MicroRNA-302 inhibits cell migration and invasion in cervical cancer by targeting DCUN1D1

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Abstract. MicroRNA serve crucial roles in a variety of human cancer types. The miR-302-367 cluster has been reported to suppress the proliferation of cervical carcinoma cells through the novel target AKT1; however, the molecular mechanism of miR-302 in cervical cancer metastasis remains unclear. The present study aimed to investigate the clinical significance of miR-302-3p expression in cervical cancer, and to examine the regulatory mechanism of miR-302-3p in the malignant phenotypes of cervical cancer cells. The present data indicated that miR-302-3p was significantly downregulated in cervical cancer tissues compared with the level in adjacent non-tumor tissues, and low expression of miR-302-3p was significantly associated with node metastasis, advanced clinical stage, and poor prognosis in patients with cervical cancer. Restoration of miR-302-3p expression caused a significant reduction in cervical cancer cell migration and invasion. Defective in cullin neddylation 1 domain containing 1 (DCUN1D1) was identified as a novel target gene of miR-302-3p, and miR-302-3p negatively regulated the mRNA and protein expression of DCUN1D1 in cervical cancer HeLa cells. Additionally, overexpression of DCUN1D1 rescued the effects of miR-302-3p on the migration and invasion of cervical cancer cells. Furthermore, DCUN1D1 was upregulated in cervical cancer tissues compared with the levels in adjacent tissues, and its high expression was associated with node metastasis, advanced clinical stage, and shorter survival time in patients with cervical cancer. Notably, a negative correlation between miR-302-3p and DCUN1D1 expression in cervical cancer tissues was observed. Taken together, the present study suggests that miR-302-3p serves a suppressive role in cervical cancer metastasis, partly at least, via directly targeting DCUN1D1. Therefore, miR-302-3p/DCUN1D1 may be a potential therapeutic target for cervical cancer treatment.

Introduction

Cervical cancer is one of the most common cancer types in women worldwide, and the majority of cases occur in developing countries, such as China (1). The poor prognosis of patients with advanced cervical cancer is largely attributed to intrinsic molecular changes (2,3). During the growth and metastasis of cervical cancer, various oncogenes and tumor suppressors have been demonstrated to serve key roles, and some of these are suggested to become potential therapeutic targets for cancer treatment (4-6).

MicroRNA (miRNA) are a class of small non-coding RNA (7,8). They directly bind to the 3’ untranslated region (UTR) of their target mRNA, and cause translation repression or mRNA degradation; thus, they are important regulators of gene expression (9,10). Various miRNA have been demonstrated to be involved in a variety of cellular biological processes, including cell proliferation, differentiation, survival, migration and invasion (8,11-13). Additionally, a large number of miRNA, including miR-181 (14), -186 (15), -126 (16) and -424 (17), have been reported to serve promoting or suppressive roles in tumor growth and metastasis of various human malignancies, such as cervical cancer.

Among these miRNA, miR-302-3p is a member of the miR-302-3p/367 cluster and acts as a tumor suppressor in several cancer types (18,19). For instance, miR-302-3p may inhibit the tumorigenicity of endometrial cancer cells by suppressing cyclin D1 and cyclin-dependent kinase 1 (19). In addition, forced expression of miR-302-3p suppresses tumorigenic gene expression patterns in glioblastoma cells and abolishes transformation-related phenotypes (18). A study by Cai et al (20) reported that the miR-302-367 cluster suppresses the proliferation of cervical carcinoma cells through the novel target AKT1. However, the regulatory mechanism of miR-302-3p underlying cervical cancer metastasis remains largely unknown.

