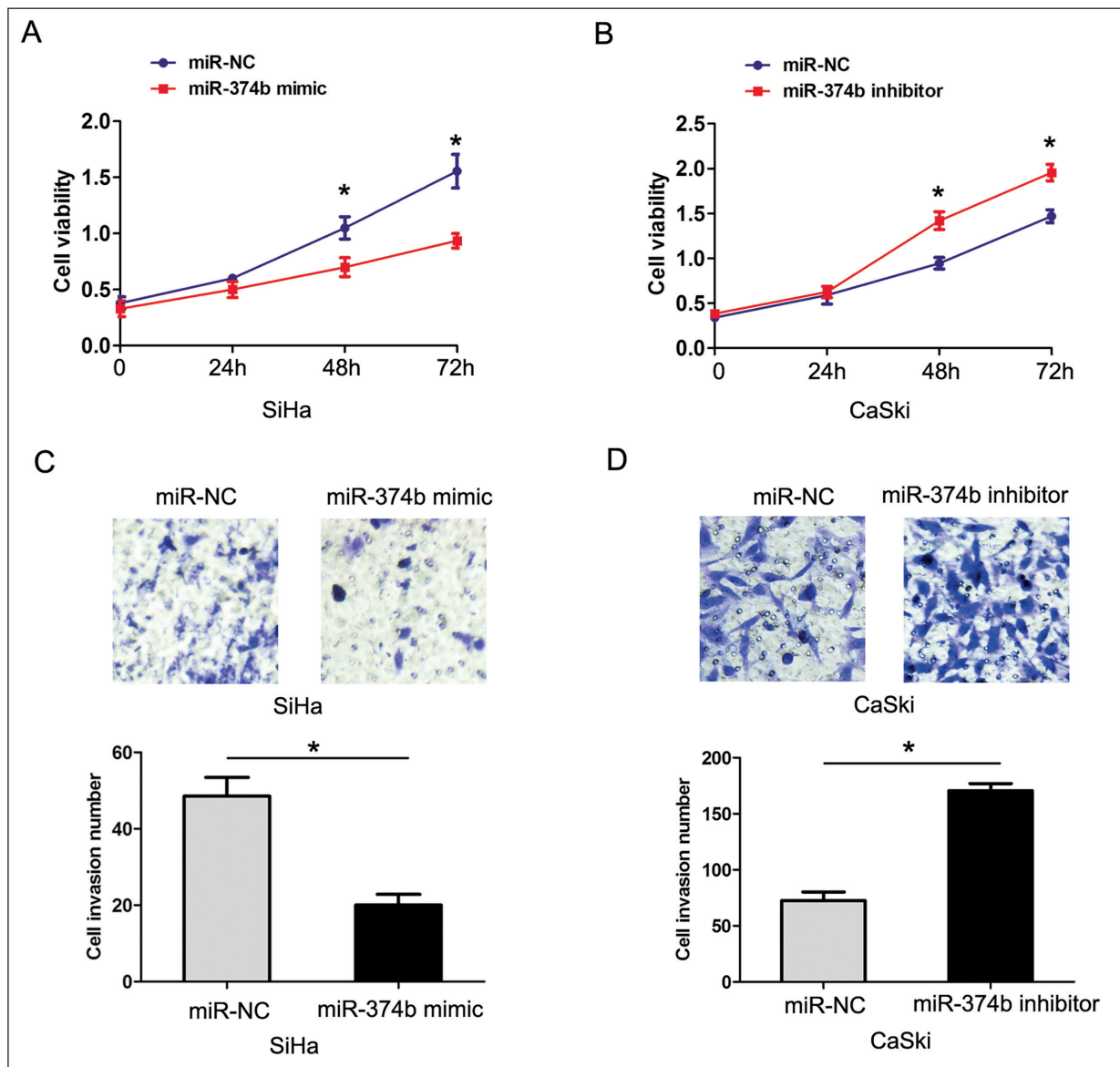


Figure 2. MiR-374b inhibits cell proliferation and invasion of cervical cancer. (A) CCK8 cell proliferation assays were used to evaluate cell proliferation after miR-NC or miR-374b mimic was transfected into SiHa cells. (B) CCK8 cell proliferation assays were used to evaluate cell proliferation after miR-NC or miR-374b inhibitor was transfected into Caski cells. (C) Transwell cell invasion assays were used to evaluate cell invasion after miR-NC or miR-374b mimic was transfected into SiHa cells. (D) Transwell cell invasion assays were used to evaluate cell invasion after miR-NC or miR-374b inhibitor was transfected into Caski cells. Each experiment was performed at least three times. * $p < 0.05$.

