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MicroRNA-183-5p Inhibits Aggressiveness of Cervical Cancer Cells by Targeting Integrin Subunit Beta 1 (ITGB1)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Wei Zhang*
CF 2 Mingkai Zhang*
BCEF 3 Lantao Liu
CE 4 Dan Jin
ABE 3 Pengyu Wang
ACEFG 3 Jing Hu

1 Affiliated Hongqi Hospital, Mudanjiang Medical University, Mudanjiang, Heilongjiang, P.R. China
2 Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi, P.R. China
3 School of Basic Medicine, Mudanjiang Medical University, Mudanjiang, Heilongjiang, P.R. China
4 Mudanjiang Women and Children's Hospital, Mudanjiang, Heilongjiang, P.R. China

* These authors contributed equally to this work

Corresponding Author: Jing Hu, e-mail: jinghu_2001@hotmail.com

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Background: Accumulating studies demonstrate that microRNAs play crucial roles in multiple processes of cancer progression. Lower levels of miR-183 have ben observed in diverse types of tumors but the mechanism and precise function of miR-183-5p in cervical cancer have largely not been investigated.

Material/Methods: The level of miR-183-5p in different cervical cancer cell lines and clinical tissues was detected qRT-PCR assays. Transwell and wound-healing migration assays were conducted to assess the functional roles of miR-183-5p in over-expressing cervical cancer cells *in vitro*. Rescue assays were carried out to confirm the contribution of integrin subunit Beta 1 (ITGB1) to the aggressiveness of cancer cells regulated by miR-183-5p.

Results: miR-183-5p was reduced in clinical tissues of cervical cancer and cell lines when compared to the normal subjects and normal cervical epithelial cell line, respectively. In addition, over-expression of miR-183-5p markedly inhibited migration and invasion in cervical cancer cells, and increased aggressiveness was observed in miR-183-5p inhibitor transfected cells. Furthermore, the luciferase reporter assays revealed that ITGB1 was the gene directly regulated by miR-183-5p. Notably, a negative association between the ITGB1 and miR-183-5p was found, and the gene expressions of ITGB1 was mediated by miR-183-5p in cervical cancer cells.

Conclusions: miR-183-5p serves as a latent anti-oncogene by targeting the metastasis-promoter gene, ITGB1.

MeSH Keywords: Cell Migration Assays • MicroRNAs • Neoplasm Invasiveness • Uterine Cervical Neoplasms

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Background

Cervical cancer remains one of the frequently diagnosed cancers among females worldwide [1,2]. Although the clinical outcome of therapy in patients improves through earlier diagnosis, surgical resection, chemotherapy/radiation therapy, the prognosis of advanced disease still remains unsatisfactory [3,4]. The main reason for the death of patients with cervical cancer is cancer progression and metastasis. Hence, the current research investigated the underlying molecular mechanisms that participate in progression of cervical cancer [5].

MicroRNAs (miRNAs), which are small single-stranded RNA molecules, consist of 18–22 nucleotides [6]. Previous studies demonstrated that miRNAs participate in the mediation of cells malignant growth, differentiation, and apoptotic cellular processes. Recently, studies subsequently confirmed that miRNAs are involved in the pathogenesis of various human diseases, including cancer and nervous system diseases [7,8]. Importantly, researchers have also demonstrated that miRNAs are able to regulate tumor formation, invasion, and metastasis by directly binding to the 3'-UTR of the target gene [9]. Moreover, it was reported that miR-183 is related to the metastasis of several cancers, including osteosarcoma and pancreatic neuroendocrine tumor [10,11]. In colorectal cancer, miR-183 is increased in primary colorectal cancer tissue compared to that in the paracarcinoma tissue, and the Wnt/CTNNB1/miR-183 signaling axis might be a promising biomarker for the recurrence and prognosis of colorectal cancer [12]. In addition, miR-183 facilitates the growth of cancer cells through inhibition of FoxO1 in non-small cell lung carcinoma [13]. Although abundant evidence from previous studies indicated the vital roles of miR-183 in diverse cancers, the possible mechanisms of miR-183-5p in metastasis and aggressiveness of cervical neoplasm remain unknown.

Tumor metastasis is one of the major problems in cancer therapy and urgently requires more effective control [14]. Among metastasis-associated genes, integrins mediate cell-cell as well as tumor cell-extracellular matrix crosstalk by exchanging signals across cellular membranes of cancer cells [15]. Integrins are heterodimers consisting of 8β and 18α subunits. For example, integrin β1 is a member of the β sub-family, which forms dimers with different α subunits (α1, α2, α3, α4, α5, α6, α7, and αV). Integrin β1 (ITGB1) has vital roles in growth and motility in breast cancer, non-small cell lung cancer, gastric cancer, and liver cancer [16,17]. In esophageal squamous cell carcinoma (ESCC), integrin α6β1and α6β4 are preferentially located at the invasive front of tumor mass as compared to the normal epithelium, and this change is positively correlated with tumor progression [18]. In non-small cell lung carcinoma, miR-134 inhibits the mobility and invasion of tumor cells via modulating ITGB1 [19]. Another study demonstrated that ITGB1 is the potential target of miR-493-5p and that the quantity of ITGB1 is associated with the prognosis of non-small-cell carcinoma [20]. Although a few studies have confirmed that ITGB1 is regulated by several miRNAs in different types of human cancer, the associations between miR-183-5p and ITGB1 in cervical carcinoma are not entirely known.

