

RESEARCH ARTICLE

miR-92a promotes cervical cancer cell proliferation, invasion, and migration by directly targeting *PIK3R1*

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Abstract

Objective: To clarify the role of miR-92a in regulating the malignant progression of cervical cancer and its specific molecular mechanism.

Methods: qRT-PCR was used to detect the differential expression of miR-92a in cervical cancer and adjacent tissues. The effects of overexpression of miR-92a on the proliferation, migration, and invasion of HeLa and SiHa cells were tested. Luciferase assays and rescue experiments were used to investigate the regulatory mechanism of miR-92a on its downstream gene *PIK3R1* and their interaction in the progression of cervical cancer.

Results: miR-92a was significantly up-regulated in cervical cancer tissues. Overexpression of miR-92a significantly increased the ability of cervical cancer cells to proliferate, migrate, and invade. *PIK3R1* was identified as a downstream gene of miR-92a. In cervical cancer tissues, *PIK3R1* was found to be down-regulated and negatively correlated with the level of miR-92a. Overexpression of *PIK3R1* reversed the promotional effect of overexpressed miR-92a on the proliferation, migration, and invasion of cervical cancer.

Conclusion: miR-92a is up-regulated in cervical cancer tissues. miR-92a promotes the malignant development of cervical cancer by negatively regulating *PIK3R1*.

KEYWORDS

cervical cancer, miR-92a, *PIK3R1*

1 | INTRODUCTION

Cervical cancer is one of the most common malignant tumors in women, and its incidence is second only to breast cancer, colorectal cancer, and lung cancer.¹ According to incomplete statistics from the World Health Organization, there are more than 500,000 new cases worldwide each year, with increasing incidence year by year and reduced age of onset.² Cervical cancer causes approximately 300,000 deaths every year, of which 85% occur in developing countries, and the cancer seriously affects the quality of life of women.^{3,4} Therefore, understanding the pathogenesis of cervical cancer and

looking for potential prognosis and targeted therapy indicators are of great significance for improving the survival rate of patients with cervical cancer.

MicroRNA molecules (microRNA, miRNA) are small non-protein-coding RNAs that regulate the expression of target genes at the post-transcriptional level.^{5,6} miRNAs bind to the 3'-untranslated region (three prime untranslated region, 3'-UTR) of the target mRNA and regulate gene expression by shearing the mRNA or inhibiting translation. Previous studies have shown that the abnormal expression of miRNA is related to a variety of human malignancies including cervical cancer.^{7,8} miR-92a is a novel miRNA molecule discovered in

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recent years. It is considered to be a tumor promoter in colorectal cancer,⁹ liver cancer,¹⁰ gastric cancer,¹¹ and renal cell carcinoma¹² where it shows up-regulated expression and appears to regulate cell functions such as tumor cell proliferation, migration, and apoptosis. However, the function of miR-92a in cervical cancer and its mechanism of action are still unclear.

Phosphoinositide 3-kinase regulatory subunit 1 (*PIK3R1*) is significantly reduced in a variety of human tumor tissues compared with normal control tissues, including lung, prostate, liver, kidney, and breast cancers.^{13,14} It has been reported that decreased expression of *PIK3R1* mRNA and the *PIK3R1*-encoding protein p85 α is related to reduced metastasis-free survival in patients with breast cancer.¹⁵ In a mouse liver cancer model, the liver-specific *PIK3R1* knockout and an 80%–90% reduction in p85 α protein expression lead to PI3K pathway activation and corresponding tumor progression. P85 α can stabilize PTEN, and PTEN expression in these *PIK3R1* knockout tumors is also reduced.¹⁶ These findings indicate that the dysregulation of *PIK3R1* expression plays a key role in cancer development. In addition, *PIK3R1* has been shown to be a functional target of many miRNAs involved in the regulation of cancer progression.¹⁷ However, the role of miRNA and *PIK3R1* in cervical cancer requires further study.