MiR-374b Targets FOXM1 and Regulates its Expression in Cervical Cancer

By miRanda (www.microRNA.org) prediction software, we found that FOXM1, a member of the FOX super family of transcription factors, was a potential target of miR-374b (Figure 3A). FOXM1 inhibition could suppress cervical cancer cell viability, migration and invasion¹³. We speculated that FOXM1 may be regulat-

ed by miR-374b in cervical cancer progression. Furthermore, we constructed the 3'-UTR-FOXM1-WT containing the miR-374b predicted binding site or 3'-UTR-FOXFM1-MUT plasmids. The SiHa cell was co-transfected with 3'UTR-FOXM1-WT or 3'UTR-FOXFM1-MUT luciferase reporter vector and miR-NC or miR-374b mimic. The results showed that luciferase activity was significantly reduced in miR-374b

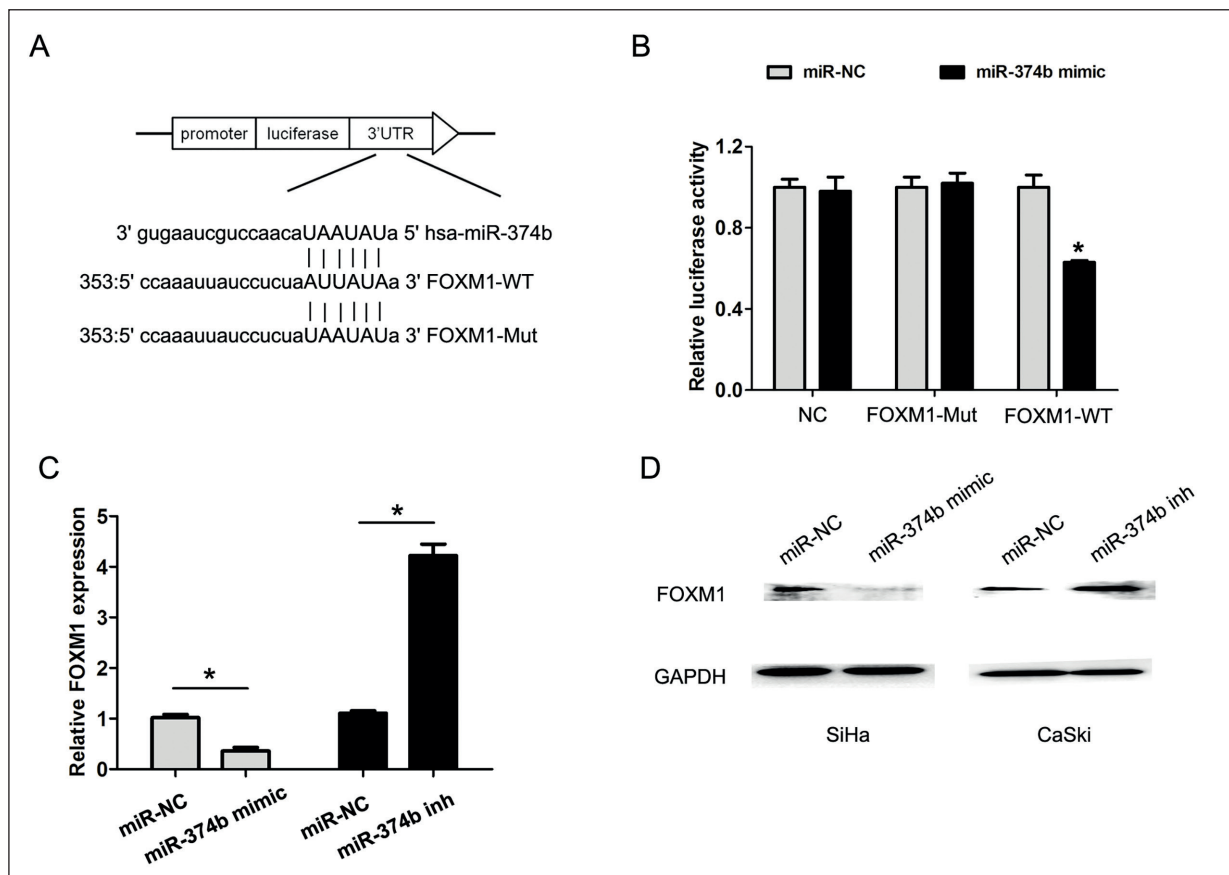


Figure 3. MiR-374b targets FOXM1 and regulates its expression in cervical cancer cells. **(A)** A schematic of the bioinformatics predicted seed region in the 3'UTR of FOXM1, as well as mutated 3'UTR of FOXM1 used in this study. **(B)** Effect of miR-374b mimic or miR-NC on the luciferase activity of the plasmid FOXM1-3'UTR-WT and FOXM1-3'UTR-MUT in SiHa cells. **(C)** QRT-PCR analysis of FOXM1 mRNA expression after SiHa cells were transfected with miR-NC or miR-374b mimic and in Caski cells were transfected with miR-NC or miR-374b inhibitor. **(D)** Western blot analysis of FOXM1 protein expression after SiHa cells were transfected with miR-NC or miR-374b mimic and in Caski cells were transfected with miR-NC or miR-374b inhibitor. Each experiment was performed at least three times. * $p < 0.05$.