In the present study, we examined the expression of miR-183-5p in cervical cancer and its relationship with metastasis in patients. The functions of miR-183-5p in cervical cancer cells mobility and invasiveness capability have not been previously investigated. In the present study, we explored the precise roles of miR-183-5p in cervical cancer cells migration and invasion and revealed the potential target of miR-183-5p.

Material and Methods

Cell lines and tissues samples

Cervical cancer cell lines (SiHa, C-33 A, C-4-I, and CaSki) and the normal cervical epithelial cell line (ECT1/E6E7) were brought from GuangZhou Jennio Biotech Co., Ltd. (Guangzhou, China). Cells were cultured in 1640 or DEME supplemented with 10% FBS at 37°C with 5% CO_2. We collected 43 cases of cervical cancer from patients who underwent surgical resection from February 2002 to November 2016 at Mudanjiang Medical University. The clinical samples were stored in liquid nitrogen following surgical removal from patients. No patients received additional treatment before surgery. Our study was approved by the Ethics Board of Mudanjiang Medical University. All participants provided written informed consent.

Cell transfection

miR-183-5p, miR-control (miR-NC), miR-183-5p inhibitor (miR-183-5p^{inhi}), and miR-NC inhibitor (miR-NC^{inhi}) were supplied by GenePharma (Shanghai, China). The shRNA target ITGB1 gene was provided by Guangzhou RiboBio (Guangzhou, China). The expression construct of ITGB1 was produced by subcloning PCR amplified full-length of ITGB1 cDNA into pMSCV retrovirus plasmid. The coding sequences of 3'-UTR ITGB1 was amplified by PCR and cloned into pHY-LV-Report 3.1 vectors (GenePharma). The miR-183-5p, miR-NC, miR-183-5p^{inhi}, miR-NC^{inhi}, and pMSCV retrovirus plasmid were transfected using Lipofectamine® 2000 reagent (Invitrogen).

qRT-PCR assays

RNA was prepared from either cells or tissue samples using Trizol (Invitrogen). To detect the quantity of miR-183-5p, qRT-PCR analysis was used and U6 was used as the control. To assess the level of ITGB1, RNAs were reversely transcribed

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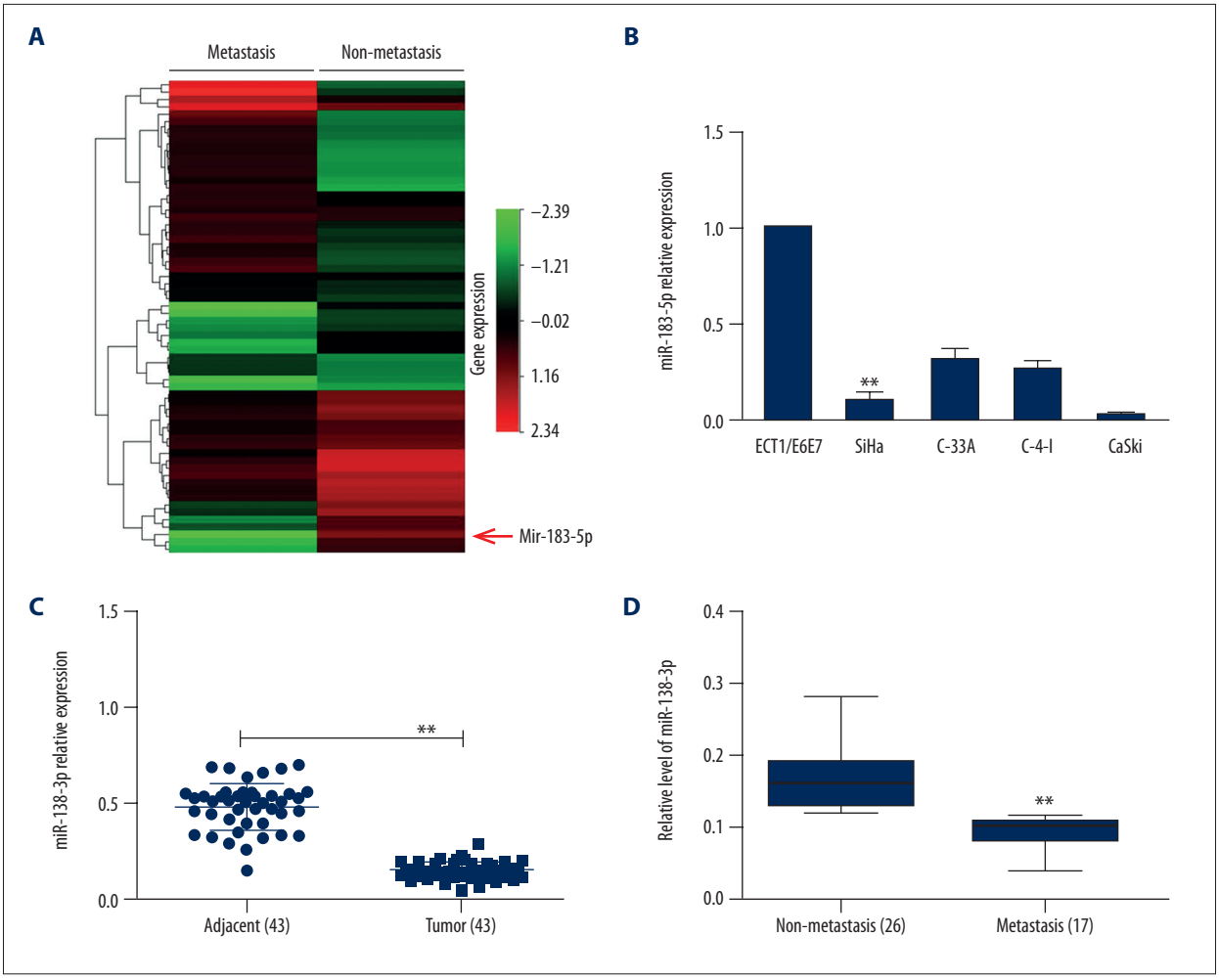