In our study, we found that the expression of miR-92a in cervical cancer tissues was significantly higher than that in adjacent tissues. miR-92a can promote the proliferation, migration, and invasion of cervical cancer cells. Mechanistically, *PIK3R1* was confirmed as a target of miR-92a. In conclusion, our observations indicate that miR-92a-*PIK3R1* can regulate the malignant biological characteristics of cervical cancer.

2 | MATERIALS AND METHODS

2.1 | Cell culture

The cell cryopreservation tube removed from the -80°C refrigerator was placed in a 37°C water bath for 5 min, and immediately resuspended in DMEM (Gibco) containing 10% FBS. Cells were cultured in a constant temperature incubator at 37°C and 5% CO_2 . The cell culture medium was changed every other day.

2.2 | Total RNA extraction

One milliliter of TRIzol was added to the cervical cancer tissue sample, and a tissue homogenizer was used to crush the tissue into a slurry. Two hundred microliters of CHCl_3 was then added; the material was vortexed and allowed to stand on ice for 3 min; after centrifugation, the supernatant was retained; and 500 μl IPA was then added. The sample was mixed by inversion on ice for 10 min and centrifuged, the supernatant was discarded, and 1 ml of 75% ethanol was added to the pellet to wash. After recentrifugation, the supernatant was discarded, and the pellet was washed once and allowed to

dry naturally. An appropriate amount of RNase-free water was then added and gently pipetted to fully dissolve the RNA.

2.3 | qRT-PCR

Appropriate amounts of RNA were reverse-transcribed into cDNA using the reverse transcription kit (Gima). The NovoStart SYBR qPCR SuperMix Plus (Novoprotein) was used for real-time PCR analysis. The relative expression of miR-92a in the cells was calculated according to the $2^{-\Delta\Delta\text{Ct}}$ formula using U6 as the internal reference (Table S1).

2.4 | Cell transfection

Cells were plated in 6-well plates at a density of 50%–60% per field when viewed under the microscope. A serum-free culture medium was added, and the cells were transfected with small RNA (Table S2) using Lipofectamine 2000. Cells were incubated at 37°C for 5 h before changing the medium to complete medium and culturing for 24–48 h.

2.5 | MTT assay

Cells were plated at 5000 cells per well in 96-well plates the day before transfection. Cells were divided into three groups for transfection with small interfering RNA. After 0, 24, 48, 72, and 96 h, 20 μl MTT reagent was added to each well and incubated at 37°C for 4 h. The medium was aspirated and 150 μl DMSO added to each well. A microplate reader was used to detect the absorbance (OD) value of each sample at 490 nm.

2.6 | Colony formation assay

Logarithmic growth phase cells were inoculated into 6-well plates one day before transfection and were divided into three groups for transfection with small interfering RNA. After transfection, 500 cells per well were inoculated into a new 6-well plate and placed in an incubator. After 12 days of culture, cells were fixed with 4% paraformaldehyde and stained with 0.1% crystal violet staining solution, and the visible colonies were counted manually.

2.7 | Wound healing assay

Three equidistant lines were drawn on the bottom of each well of a 6-well plate. Appropriate amounts of logarithmic growth phase well were inoculated into each cell and divided into three groups for siRNA transfection in advance. A pipette tip was used to scratch the cells horizontally, and the marked cells were washed with phosphate-buffered saline before adding serum-free medium

and culturing at 37°C and 5% CO₂ for 0, 24, and 48 h before being photographed.

2.8 | Transwell assay

Forty-eight hours after transfection, the cells in each group were collected by trypsinization and counted; 4×10^4 cells were added to 100 μ l serum-free medium and mixed, and then added to the bottom of the upper chamber of the Transwell chamber. The complete medium containing 10% FBS was added to the lower chamber, and the apparatus was placed in an incubator for 48 h. The cells were then fixed with 4% paraformaldehyde and stained with 0.1% crystal violet staining solution. Micrographs were taken to count the number of cells that had penetrated the membrane.