Defective in cullin neddylation 1 domain containing 1 (DCUN1D1) serves as an accessory E3 in neddylation by binding to cullin and Ubc12 to allow efficient transfer of Nedd8, and promotes nuclear translocation and assembly of the neddylation E3 complex (21). Recently, miR-218 was reported to inhibit cervical cancer cell migration and invasion by targeting DCUN1D1 (22). However, whether DCUN1D1 is also regulated by other miRNA in cervical cancer remains unclear.
Therefore, the present study aimed to investigate the clinical significance of miR-302-3p expression in cervical cancer. The regulatory mechanism of miR-302-3p in the malignant phenotypes of cervical cancer cells was also examined.

Materials and methods

Clinical tissue samples. Cervical cancer tissues and matched adjacent normal tissues were collected from 68 patients with cervical cancer at the First Affiliated Hospital of Xinxiang Medical University (Weihui, China) between September 2010 and May 2012. The age range of the patients was 35-68 years, with a mean age of 61.6 years. The clinicopathological characteristics of the patients are summarized in Table I. The patients did not receive radiation therapy or chemotherapy prior to surgery. The present study was approved by the Ethics Committee of the First Affiliated Hospital of Xinxiang Medical University, and written informed consent was obtained from all patients. All tissues were placed in liquid nitrogen immediately after surgical resection and stored at -80°C before use.

Cell culture. The human cervical cancer HeLa cell line was purchased from the Cell Bank of Chinese Academy of Sciences (Shanghai, China). Cells were cultured in Dulbecco’s modified Eagle’s medium (DMEM; Thermo Fisher Scientific, Inc., Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS; Thermo Fisher Scientific, Inc.) at 37°C in a humidified atmosphere containing 5% CO₂.

Cell transfection. For miR-302-3p and DCUN1D1 function analysis, HeLa cells were transfected with 100 nM negative control (NC) miR (cat. no. Cmri0001; Guangzhou Fulengen Co., Ltd., Guangzhou, China), 100 µM miR-302-3p mimic (S′-uuagucucuccauguugugga-3′; Guangzhou Fulengen Co., Ltd.), or co-transfected with 100 µM miR-302-3p mimic and 100 µM of pcDNA3.1-DCUN1D1 open reading frame (ORF) plasmid (Yearbio, Changsha, China), or co-transfected with 100 nM miR-302-3p mimic and 100 ng blank pcDNA3.1 vector. Transfection was performed using Lipofectamine 2000 (Thermo Fisher Scientific, Inc.), according to the manufacturer’s protocol. Following transfection for 48 h, the expression of miR-302-3p or DCUN1D1 was evaluated.

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Total RNA was extracted from tissues and cells using TRIzol reagent (Thermo Fisher Scientific, Inc.). For miRNA expression detection, an Mir-X™ miRNA qRT-PCR SYBR® kit (Clontech Laboratories, Inc., Mountainview, CA, USA) was utilized to perform RT-qPCR, according to the manufacturer’s protocol. U6 was used as an internal reference. For mRNA expression detection, a OneStep RT-PCR kit (Qiagen, Inc., Valencia, CA, USA) was used to perform RT-qPCR, according to the manufacturer’s recommendations. GAPDH was used as an internal reference. The primer sequences used were as follows: miR-302-3p forward, 5′-GAGTCCTACTTGGTTA-3′ and reverse, 5′-GAACAT GCCTGGATATCAGACTCTC-3′; U6 forward, 5′-GGCTCG GACGCACATATA-3′ and reverse, 5′-AACGCGTCACGA ATTTGCCT-3′; DCUN1D1 forward, 5′-TGCTCATTGGGAA CTTAGTGC-3′ and reverse, 5′-CGCAATCATCGTAC TGAAGTCT-3′; and GAPDH forward, 5′-ACAACCTTTGGTA TCCTGGAAGG-3′ and reverse, 5′-GCCATACGCGCACACAG TTC-3′. The reaction conditions were as follows: 95°C for 3 min, followed by 40 cycles of 95°C for 30 sec and 60°C for 30 sec. The relative expression was analyzed using the 2⁻ΔΔCq method (23).