Figure 1. miR-183-5p was under-expressed in cervical carcinoma. (**A**) Microarray analysis results of miRNA in uterine cervix cancer tissues and corresponding control. (**B**) The expression quantity of miR-183-5p in 4 cervical cancer cell lines (SiHa, C-33 A, C-4-I, and CaSki) and ECT1/E6E7 was analyzed by qRT-PCR. ** $P<0.01$, compared to ECT1/E6E7 cells. (**C**) miR-183-5p was reduced in primary cancer samples compared to matched normal tissues, as shown in qRT-PCR results. (**D**) miR-183-5p in clinical cervical cancer specimens with or without peritoneal metastasis was detected by qRT-PCR. ** $P<0.01$, compared to non-metastasis.

using the PrimeScript RT reagent kit (Takara, Dalian, China). cDNAs were augmented using SYBR Premix DimerEraser (Takara, Dalian, China) in the 7900HT system, and the fold change was calculated using $2^{-\Delta\Delta Ct}$ method. GAPDH gene was used as the control.

Wound closure and invasion assay

Cell monolayers were scratched using 10-µl pipette tips to generate wound gaps. After 24 h, the cells migration was photographed and the cell migration distance was measured. Cells were plated into the upper Matrigel invasion chamber (BD Biosciences) in the absence of FBS. Into the lower chamber we added 600 µl medium containing 10% FBS. After 24 h, the bottom cells of the chamber were stained with 1% crystal violet. Invaded cells were counted in 5 randomly selected fields in each well.

Luciferase assays

The 3'-UTR of the ITGB1 segment was amplified by PCR and fused into pHY-LV-Report 3.1 vector. A mixture of pHY-LV-3'-UTR, miR-NC, or miR-183-5p plasmids was co-transfected into the indicated cells using Lipofectamine® 2000 reagent (Invitrogen). Luciferase activity was measured 24 h later using the Dual Luciferase assay system (Promega).

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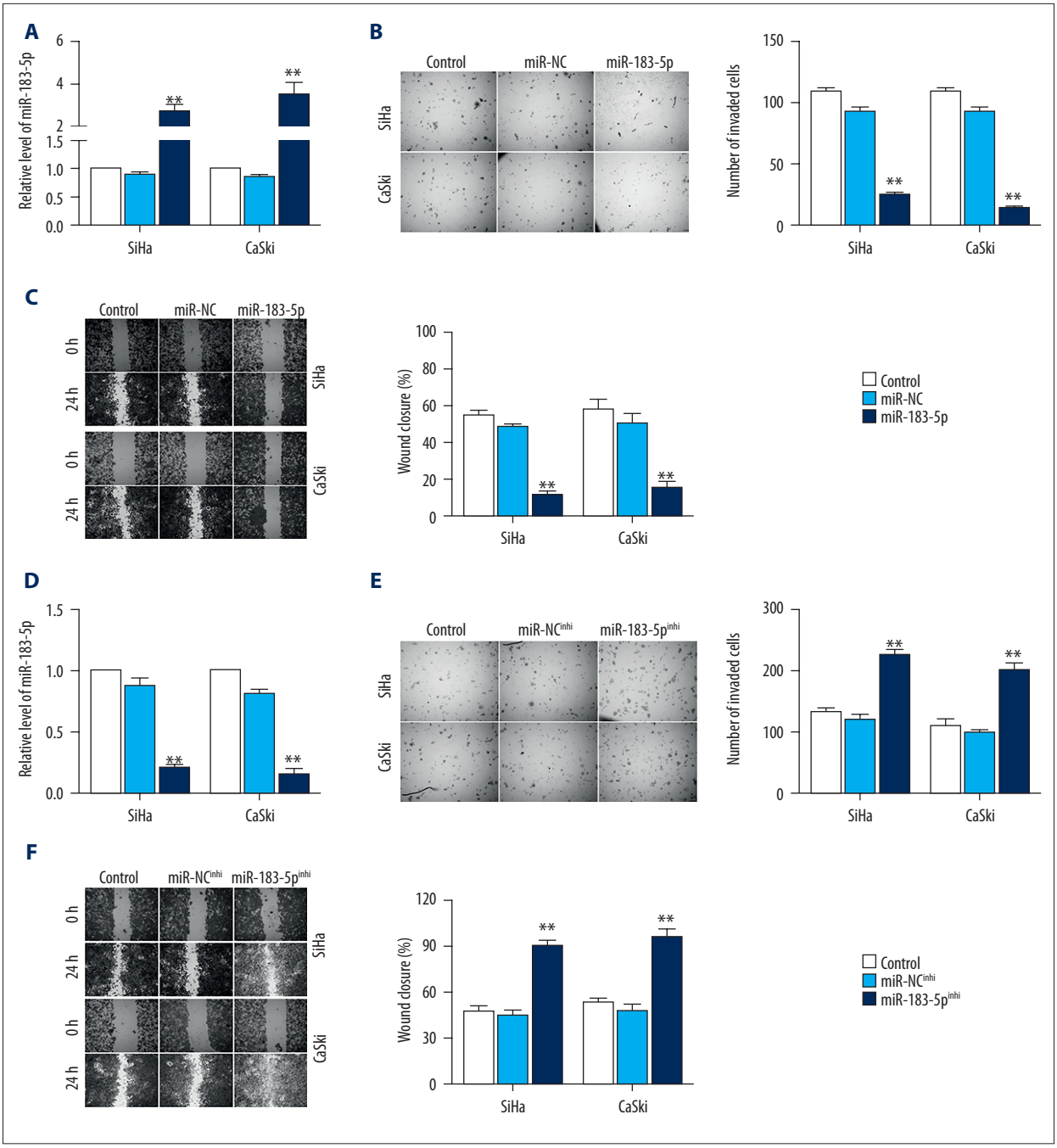