2.9 | Western blot

The transfected cells were lysed with RIPA reagent and centrifuged to obtain the protein lysate. The lysate was mixed with an equal volume of SDS loading buffer and boiled to prepare the denatured protein, 50 μ g of which was separated on SDS-PAGE. The electrophoresed proteins were transferred to PVDF membranes by the wet transfer method. The membranes were blocked with 5% skim milk for 1 h and incubated with the primary antibodies overnight at 4°C. The secondary antibodies were incubated for 1 h at room temperature, and the protein bands were exposed by ECL chemiluminescence.

3 | RESULTS

3.1 | miR-92a was up-regulated in cervical cancer tissues

It is well known that miRNAs play important regulatory roles in cervical cancer. Although there are many reports that miRNAs are abnormally expressed in cervical cancer, there are still many miRNAs whose functions in cervical cancer have not been verified. We used cervical cancer microarray data to select miR-92a as it has significant differences from other candidate miRNAs.¹⁸ First, we verified the expression of miR-92a in cervical cancer tissues. We used qRT-PCR to detect the expression of miR-92a in 13 pairs of cervical cancer and adjacent tissues, finding that miR-92a expression was significantly higher in cervical cancer tissues (Figure 1A and B).

3.2 | miR-92a promotes cell proliferation, migration, and invasion in vitro

To further explore the effects of miR-92a on the proliferation, migration, and invasion of cervical cancer cells, the gain of function

and loss of function were determined. First, we designed and synthesized miR-92a inhibitor. We found that the miR-92a inhibitor can significantly down-regulate the expression of miR-92a by 47%–66% (Figure 1C). In addition, we used miR-92a mimics to perform ectopic expression of miR-92a and found that miR-92a may be up-regulated 2500- to 10000-fold (Figure 1D). MTT and colony formation experiments showed that knocking down miR-92a inhibited the proliferation of HeLa and SiHa cells. In contrast, overexpression of miR-92a had an opposite effect on proliferation, indicating that miR-92a promotes the proliferation of HeLa and SiHa cells (Figure 2A and B). Wound healing and invasion experiments showed that knockout of miR-92a inhibited the migration and invasion of HeLa and SiHa cells, and overexpression promoted the migration and invasion of HeLa and SiHa cells (Figure 2C and D).

3.3 | PIK3R1 was identified as a direct target of miR-92a

The cell function experiments demonstrated that miR-92a can promote the proliferation, invasion, and migration of cervical cancer cells. We suspected that miR-92a may affect the progression of cervical cancer through a specific molecular mechanism. Many studies have shown that miRNA can specifically bind and regulate the expression of target genes to regulate tumor progression.¹⁹ We used StarBase software (<http://starbase.sysu.edu.cn/>, v3.0) to predict that miR-92a interacts with *PIK3R1* (Figure 3A). To verify this, we knocked down and overexpressed miR-92a in HeLa and SiHa cells and found that *PIK3R1* expression was clearly regulated by miR-92a (Figure 3B). To further corroborate this interaction, we conducted a dual-luciferase gene reporter experiment. The results showed that after co-transfection of miR-92a mimics with the *PIK3R1* wild type, the luciferase activity was significantly reduced, while after co-transfection of miR-92a mimics with *PIK3R1* mutant type, there was no significant change in luciferase activity (Figure 3C), indicating that miR-92a can interact with *PIK3R1*.

3.4 | miR-92a promotes cell proliferation, migration, and invasion by regulating PIK3R1

To further verify whether miR-92a promotes the progression of cervical cancer by regulating the expression of *PIK3R1*, we co-transfected the miR-92a inhibitor and *PIK3R1* siRNA in HeLa and SiHa cells, and found that compared with *PIK3R1* siRNA transfection alone, transfection of the miR-92a inhibitor significantly inhibited cell proliferation, migration, and invasion (Figure 4A–E). Western blotting results showed that when only *PIK3R1* siRNA was transfected, the *PIK3R1* protein level was significantly inhibited. After co-transfection of the miR-92a inhibitor and *PIK3R1* siRNA, the expression level of *PIK3R1* was restored to a certain extent (Figure 4F).