Cell migration analysis. HeLa cells were cultured to full confluence in a 6-well plate (5x10⁵ cells/well). The cell monolayer was scraped with a 200-µl pipette tip, generating a wound ~1 mm wide. Following three washes with DMEM, cells were incubated in DMEM supplemented 10% FBS at 37°C. After 48 h, cells were photographed under a light microscope (Olympus Corporation, Tokyo, Japan) at magnification x40.

Cell invasion analysis. A Matrigel pre-coated Transwell chamber (BD Biosciences, Franklin Lakes, NJ, USA) was used to study cell invasion. A HeLa cell suspension (3x10⁵ cells/ml) was prepared in DMEM, which was added into the upper chamber. Following this, 300 µl DMEM supplemented with 10% FBS was added into the lower chamber. After incubation at 37°C for 24 h, the cells not invading through the membrane in the filter were wiped out carefully with a cotton-tipped swab, while the cells invading through the membrane were stained with 0.1% crystal violet (Beyotime Institute of Biotechnology, Haimen, China) for 10 min at room temperature. The invading cells were counted under a light microscope (Olympus Corporation) at magnification x400.

Bioinformatics prediction and dual-luciferase reporter gene assay. TargetScan online software was used to predict the potential target genes of miR-302-3p (24). The wild type (WT) of DCUN1D1 3′UTR containing the binding sites of miR-302-3p or the mutant (MT) type of DCUN1D1 3′UTR lacking the binding sites of miR-302-3p was amplified, which was then subcloned into the downstream of the Renilla luciferase gene in the psiCHECK-2 vector (Promega Corporation, Madison, WI, USA). HeLa cells were co-transfected with WT or MT DCUN1D1 3′UTR luciferase reporter gene plasmid, and miR-302-3p mimic or NC, using Lipofectamine 2000 according to the manufacturer’s protocol. After 48 h, the cells were assayed for luciferase activity using a Dual-Luciferase Reporter Assay System (Promega Corporation). The firefly luciferase activities were normalized to Renilla luciferase activity.

Western blot analysis. Tissues and cells were lysed in cold radioimmunoprecipitation assay buffer (Beyotime Institute of Biotechnology), and the protein concentration was determined using a BCA Protein Assay kit (Pierce; Thermo Fisher Scientific, Inc.), according to the manufacturer’s protocol. A total of 80 µg protein was separated using 12% SDS-PAGE and transferred to a polyvinylidene fluoride (PVDF) membrane (Thermo Fisher Scientific, Inc.). The membrane was subsequently blocked in 5% non-fat dried milk in PBS (Thermo Fisher Scientific, Inc.) at room temperature for 3 h. Following three washes with PBS, the membrane was incubated with rabbit anti-human DCUN1D1 antibody (1:50; ab181233; Abcam, Cambridge, MA, USA) or rabbit anti-human GAPDH antibody (1:50; ab9485; Abcam) for 3 h at room temperature.
Following three washes with PBS, the membrane was incubated with horseradish peroxidase conjugated goat anti-rabbit secondary antibody (1:5,000; ab6721; Abcam) for 40 min at room temperature. Following three washes with PBS, the immune complex on the PVDF membrane was detected using an Enhanced Chemiluminescence Western Blotting kit (Pierce; Thermo Fisher Scientific, Inc.). The protein expression was determined using Image-Pro Plus software 6.0 (Media Cybernetics, Inc., Rockville, MD, USA), and GAPDH was used as an internal control.

Statistical analysis. Data were presented as the mean ± standard deviation. SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA) was used to perform statistical analysis. Differences were analyzed using a Student’s t-test for two-group comparison, or one-way analysis of variance for comparison of more than two groups with Turkey’s post hoc test. The association between the gene expression and clinicopathological characteristics was examined using the χ² test. The Kaplan-Meier method was used to conduct survival analysis. Pearson correlation analysis was performed to examine the correlation between the miR-302-3p and DCUN1D1 expression. P<0.05 was considered to indicate a statistically significant difference.