Figure 2. miR-183-5p inhibited the mobility of cervical carcinoma cells. (**A**) CaSki and SiHa cells were transfected with miR-183-5p, and its expression was determined using qRT-PCR method. (**B**) Transwell assays were conducted to detect the effect of miR-183-5p transfection on cells invasion. (**C**) CaSki and SiHa cells were both transfected with miR-183-5p and wound-healing assay was conducted. (**D**) Two cervical carcinoma cell lines were transfected with the miR-183-5p^{inhi}, and then its level was determined by qRT-PCR. (**E**) Transwell assays revealed that the reduction of miR-183-5p increased the invasive abilities of 2 cell lines. (**F**) Both cervical cancer cells were transfected with miR-183-5p^{inhi} and wound closure analysis was performed. The number of invaded cells was counted. ** P<0.01, compared to control.

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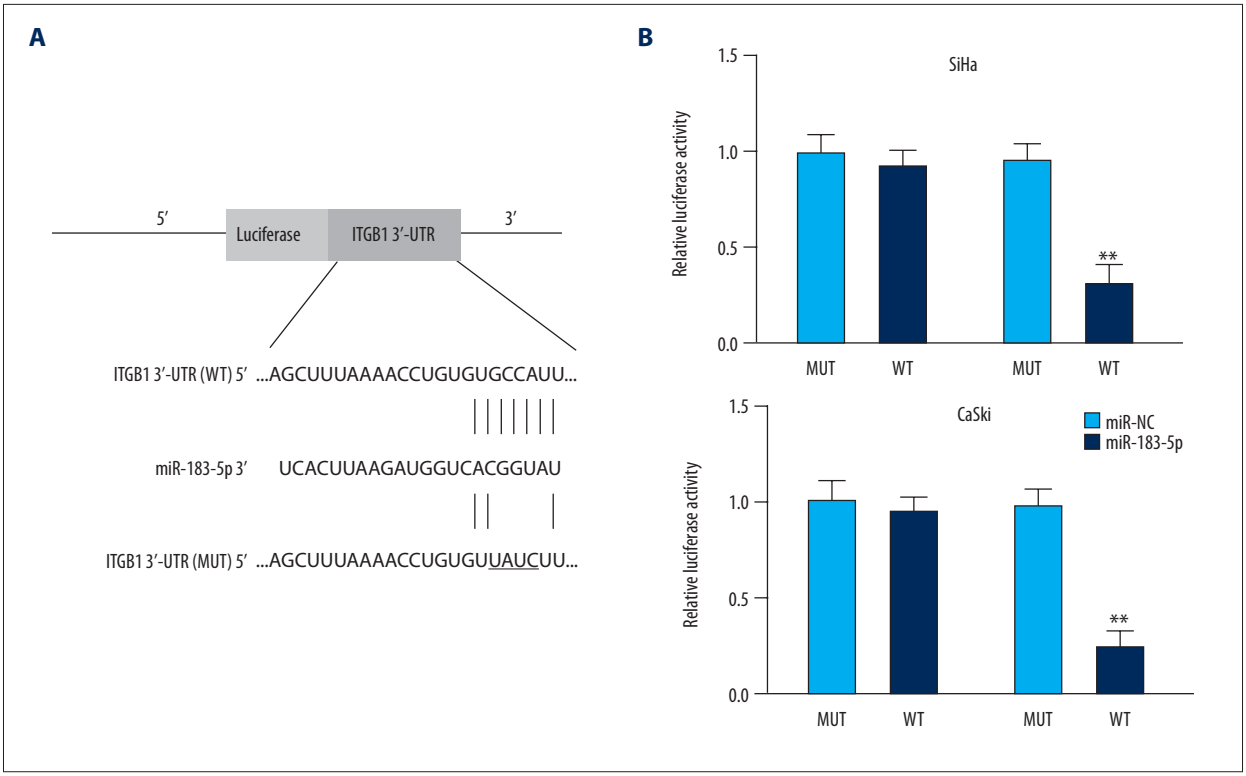

Figure 3. Confirmation of binding sites between ITGB1 and miR-183-5p. (**A**) Bioinformatics websites (microRNA.org, TargetScan, and miRTar) predicted that the 3′-UTR of ITGB1 contains the binding sites of miR-183-5p. (**B**) Dual luciferase reporter assay was conducted in SiHa and CaSki cell lines. Luciferase activities were decreased in cells co-transfected with miR-183-5p and WT-ITGB1-3′UTR, contrasted to cells transfected miR-NC. The average values of normalized 3′-UTR luciferase intensity were calculated from 3 independent experiments.** *P*<0.01, compared to miR-NC.

Immunoblotting analysis

Cell lysates were extracted using RIPA buffer containing protease inhibitors. We fractionated 25 μg lysates by 8% SDS-PAGE and transferred it to the PVDF membranes (Roche). The membranes were subjected to Western blotting assays, and the ECL detection system (Thermo Scientific) was used for signal assessment.