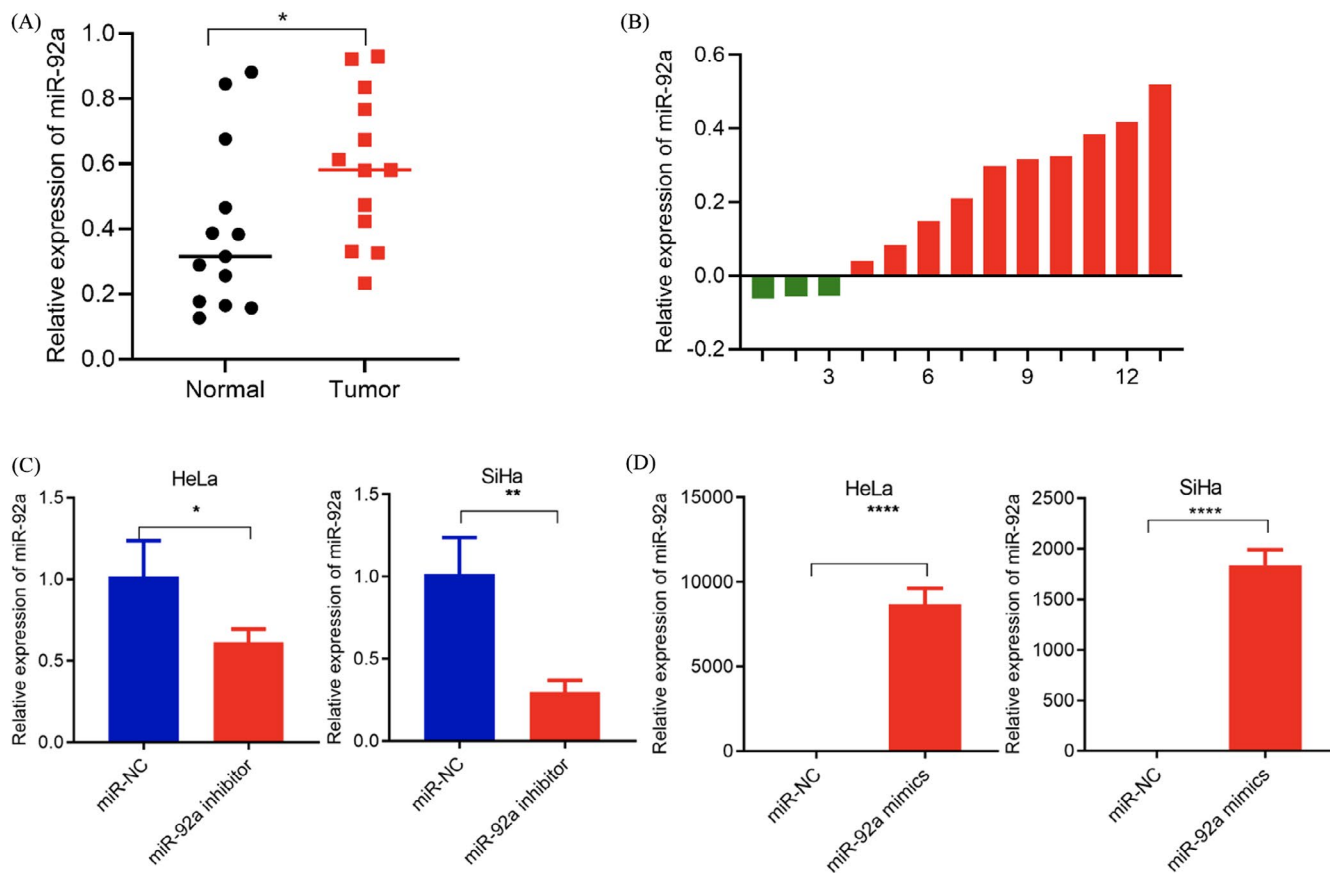


FIGURE 1 Increased expression of miR-92a in cervical cancer tissues. (A, B) qRT-PCR confirmed that the expression of miR-92a in 13 cervical cancer tissues was higher than that in normal tissues. (C) qRT-PCR results showed that the miR-92a inhibitor can specifically reduce the expression of miR-92a. (D) qRT-PCR results showed that miR-92a mimics can specifically up-regulate the expression of miR-92a. Data are presented as the mean \pm SD from three independent experiments. * $p < 0.05$, ** $p < 0.01$, and **** $p < 0.001$