mimic plus 3'-UTR-FOXM1-WT luciferase reporter vector transfected SiHa cells compared to other groups (Figure 3B). Consistent with the luciferase assay results, we demonstrated that FOXM1 mRNA and protein expression were also reduced when miR-374b mimic was transfected into SiHa cells, compared to corresponding control group; however, FOXM1 mRNA and protein expression were increased when miR-374b inhibitor was transfected into Caski cells, compared to corresponding control group (Figure 3C-3D). These results indicated that miR-374b targeted FOXM1 and regulated its expression in cervical cancer.

Reduced Expression of FOXM1 Rescues Cell Proliferation and Invasion Ability in miR-374b Downregulated Cervical Cancer Cells

To confirm miR-374b suppressed cell proliferation and invasion by directly targeting FOXM1, we knocked down FOXM1 using a siRNA against FOXM1 (Figure 4A). CCK8 assay results showed that knockdown of FOXM1 inhibited cell proliferation compared to si-NC group. However, after cells were co-transfected with si-FOXM1 and miR-374b inhibitor at 48 h, decreased cell proliferation capability induced by si-FOXM1 in CaSki cells was reversed (Figure 4B). These results

indicated that restoration of miR-374b abolished the inhibition of proliferation by si-FOXM1. In consistent with cell proliferation capability, after cells were co-transfected with si-FOXM1 and miR-374b inhibitor at 48 h, decreased cell invasive capability induced by si-FOXM1 in CaSki cell lines was also reversed (Figure 4C-4D). Thus, our results indicated that miR-374b regulated cell proliferation and invasion by targeting FOXM1.

Discussion

Recent studies have indicated that many miRNAs have been shown to play crucial roles in carcinogenesis of cervical cancer. MiR-374b had a limited number of studies in tumor devel-

opment and progression in the previous study. MiR-374b-5p suppresses RECK expression and promotes gastric cancer cell invasion and metastasis¹⁴. Higher miR-374b-5p expression was independently associated with a favorable triple-negative breast cancer outcome¹⁵. Downregulation of miR-374b was identified as be directly involved in acquisition of the drug-resistant phenotype in pancreatic cancer cells¹⁶. Recent study showed that miR-374b inhibits colon cancer cell proliferation and invasion through downregulation of LRH-1 expression¹². However, the role of miR-374b expression in cervical cancer remains little known. In present study, downregulation of miR-374b expression was frequently examined in cervical cancer tissues compared with normal counterparts. Association of miR-374b expression with lymph node metastasis and advanced FIGO