Statistical analysis

The data are presented as mean ±SD and *P*<0.05 was considered a statistically significant difference. Survival was evaluated using the Kaplan-Meier method, and the relationship between ITGB1 and miR-183-5p was evaluated using Pearson's correlation.

Results

miR-183-5p is under-expressed in cervical cancer

To identify the potential miRNAs that were aberrantly expressed in metastatic cervical cancer, we compared the expression pattern of miRNAs between cervical cancers with metastasis *vs.* cervical cancer without metastasis using the GEO data set GSE102969. The heat map generated using differential genes revealed that miR-183-5p was expressed at remarkably lower levels (fold change=–2.36 and P-value <0.05) in patients with metastasis (Figure 1A). To further assess the quantity of miR-183-5p in disparate cervical cancer cell lines – SiHa, C-33 A, C-4-I, CaSki, and normal cervical epithelial cells (ECT1/E6E7) – were selected for qRT-PCR assays. As displayed in Figure 1B, miR-183-5p was relatedly expressed at lower levels in all cancer cell lines as compared to that in the normal cervical epithelial cell line. We collected 43 pairs of cervical cancer samples and normal tissues to conduct future analysis. After qRT-PCR analysis, miR-183-5p was markedly lower in cancer samples in comparison to the matched control tissues (Figure 1C). In addition, based on the clinical progression, miR-183-5p was remarkably lower in patients with metastasis when compared to the patients without metastasis (Figure 1D).

MiR-183-5p regulates the migration and invasion abilities of cervical carcinoma cells *in vitro*

Previously, the association between alteration of miRNAs and migration and invasion of several cancer cell lines was

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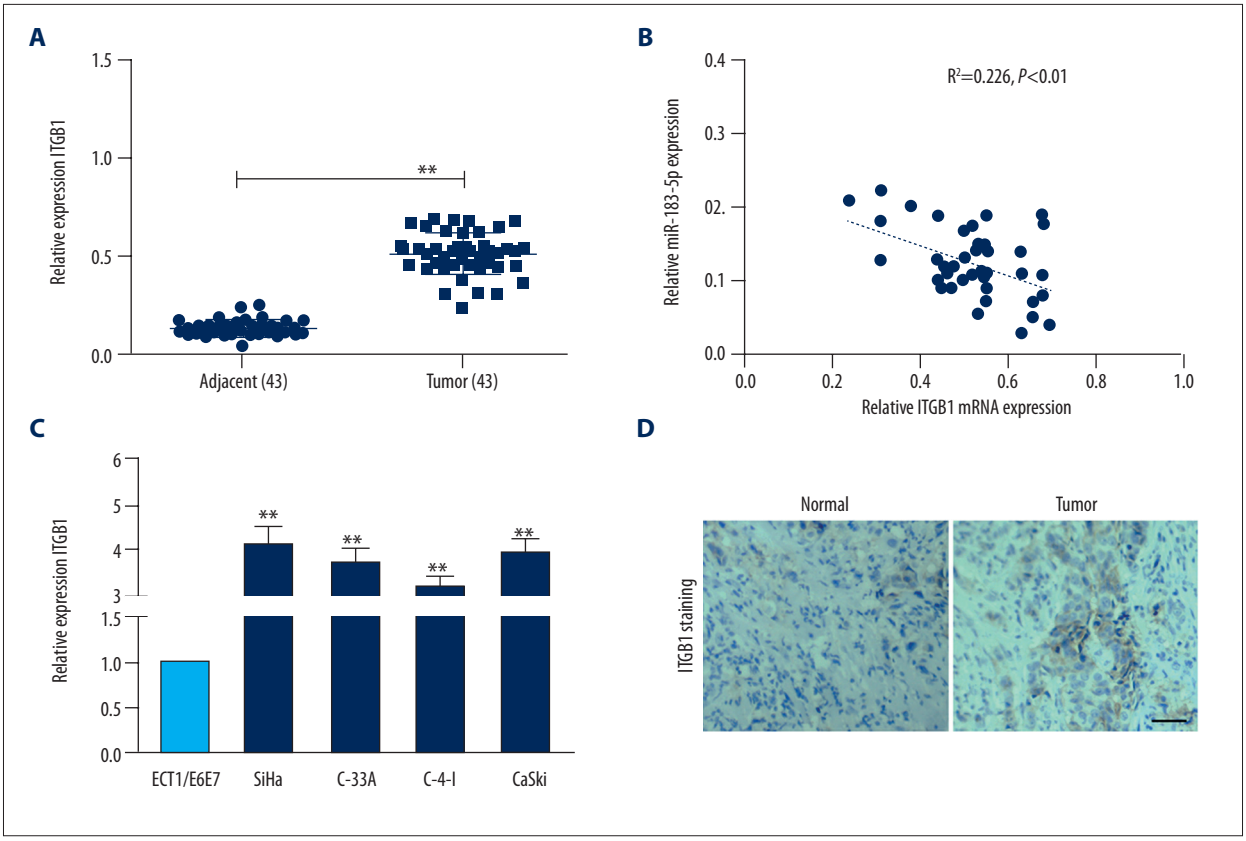