4 | DISCUSSION

As a type of non-coding small RNA with a length of about 19–25 oligonucleotide sequences in eukaryotic cells, miRNAs play roles similar to oncogenes or tumor suppressor genes in multiple biological processes such as cell proliferation, apoptosis, and migration.^{20–22} Different miRNAs regulate the mRNAs of different target genes forming a complex RNA regulatory network that is frequently both cell- and tissue-specific. The human genome contains thousands of miRNAs. Compared with the large number of siRNA fragments, miRNAs are highly conserved and time-sequential.²³ Their mechanism of action is still not well understood.

Previous studies have demonstrated the involvement of miR-92a in the occurrence and development of tumors. For example, miR-92a functions as an oncogenic miRNA in colorectal cancer by regulating the PI3K/AKT pathway mediated by PTEN²⁴ and promotes the proliferation, migration, and invasion of esophageal squamous cell carcinoma by regulating PTEN.²⁵ In contrast, miR-92a is significantly down-regulated in Wilms' tumor, where it inhibits the proliferation, migration, and invasion of Wilms' tumor cells and induces apoptosis by targeting FRS2.²⁶ In this study, miR-92a was found to be highly expressed in cervical cancer tissues. In the cell function

experiments, we used HeLa and SiHa cells to investigate the relationship between the expression of miR-92a and the proliferation and invasion of cervical cancer cells. The results suggested that miR-92a may act as an oncogene in cervical cancer. In addition, we used dual-luciferase reporter gene detection to demonstrate for the first time that miR-92a is related to the proliferation, migration, and invasion of cervical cancer cells through targeted regulation of *PIK3R1*.

The *PIK3R1* gene is located on chromosome 5q13.1 and encodes the regulatory subunit of type I PI3K. The PI3K/AKT signaling pathway participates in the regulation of various cell functions including cell proliferation, migration, and invasion.^{27,28} The *PIK3R1* gene plays an important role in a variety of tumors such as ovarian cancer, colon cancer, hepatocellular carcinoma, and breast cancer.²⁹ Numerous studies have shown that miRNAs can affect tumor cell proliferation, apoptosis, and invasion by regulating the expression of *PIK3R1* mRNA. For example, miR-486-5p promotes pancreatic cancer cell migration and invasion by directly targeting *PIK3R1*,³⁰ which is also targeted by miR-455 to promote the proliferation and migration of kidney cancer cells.³¹ In addition, miR-21 directly targets *PIK3R1* and activates the PI3K/AKT signaling pathway, thereby promoting breast cancer cell growth, migration, and invasion.³² This study found that knocking down