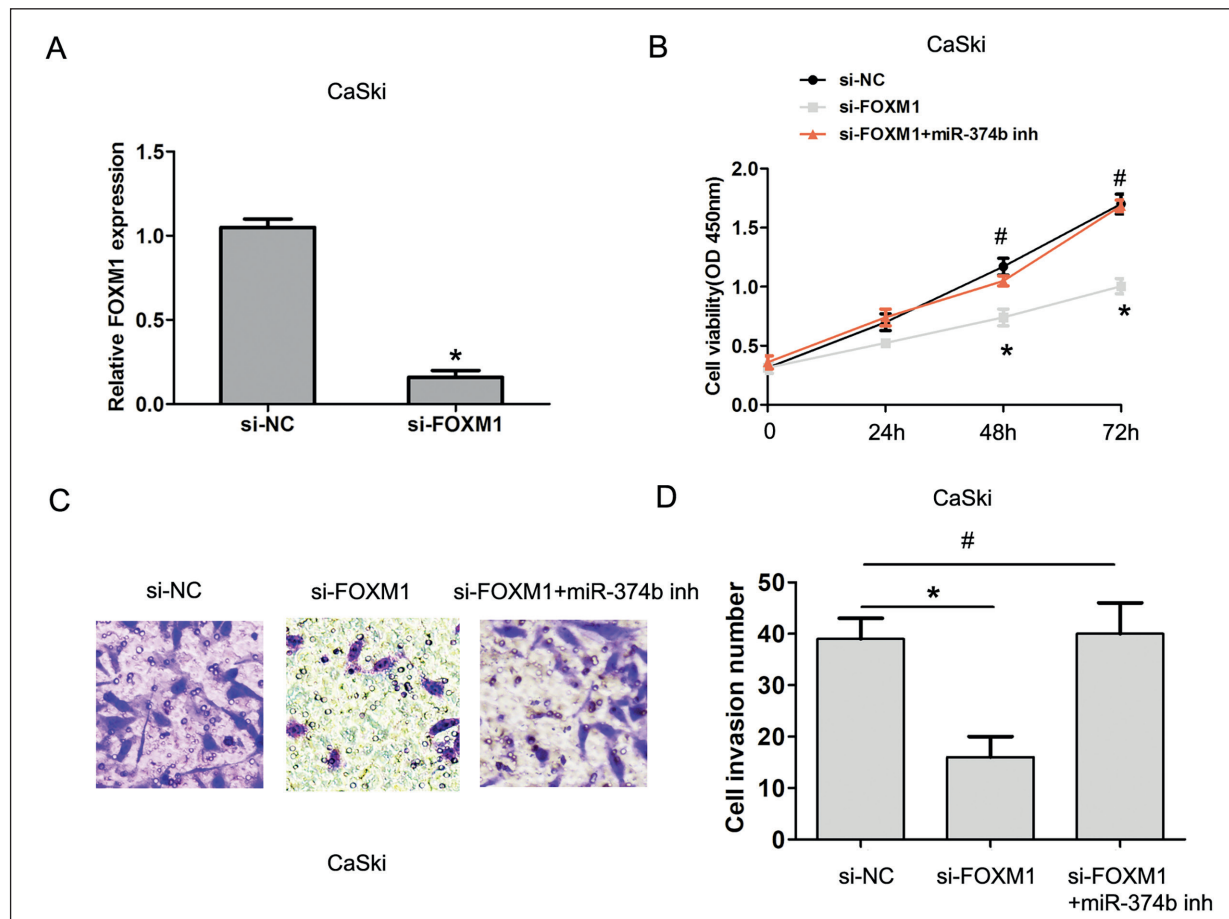


Figure 4. Reduce expression of FOXM1 rescued cell proliferation and invasion ability in miR-374b downregulated cervical cancer cells. **(A)** QRT-PCR analysis of FOXM1 mRNA expression after Caski cells were transfected with si-NC or si-FOXM1. **(B)** CCK8 cell proliferation assays were used to evaluate cell proliferation after si-NC or si-FOXM1 or si-FOXM1+miR-374b inhibitor was transfected into Caski cells. **(C-D)** Transwell invasion assays were used to evaluate cell invasion after si-NC or si-FOXM1 or si-FOXM1+miR-374b inhibitor was transfected into Caski cells. Each experiment was performed at least three times. * $p < 0.05$ #, not statistically significant.

stage was found. Moreover, ectopic expression of miR-374b could significantly decrease cell proliferation and invasion ability. On the contrary, reduced expression of miR-374b could significantly increase cell proliferation and invasion ability. Dual luciferase reporter assay, qRT-PCR, and Western blotting analysis showed that miR-374b suppressed cell proliferation ability via affecting FOXM1. FOXM1, a member of the FOX superfamily of transcription factors, has been identified as key oncogene in tumors. Over-expression of FOXM1 transcription factor is associated with cervical cancer progression and pathogenesis¹⁷. FOXM1 promotes tumor cell invasion and correlates with poor prognosis in early-stage cervical cancer¹⁸. FOXM1 was identified as target of miRNAs involved in cervical cancer progression. MiR-342-3p suppresses proliferation, migration and invasion by targeting FOXM1 in human cervical cancer¹⁹. MiR-214 inhibits cell migration, invasion and promotes the drug sensitivity in human cervical cancer by targeting FOXM1²⁰. These results indicated that FOXM1 expression play crucial role in cervical cancer. In the study, reduced expression of FOXM1 significantly suppressed cell proliferation and invasion abilities. After cells were cotransfected with miR-374b inhibitor and si-FOXM1, reduced cell proliferation and invasion induced by si-FOXM1 was reversed, which indicated that miR-374b regulated cell proliferation and invasion by targeting FOXM1.

Conclusions

We found that miR-374b was frequently down-regulated in cervical cancer tissues. Ectopic expression of miR-374b could significantly decrease cell proliferation. Furthermore, we verified that miR-374b suppressed cell proliferation ability via affecting FOXM1 expression. Thus, these results indicated that miR-374b acted as tumor suppressor and may serve as a potential target of cervical cancer treatment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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