Figure 4. ITGB1 was over-expressed in cervical carcinoma and negatively associated with the miR-183-5p. (**A**) Expression of ITGB1 in 43 cases of cervical carcinoma specimens and the corresponding control tissues were analyzed using qRT-PCR. ** $P<0.01$, compared to adjacent tissues. (**B**) Linear correlation analysis between ITGB1 and miR-183-5p in cervical carcinoma using Spearman's correlation analysis (n=43, $R^2=0.226$; $P<0.01$). (**C**) The levels of ITGB1 in 4 cervical carcinoma cell lines were determined by qRT-PCR analysis. ** $P<0.01$, compared to ECT1/E6E7 cells. (**D**) Immunohistochemical staining of ITGB1 in normal and cervical cancer tissues.

demonstrated, and it was hypothesized that the down-regulation of miR-183-5p was related into invasion ability and mobility in cervical cancer cells. In order to test this hypothesis, CaSki and SiHa cells were transfected with miR-183-5p to generate miR-183-5p over-expression cells. The level of miR-183-5p following 2 cell lines transfection is shown in Figure 2A. Transwell invasion and wound-healing analyses were then conducted. The results suggest that the migration (Figure 2B) and invasion (Figure 2C) capacity of the 2 cell lines that were transfected with miR-183-5p were remarkably lower than in the parent cells. By contrast, CaSki and SiHa cells transfected with miR-183-5p inhibitor (miR-183-5p^{inhi}) exhibited less aggressiveness (Figure 2D, 2E). These findings indicate that miR-183-5p affects migratory and invasive abilities of cervical cancer cells.

ITGB1 is identified as the direct target of miR-183-5p

miRNAs control the expression of target genes and regulate cancer cellular processes, including growth and metastasis. Therefore, bioinformatics websites, including microRNA.org, TargetScan, and miRTar were selected to predict latent targets of miR-183-5p. Bioinformatics analysis pointed to a putative binding site of miR-183-5p in the 3'-UTR of ITGB1 (Figure 3A). To confirm whether ITGB1 was the direct target of miR-183-5p, the wild-type (WT) (WT-ITGB1-3'UTR) and mutant (MUT) ITGB1 3'-UTR (MUT-ITGB1-3'UTR) were fused to the pHY-LV-Report 3.1 vector downstream of the luciferase reporter gene (Figure 3A). Then, and SiHa and CaSki cells were co-transfected in combination with pHY-LV-Report 3.1 vector and either miR-NC or miR-183-5p. As presented in Figure 3B, the luciferase activity was obviously inhibited in the cells co-transfected with miR-183-5p and WT-ITGB1-3'-UTR compared with the miR-NC group.

miR-183-5p expression is negatively correlated with ITGB1 levels

To determine the association between ITGB1and miR-183-5p, the expression of ITGB1 in 43 cases of cervical cancer tissues was assessed. The levels of ITGB1 were increased in cervical

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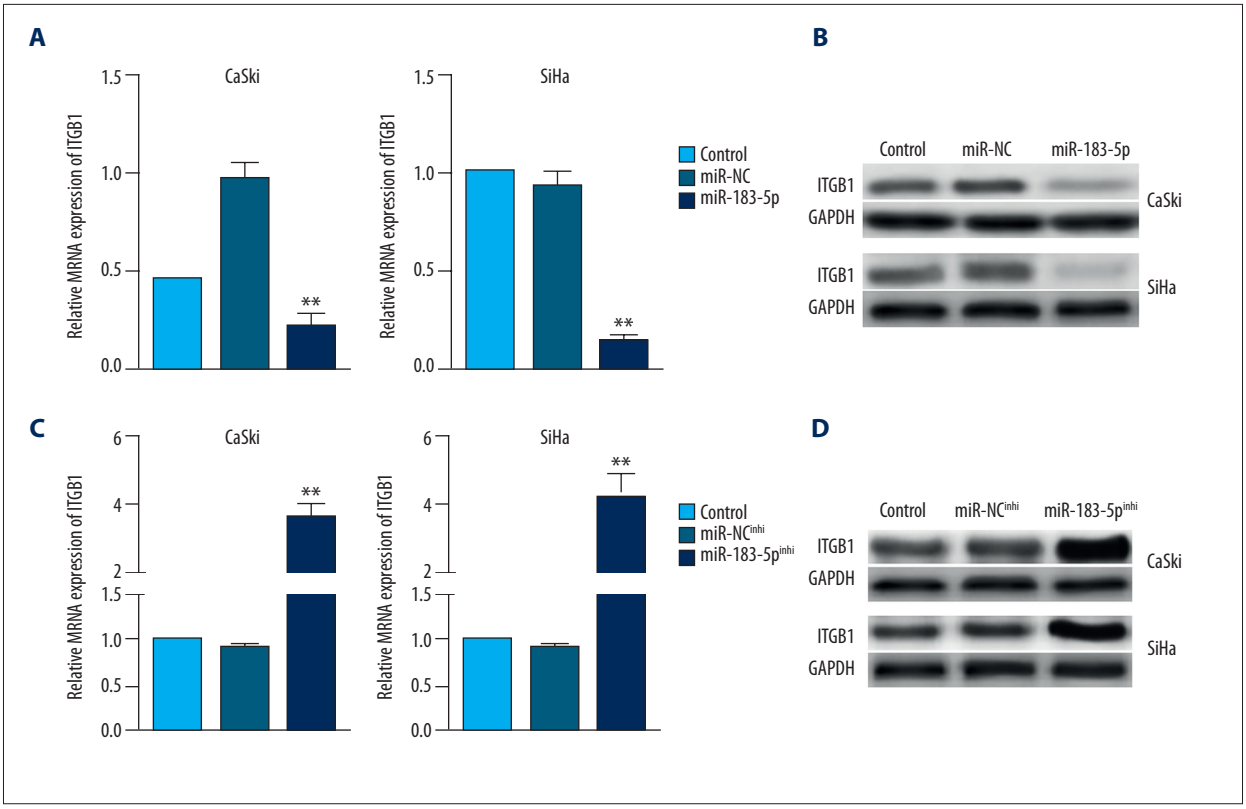