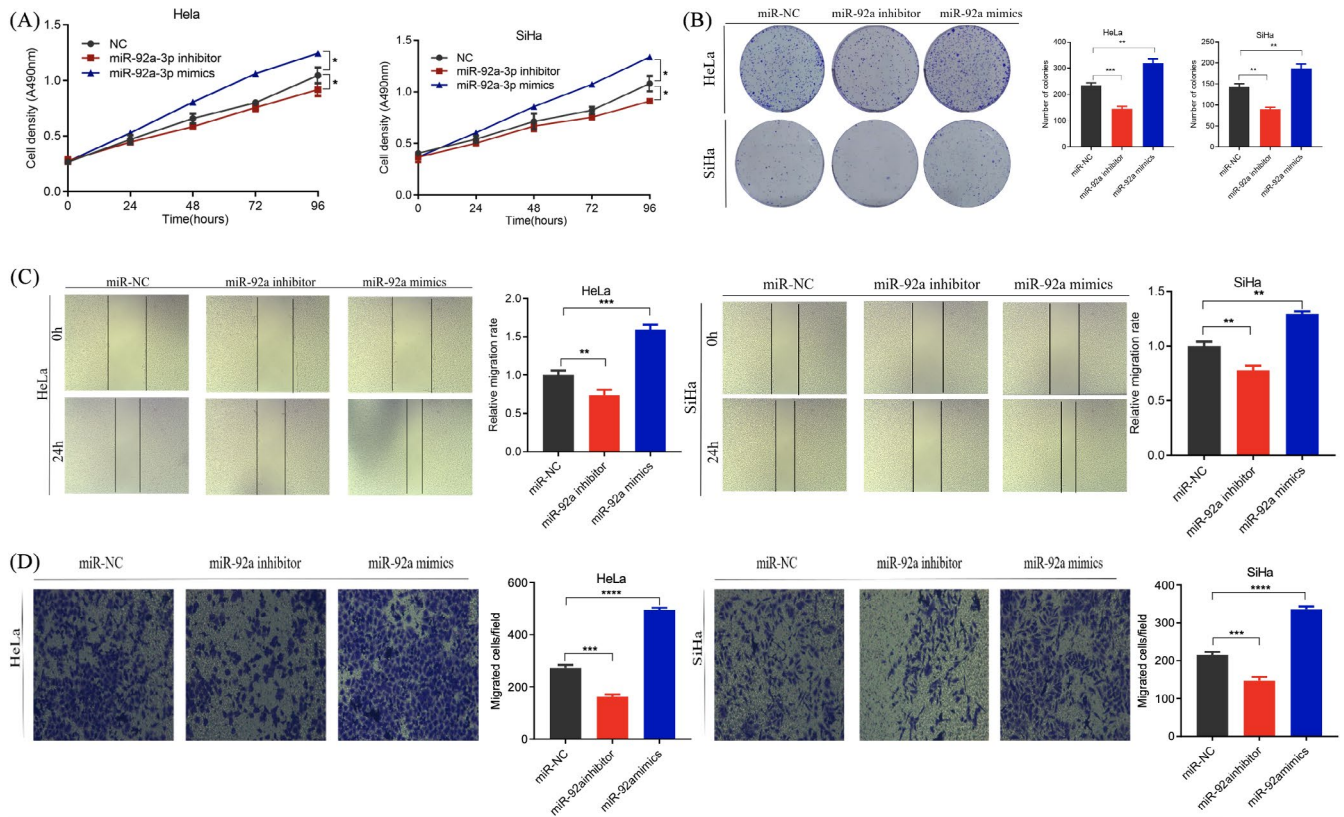


FIGURE 2 miR-92a promotes the proliferation, invasion, and migration of cervical cancer cells. (A) Cell viability detected by the MTT method after transfection of miR-NC, miR-92a inhibitor, or miR-92a mimics in HeLa and SiHa cells. (B) Cell proliferation detected by the clone formation method. (C) Cell migration detected by the cell scratch test. (D) Cell invasion detected by the Transwell assay. Data are presented as the mean \pm SD from three independent experiments. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$

(A) Binding Site *hsa-miR-92a* on *PIK3R1*

| BindingSite | Class | Alignment |
|---------------------------|-------|--|
| chr5:67596002-67596023[+] | 8mer | Target: 5' ucucacaaacAUAAGUGCAAu 3' : miRNA : 3' uguccggcccUGUUCACGUUau 5' |