Results

miR-302-3p is downregulated in cervical cancer. In the present study, RT-qPCR data demonstrated that the miR-302-3p expression level was significantly reduced in cervical cancer tissues compared with that in adjacent non-tumor tissues (Fig. 1A). The patients with cervical cancer were subsequently divided into a high miR-302-3p group and low miR-302-3p group based on the mean value of miR-302-3p expression. It was demonstrated that low miR-302-3p expression was significantly associated with advanced clinical stage and node metastasis (Table I), suggesting that downregulation of miR-302-3p may contribute to the malignant progression of cervical cancer. Following this, the association between miR-302-3p expression and the prognosis of patients with cervical cancer was studied. Data of Kaplan-Meier analysis indicated that patients in the low miR-302-3p group had a significantly shorter survival time compared with that of the patients with high miR-302-3p expression (Fig. 1B).

miR-302-3p inhibits cell migration and invasion in cervical cancer. As low expression of miR-302-3p was associated with node metastasis in cervical cancer, the role of miR-302-3p in the regulation of cervical cancer cell migration and invasion was investigated. HeLa cells were transfected with miR-302-3p mimic or scramble miR mimic. RT-qPCR data indicated that the miR-302-3p expression levels were significantly increased in the miR-302-3p group compared with the level in the control group (Fig. 2A). However, transfection with scramble miR mimic did not significantly affect the expression of miR-302-3p in HeLa cells compared with the level in the control group (Fig. 2A). Wound healing and Transwell assays were subsequently conducted to evaluate cell migration and invasion. The present data indicated that overexpression of miR-302-3p significantly inhibited the migration and invasion of HeLa cells compared with that observed in the NC group (Fig. 2B and C). Therefore, miR-302-3p may have suppressive effects on the metastasis of cervical cancer.

<table>
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Table I. Association between miR-302-3p expression and clinicopathological characteristics of patients with cervical cancer.
miR-302-3p directly targets DCUN1D1 in cervical cancer cells. The potential target genes of miR-302-3p were explored, and TargetScan online software indicated that DCUN1D1 was a putative target gene of miR-302-3p (Fig. 3A). In addition, their target relationship was evolutionally conserved (data not shown). Luciferase reporter plasmids containing the WT and MT type of DCUN1D1 3’UTR were generated (Fig. 3B). Luciferase reporter gene assay results indicated that the luciferase activity was significantly decreased in the presence of miR-302-3p in HeLa cells transfected with WT DCUN1D1 3’UTR luciferase reporter plasmid compared with the level in the control group. However, there was no significant effect on luciferase activity when transfection with the MT type of DCUN1D1 3’UTR luciferase reporter plasmid was...
Figure 3. miR-302-3p directly targets DCUN1D1 in cervical cancer cells. (A) DCUN1D1 is a putative target gene of miR-302-3p. (B) The WT or MT types of DCUN1D1 3'UTR luciferase reporter plasmids were generated. (C) The luciferase activity was significantly decreased in the presence of miR-302-3p in HeLa cells transfected with WT DCUN1D1 3'UTR luciferase reporter plasmid, but not reduced when transfected with the MT type DCUN1D1 3'UTR luciferase reporter plasmid. **P<0.01 vs. WT control. WT, wild type; MT, mutant; NC, negative control; UTR, untranslated region; DCUN1D1, defective in cullin neddylation 1 domain containing 1.

Figure 4. DCUN1D1 expression is negatively regulated by miR-302-3p in HeLa cells. The (A) mRNA and (B) protein expression levels of DCUN1D1 were examined in HeLa cells transfected with miR-302-3p mimic or scramble miR mimic (NC), respectively. Then, HeLa cells were transfected with NC inhibitor or miR-302-3p inhibitor. (C) After transfection, quantitative real-time PCR was used to evaluate the miR-302-3p expression level. The (D) mRNA and (E) protein expression levels of DCUN1D1 were also evaluated. *P<0.01 vs. NC; **P<0.01 vs. miR-302-3p inhibitor. DCUN1D1, defective in cullin neddylation 1 domain containing 1; NC, negative control.
conducted (Fig. 3C). These findings indicate that DCUN1D1 is a target gene of miR-302-3p in HeLa cells.