Figure 5. miR-183-5p regulated the expression of ITGB1. (**A**) Compared with the level of ITGB1 in miR-NC-transfected or miR-183-5p-transfected cells. Transfection of miR-183-5p in both CaSki and SiHa cell lines significantly inhibited the mRNA level of ITGB1. (**B**) The expression of ITGB1 in cells after transfection of miR-183-5p was inhibited, as shown in Western blotting results. (**C**) CaSki and SiHa cells were transfected miR-183-5p^{inhi} and the mRNA level of ITGB1 was determined by qRT-PCR assays. (**D**) miR-183-5p^{inhi} was transfected into 2 cell lines, and protein level of ITGB1 was determined by immunoblotting. ** $P<0.01$, compared to control.

cancer in comparison to that in the matched normal samples (Figure 4A). Subsequently, linear correlation testing was carried out to analyze the relationship between ITGB1 and miR-183-5p. As presented in Figure 4B, the level of ITGB1 protein was negatively correlated with miR-183-5p in cervical carcinoma samples. In addition, to verify that miR-183-5p regulated the level of ITGB1 in uterine cervix cancer cells, qRT-PCR assays were performed to assess the level of ITGB1 in diverse cervical cancer cell lines. In comparison to ECT1/E6E7 cells, the quantity of ITGB1 was remarkably increased in the cervical cancer cells (Figure 4C). We next examined ITGB1 protein levels by immunohistochemistry in human cervical cancer tissues and found ITGB1 was expressed at higher levels in the cancer tissues compared to corresponding normal tissues (Figure 4D). Thus, up-regulation of ITGB1 was correlated with miR-183-5p in human cervical cancer.

miR-183-5p regulates ITGB1 in cervical carcinoma cell lines

To verify the critical roles of miR-183-5p in the expression of ITGB1, qRT-PCR and immunoblotting assays were conducted to measure its level in SiHa and CaSki cells transfected with miR-183-5p or miR-183-5p^{inhi}. The results indicated that up-regulation of miR-183-5p boosted the expression of ITGB1 in SiHa and CaSki cells (Figure 5A, 5B). By contrast, remarkable suppression of ITGB1 was noticed in the 2 cervical carcinoma cell lines transfected with miR-183-5p^{inhi} compared to miR-NC-treated cells (Figure 5C, 5D).

MiR-183-5p inhibits aggressiveness of cervical cancer cells via targeting ITGB1

Considering the aforementioned data, whether ITGB1 is the target of miR-183-5p, which affects cellular mobility and invasion, was further investigated. CaSki and SiHa cells were simultaneously co-transfected in combination pMSCV-ITGB1 with miR-183-5p, and ITGB1 was measured by qRT-PCR (Figure 6A). Then, Transwell and wound-healing assays were conducted. As shown in Figure 6B, 6C, knock-down of ITGB1 significantly neutralized the mobility and invasiveness of CaSki and SiHa cells. Moreover, these cells were co-transfected with shITGB1 and miR-183-5^{inhi}, and ITGB1 was measured using qRT-PCR

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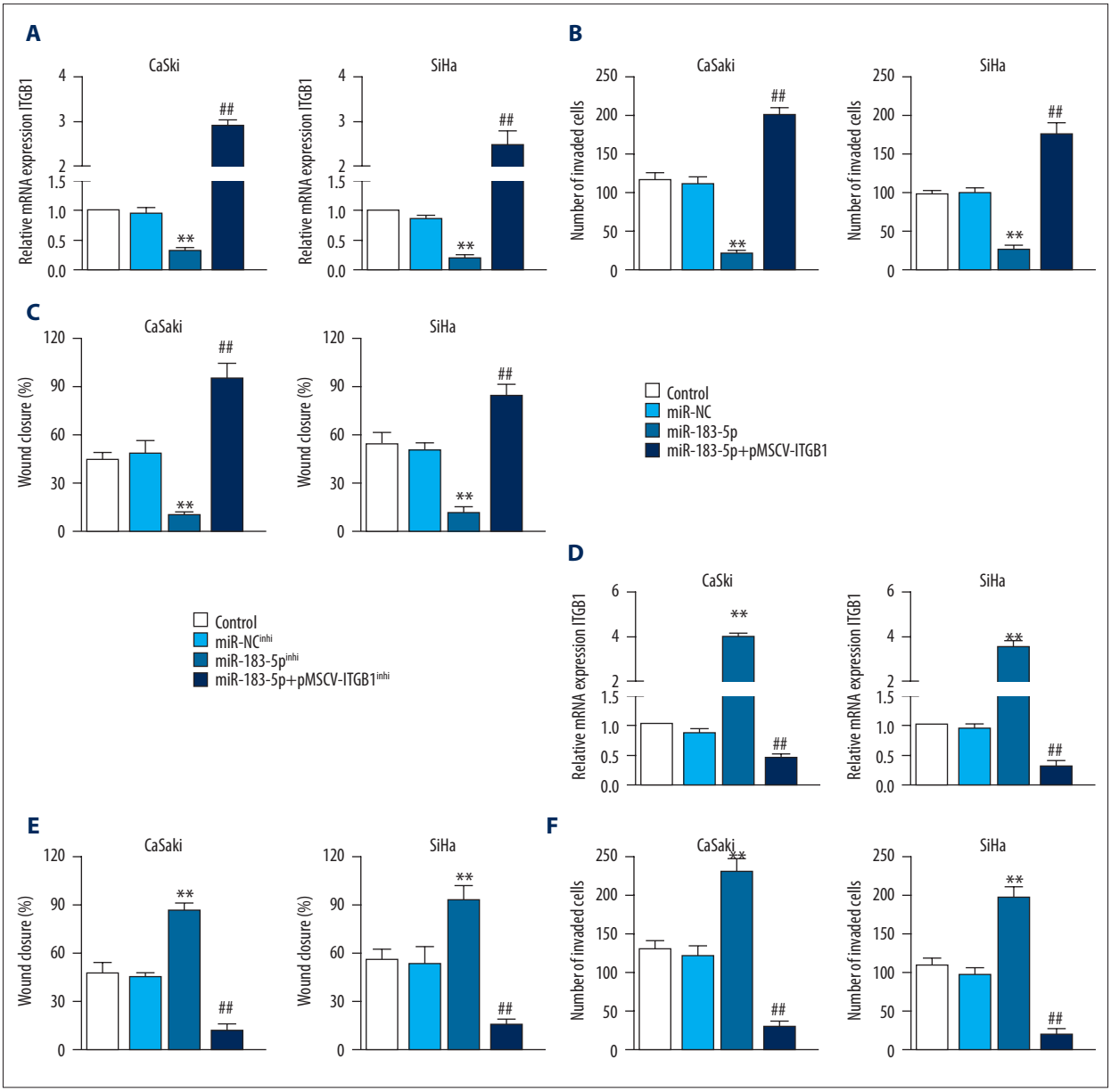