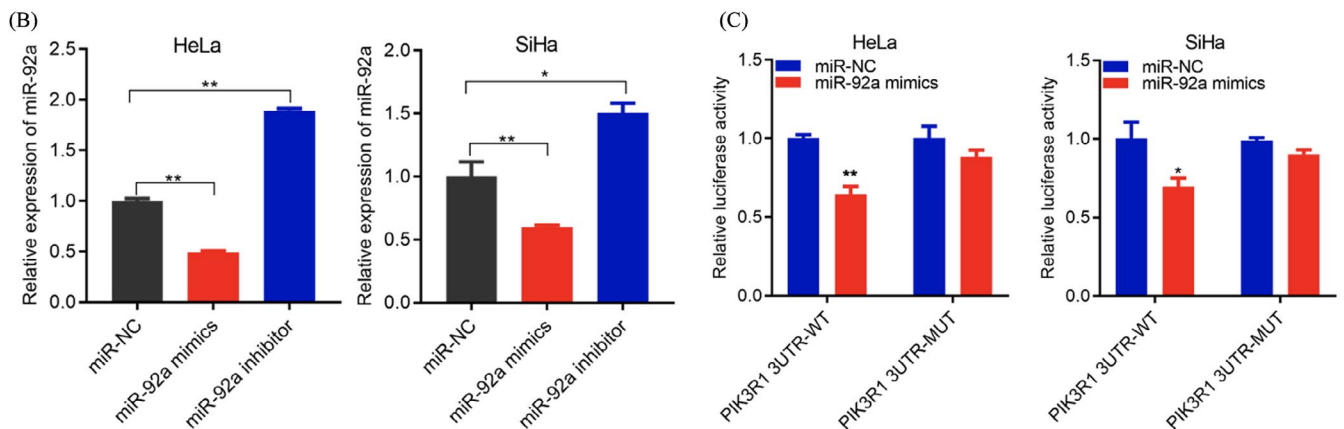


FIGURE 3 miR-92a targets *PIK3R1*. (A) StarBase prediction of miR-92a and *PIK3R1* binding. (B) qRT-PCR detection of *PIK3R1* expression in HeLa and SiHa cells after transfection with miR-92a mimics and the miR-92a inhibitor. (C) Luciferase reporter assay of the binding of miR-92a and *PIK3R1*. Data are presented as the mean \pm SD from three independent experiments. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$