**DCUN1D1 expression is negatively regulated by miR-302-3p in HeLa cells.** As miRNA generally negatively regulate the expression of their target genes, the effects of miR-302-3p on DCUN1D1 expression in HeLa cells were explored. As demonstrated in Fig. 4A and B, the mRNA and protein expression levels of DCUN1D1 in HeLa cells were significantly reduced after overexpression of miR-302-3p compared with the levels in the NC group. HeLa cells were transfected with miR-302-3p inhibitor or NC inhibitor, respectively. Following transfection, the miR-302-3p expression level was significantly reduced in the miR-302-3p inhibitor group compared with the level in the control group (Fig. 4C). Transfection with NC inhibitor demonstrated no significant effect on the miR-302-3p expression levels compared with that in the control group (Fig. 4C). mRNA and protein expression levels of DCUN1D1 were revealed to be significantly increased following inhibition of miR-302-3p compared with the levels in the NC inhibitor group (Fig. 4D and E). These data indicate that miR-302-3p could negatively regulate the expression of DCUN1D1 in HeLa cells.

**DCUN1D1 reverses the suppressive effects of miR-302-3p on cervical cancer cell migration and invasion.** Based on the above findings, it was speculated that DCUN1D1 may be involved in the miR-302-3p-mediated migration and invasion of HeLa cells. To clarify this speculation, the miR-302-3p-overexpressing HeLa cells were transfected with pcDNA3.1-DCUN1D1 ORF plasmid or blank vector. As demonstrated in Fig. 5A and B, following transfection, the mRNA and protein expression levels of DCUN1D1 in the miR-302-3p + DCUN1D1 group were significantly higher compared with those in the miR-302-3p + blank group. Furthermore, following transfection, cell migration and invasion were significantly increased in the miR-302-3p + DCUN1D1 group compared with the levels in the miR-302-3p + blank group (Fig. 5C and D). Thus, DCUN1D1 rescued the miR-302-3p-mediated inhibition of HeLa cell migration and invasion.

**DCUN1D1 is upregulated in cervical cancer.** Finally, the DCUN1D1 expression level in cervical cancer tissues was determined. RT-qPCR and western blotting data indicated that the mRNA and protein expression levels of DCUN1D1 were significantly and markedly increased in cervical cancer tissues compared with the levels in adjacent non-tumor tissues (Fig. 6A and B, respectively). In addition, Pearson correlation analysis data demonstrated an inverse correlation between the miR-302-3p and DCUN1D1 expression levels in cervical cancer tissues (Fig. 6C), suggesting that the increased expression of miR-302-3p is associated with the downregulation of DCUN1D1 in cervical cancer.
DCUN1D1 expression in cervical cancer may be due to the downregulation of miR-302-3p.

The patients with cervical cancer were divided into a high DCUN1D1 group and low DCUN1D1 group. As indicated in Table II, high expression of DCUN1D1 was significantly associated with advanced clinical stage and node metastasis in cervical cancer. In addition, the patients with high expression of DCUN1D1 demonstrated a shorter survival time compared with those with low expression of DCUN1D1. Therefore, upregulation of DCUN1D1 may contribute to the malignant progression and poor prognosis of patients with cervical cancer.