Figure 6. ITGB1 was involved in the miR-183-5p-induced inhibition of cervical cancer cells mobility and invasion. (**A**) ITGB1 mRNA levels in CaSki and SiHa cells were analyzed by qRT-PCR method following transfection with pMSCV-ITGB1 and miR-183-5p. (**B**) Migration assays analysis of CaSki and SiHa cells transfected with different plasmids. (**C**) Transwell invasion analysis of cells transfection with pMSCV-ITGB1 and miR-183-5p. (**D**) ITGB1 mRNA levels in CaSki and SiHa cells were analyzed by qRT-PCR method following transfection with shITGB1 and miR-183-5p^{inhi}. (**E**) Wound-healing analysis of CaSki and SiHa cells transfected with different plasmids. (**F**) Transwell invasion analysis of cells transfected with shITGB1 and miR-183-5p^{inhi}. ** P<0.01, compared to control. ** P<0.01, compared to miR-183-3p or miR-183-5p^{inhi}.

assays (Figure 6D). When ITGB1 expression was restored, it was able to rescue the migration and invasion that was inhibited by miR-183-5p transfected in SiHa and CaSki cells (Figure 6E, 6F). Together, these findings confirm that miR-183-5p affects the aggressiveness of cervical cancer cells via regulating ITGB1.

Discussion

In the present study, we found that miR-183-5p acts as an anti-oncogene in cervical carcinoma and that low expression of miR-183-5p is a risk factor for metastasis in patients with cervical cancer. In cervical cancer cells, high levels of miR-183-5p suppressed cellular invasiveness and migration. Furthermore,

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ITGB1 was demonstrated to be a potential novel target gene of miR-183-5p, and importantly, ITGB1 was negatively associated with miR-183-5p in cervical cancer tissues.

It has been hypothesized that miRNAs function as either tumor promoters or tumor suppressors, and thus perform vital roles in malignant tumor development and progression [21]. miR-183 acts as a tumor suppressor in osteosarcoma cells by inhibiting the LRP6-Wnt/β-catenin signaling axis [11]. miR-183 is down-regulated in nasopharyngeal carcinoma spheroids and acts as a tumor suppressor. Additional, pheochromocytomas patients with low levels of miR-183 exhibit a better survival rate and miR-183 regulates cellular apoptosis and growth in tongue squamous cell carcinoma cells [22]. From these data, it may be inferred that miR-183-5p is a potential cancer suppressor gene. However, the relationship between miR-183-5p and cervical cancer has not been thoroughly investigated. In the present study, we observed that there was a low level of miR-183-5p in tumor tissues obtained from patients with cervical cancer as compared to matched normal tissues. In addition, miR-183-5p was negatively associated with metastasis.

In vitro experiments demonstrated that up-regulation of miR-183-5p suppressed the mobility and aggrieves in cervical cancer cells. As part of the present study on how alternation of miR-183-5p affected cells aggressiveness, it was confirmed that ITGB1 is the downstream target of miR-183-5p. Previous studies proved that miRNAs negatively control protein expression through binding to the 3'-UTR of target genes [23]. In our study, luciferase reporter analysis suggested that miR-183-5p directly interacts with the 3'-UTR of the ITGB1 gene.

Conclusions

Over-expression of miR-183-5p led to the inhibition of ITGB1, whereas miR-183-5p inhibitor increased the ITGB1 level. Importantly, restoration of ITGB1 counteracted the inhibition of invasion and migration that were inhibited by miR-183-5p in cervical cancer cells. Based on these findings, we hypothesize that miR-183-5p and ITGB1 have pivotal roles in cervical cancer. In conclusion, we identified miR-183-5p as a promising tumor suppressor in cervical carcinoma; therefore, further investigations of the miR-183-5p/ITGB1 axis may provide a foundation for developing novel potential therapeutic strategies for cervical cancer.

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