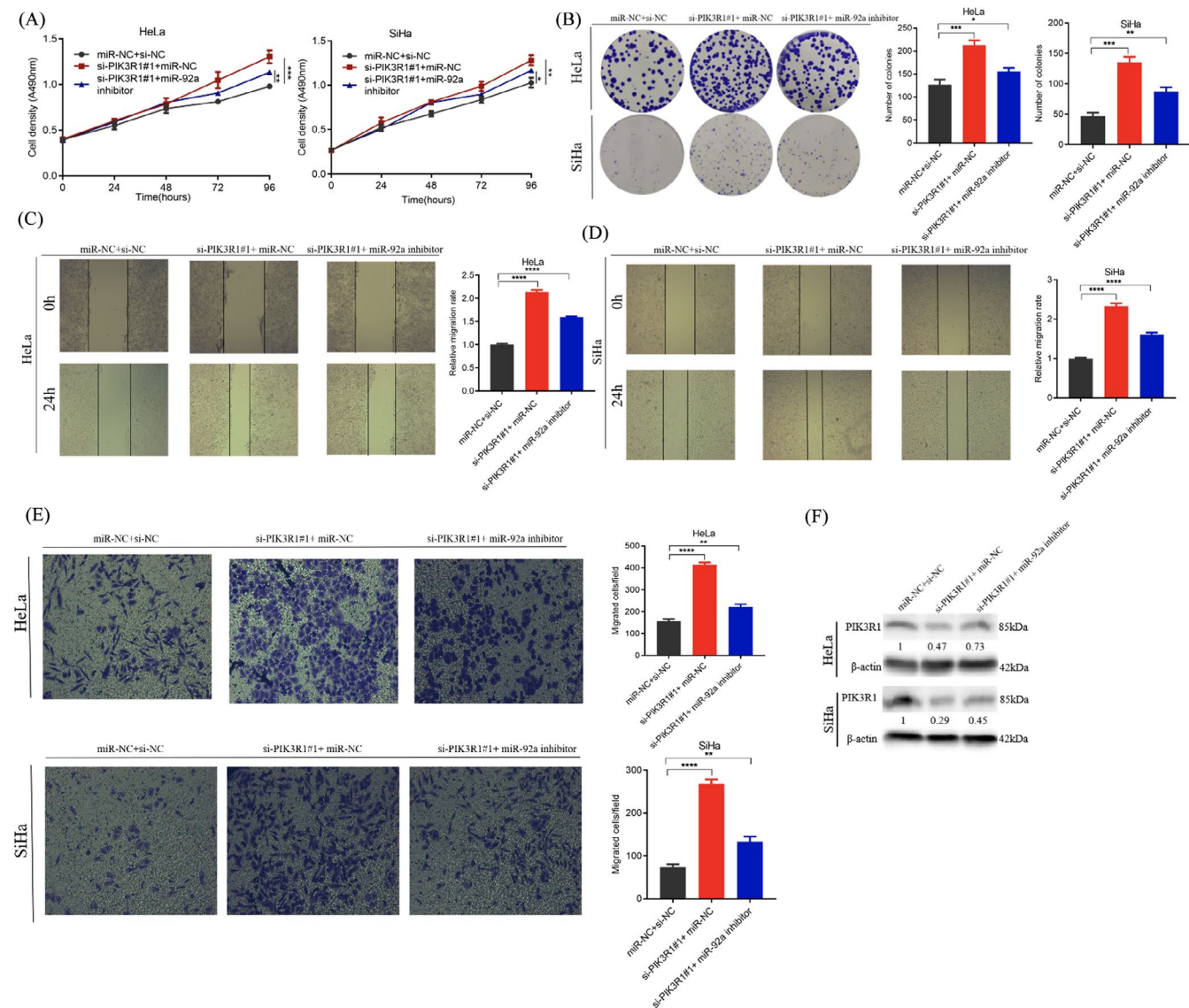


FIGURE 4 Down-regulated miR-92a reverses *PIK3R1* promotion of proliferation, migration, and invasion in cervical cancer cells. (A) MTT experiments showed that after co-transfection of the miR-92a inhibitor and *PIK3R1* siRNA, cell proliferation was partially restored. (B) Clone formation after co-transfection of miR-92a inhibitor and *PIK3R1* siRNA. (C, D) Wound healing of cell migration after co-transfection of the miR-92a inhibitor and *PIK3R1* siRNA shown by the scratch experiment. (E) Partial restoration of cell invasion and migration after co-transfection of miR-92a inhibitor and *PIK3R1* siRNA shown by the Transwell assay. (F) Western blot experiments showed that the expression level of *PIK3R1* protein after co-transfection with miR-92a inhibitor and *PIK3R1* siRNA. Data are presented as the mean \pm SD from three independent experiments. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$

PIK3R1 can promote the proliferation, migration, and invasion of cervical cancer cells, which is consistent with the functional effect of overexpression of miR-92a. In-depth studies have found that inhibiting the expression of *PIK3R1* can partially reverse the effects of miR-92a on the proliferation and invasion of HeLa and SiHa cells, indicating that miR-92a functions by regulating the expression of *PIK3R1*.

In summary, investigation of the mechanism of *PIK3R1* regulation by miR-92a and its role in the proliferation and metastasis of cervical cancer cells will assist our understanding of miR-92a's tumor-promoting mechanism and help clarify the mechanism of cervical cancer occurrence and evolution. This knowledge will

provide a new theoretical basis for the diagnosis and treatment of cervical cancer.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Lingjun Zhao designed and performed the experiments, and wrote the manuscript. Yijun Wang, Chenyang Zheng, and Lingjun Zhao contributed to experimental work and data analysis. Yijun Wang and Aner Chen conducted the experiments and revised the manuscript. All authors have read and approved the final manuscript. The

authors declare that all data were generated in-house and that no paper mill was used.

ETHICAL APPROVAL

All samples were obtained with the patient's informed consent and were carried out with the approval of the Ethics Committee of Ningbo Women and Children's Hospital.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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