**Discussion**

The molecular mechanism of miR-302 in cervical cancer metastasis has not previously been studied. The present study demonstrated that miR-302-3p was significantly downregulated in cervical cancer tissues compared with the levels in adjacent non-tumor tissues, and low expression of miR-302-3p was significantly associated with node metastasis, advanced clinical stage, and poor prognosis in patients with cervical cancer. Restoration of miR-302-3p expression caused a significant reduction in cervical cancer cell migration and invasion. DCUN1D1 was identified as a novel target gene of miR-302-3p, and miR-302-3p negatively regulated the mRNA and protein expression levels of DCUN1D1 in HeLa cells. In addition, overexpression of DCUN1D1 rescued the effects of miR-302-3p on the migration and invasion of cervical cancer cells. Furthermore, DCUN1D1 was upregulated in cervical cancer tissues compared with the levels in adjacent tissues, and its high expression was associated with node metastasis, advanced clinical stage, and shorter survival time of patients with cervical cancer. Notably, a negative correlation between miR-302-3p and DCUN1D1 expression was observed in cervical cancer tissues.

miR-302-3p is a member of the miR-302-3p-367 cluster, which has been demonstrated to be specifically expressed in human embryonic stem cells (25). Additionally, the miR-302-3p-367 cluster has potential to convert somatic cells into induced pluripotent stem cells (26). A study by Cai et al (20) investigated the role of the miR-302-3p-367 cluster in cervical carcinoma. The study indicated that ectopic expression of the miR-302-3p-367 cluster inhibited cervical cancer.
cell proliferation and tumor formation by inducing a cell cycle arrest at the G1 stage (20). It was further demonstrated that the miR-302-3p-367 cluster suppressed the expression of cyclin D1 and AKT1, while promoted the expression of p27 (Kip1) and p21 (Cip1), which contributed to the inhibition of cervical cancer cell proliferation (20). These findings suggest that miR-302-3p serves a suppressive role in the growth of cervical cancer. However, the clinical significance of miR-302-3p expression, as well as the effects of miR-302-3p on cervical cancer metastasis, have not previously been studied. The present study revealed that miR-302-3p was significantly downregulated in cervical cancer tissues compared with the levels in adjacent non-tumor tissues. In addition, low expression of miR-302-3p was associated with node metastasis and advanced clinical stage. These findings suggest that miR-302-3p may also serve inhibitory roles in the metastasis of cervical cancer. Therefore, cervical cancer cells were transfected with miR-302-3p mimic and it was demonstrated that overexpression of miR-302-3p significantly downregulated the migration and invasion of cervical cancer cells.

As miRNA function through regulating gene expression, potential targets of miR-302-3p in cervical cancer cells were explored by performing bioinformatics analysis. The data of TargetScan online software indicated that DCUN1D1 was a putative target gene of miR-302-3p, which was further confirmed by luciferase reporter gene analysis. Previous studies have demonstrated that DCUN1D1 is upregulated in squamous cell carcinoma, and promotes non-small cell lung cancer progression and brain metastasis (27,28). Recently, Jiang et al (22) reported that miR-218 inhibited epithelial-mesenchymal transition, migration and invasion by targeting Scm-like with four mbt domains 1 and DCUN1D1 in cervical cancer. However, the regulatory mechanism of DCUN1D1 expression in cervical cancer has remained obscure. The present study demonstrated that DCUN1D1 rescued the miR-302-3p-mediated inhibition of cervical cancer cell migration and invasion. Thus, the suppressive effects of miR-302-3p on cervical cancer cells may be through direct targeting of DCUN1D1. Additionally, as the present study demonstrated that DCUN1D1 was significantly upregulated in cervical cancer, and the DCUN1D1 levels were inversely correlated with the miR-302-3p levels, it may be suggested that the upregulation of DCUN1D1 may be attributed to the reduced expression of miR-302-3p in cervical cancer.

To the best of our knowledge, the present study demonstrated, for the first time, that miR-302-3p is significantly downregulated in cervical cancer, and serves a suppressive role in the migration and invasion of cervical cancer cells, partly at least, through directly targeting DCUN1D1. These findings suggest that the miR-302-3p/DCUN1D1 axis may be a potential therapeutic target for the treatment of cervical cancer.

**Competing interests**

The authors declare that they have no competing interests.

**References**


