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MiR-377-3p inhibits cell metastasis and epithelial-mesenchymal transition in cervical carcinoma through targeting SGK3

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Abstract. – OBJECTIVE: In cervical carcinoma (CC), microRNAs (miRNAs) were reported to be involved in its development. In this study, we explored how miR-377-3p regulates cell metastasis and epithelial-mesenchymal transition (EMT) in CC.

PATIENTS AND METHODS: Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR), Dual-Luciferase Assay, transwell assays, and Western blot analysis were performed to explore the dysregulation of miR-377-3p.

RESULTS: MiR-377-3p expression was decreased in CC, and the downregulation of miR-377-3p could predict poor prognosis in CC patients. Moreover, miR-377-3p overexpression repressed cell invasion and migration in CC. Similarly, miR-377-3p overexpression also inhibited EMT in CC cells. Furthermore, miR-377-3p directly targeted SGK3 in CC cells. SGK3 silence had the same function as miR-377-3p overexpression in CC. Especially, the upregulation of SGK3 abolished the inhibitory action of miR-377-3p in CC.

CONCLUSIONS: Taken together, miR-377-3p inhibited cell metastasis and EMT by suppressing SGK3 expression. Moreover, the high miR-377-3p expression could predict good prognosis of CC patients.

Key Words:
Cervical carcinoma, MiR-377-3p, Epithelial-to-mesenchymal transition, Metastasis, Prognosis, SGK3.

Introduction

The incidence of cervical carcinoma (CC) is very high in the gynecological malignant tumor, which seriously threatens the health and survival of women[1]. Currently, the incidence of CC is increasing by 2% to 3% annually, and the age of CC tends to be younger[2]. Clinical studies[3] have shown that early detection and timely treatment could prevent the occurrence of CC and reduce the mortality rate of CC patients. Moreover, the process from a precancerous lesion to CC is very long and lasts about 10 years[4]. Early CC can be completely cured. Therefore, CC is a preventable, curable gynecological malignancy, and the key is to diagnose it early and to block the precancerous lesion of CC.

MicroRNAs (miRNAs) could be used for early diagnosis of human cancers[5]. In CC, miR-124, miR-125a, miR-214, and miR-374c was reported to influence the development of CC[6-9]. Among a number of miRNAs, miR-377-3p in CC caught our attention, because miR-377-3p has been found to be associated with the cervical squamous cell carcinoma metastases[10]. Moreover, the abnormal expression of miR-377 was found in hepatocellular carcinoma, osteosarcoma, and glioblastoma[11-14]. However, the relationship between miR-377-3p and EMT in CC still remains unknown. EMT, as a vital biological process, could regulate the abilities of cell migration and invasion[15,16]. The expressions of RhoE, TGF-b1, and SIP1 have been found to influence the occurrence of EMT[17-19]. Hence, it is important to investigate EMT in CC.

In the current study, we identified the abnormal expression of miR-377-3p in CC tissues and cell lines. And the effects of miR-377-3p on cell metastasis and EMT by regulating SGK3 were examined in CC as well. We hope that these findings could contribute to the early diagnosis of CC patients.

Patients and Methods

Clinical Tissues

Seventy-seven CC patients in the Xianyang Central Hospital participated in this study. Before the experiment began, we acquired the informed consents from all CC patients. Experimental CC and normal tissues were acquired from these patients. Seventy-seven CC patients did not receive any treatment except for surgery. The approval of this research was

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acquired from the Institutional Ethics Committee of Xianyang Central Hospital. All patients provided written informed consent. This work was conducted in accordance with the Declaration of Helsinki.

Cell Culture and Transfection

Normal human cervical epithelial cell line (H8) and HeLa, CaSki, SiHa, HEK293 cell lines were used for this experiment. These cell lines came from the Institute of Biochemistry and Cell Biology (Chinese Academy of Sciences, Shanghai, China). The growth conditions of these cells were 5% CO_2 at 37°C, and culture solution (90% DMEM +10% FBS). Next, miR-377 mimics, inhibitor or SGK3 siRNA (si-SGK3; RiboBio, Guangzhou, China) was transfected to HeLa cells, respectively using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA).

Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

The total RNA extraction was performed by TRIzol reagent (Sigma-Aldrich, St. Louis, MO, USA). QRT-PCR was performed using SYBR Green Master Mix II (TaKaRa, Dalian, China) based on the manufacturer's instructions. MiR-337-3p or SGK3 was normalized by U6, and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as the internal reference. The $2^{-\Delta\Delta ct}$ method was applied to calculate their expressions. The primer sequences were shown in Table I.

Dual-Luciferase Assay

The pGL3-basic vectors (RiboBio, Guangzhou, China) containing the 3′-untranslated region (3′-UTR) of wt-SGK3 or mut-SGK3 were conducted. Then, the above Luciferase vector and miR-377-3p mimics were transfected to HEK293T cells. After incubation of 48 h, the Luciferase activities were detected by Dual-Luciferase System (Promega, Madison, WI, USA).

Transwell Assays

Cell migration and invasion were assessed using the transwell chambers. As for cell invasion, the upper chamber was added with Matrigel. Next, the upper chamber was put with the transfected HeLa cells (1×10^5 cells/well). And 10% FBS was added into the lower chamber. After incubation of 24 h at 37°C, the moved cells were fixed and stained for 30 min. Finally, the moved cells were examined under a light microscope (SNICO, Shenzhen, China).

Western Blot Analysis

The radioimmunoprecipitation assay (RIPA) lysis buffer (Beyotime, Shanghai, China) was used to obtain the protein samples. Next, 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) was used to separate 25 μg proteins. The protein samples were transferred to polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). After being blocked with 5% non-fat milk, the protein was incubated with rabbit monoclonal anti-SGK3 (1:2000; Abcam, Cambridge, MA, USA), rabbit monoclonal anti-GAPDH antibody (1:1000; Epitomics, Burlingame, CA, USA) overnight at 4°C. Next, the diluted secondary antibodies (1:2000; Abcam, Cambridge, MA, USA) were applied to incubate the protein for 2 h. Finally, enhanced chemiluminescence (ECL; Pierce, Rockford, IL, USA) was applied to measure the protein expression. E-cadherin, N-cadherin, and Vimentin antibodies were also purchased from Abcam (Cambridge, MA, USA).

Statistical Analysis

Data are shown as mean ± SD, which were analyzed using GraphPad Prism 6 (GraphPad Software, Inc., San Diego, CA, USA) and the Statistical Product and Service Solutions (SPSS) 19.0 (SPSS, Corp., Armonk, NY, USA). The Chi-square test and Univariate Kaplan-Meier method with the log-rank test

Table I. The primer sequences.

	Primer sequences
miR-377-3p	forward, 5'-AUC ACA CAA AGG CAA CUU UUG U-3' reverse, 5'-AAA AGU UGC CUU UGU GUG AUU U-3'
SGK3	forward, 5'-CCA GGA GTG AGT CTT ACA G-3' reverse, 5'-CCA GCC ACA TTA GGA TTA-3'
U6	forward, 5'-CTC GCT TCG GCA GCA CA-3' reverse, 5'-AAC GCT TCA CGA ATT TGC GT-3'
GAPDH	forward, 5'-TGC ACC ACC AACT GCT TAG C-3' reverse, 5'-GGC ATG CAC TGT GGT CAT GAG-3'.

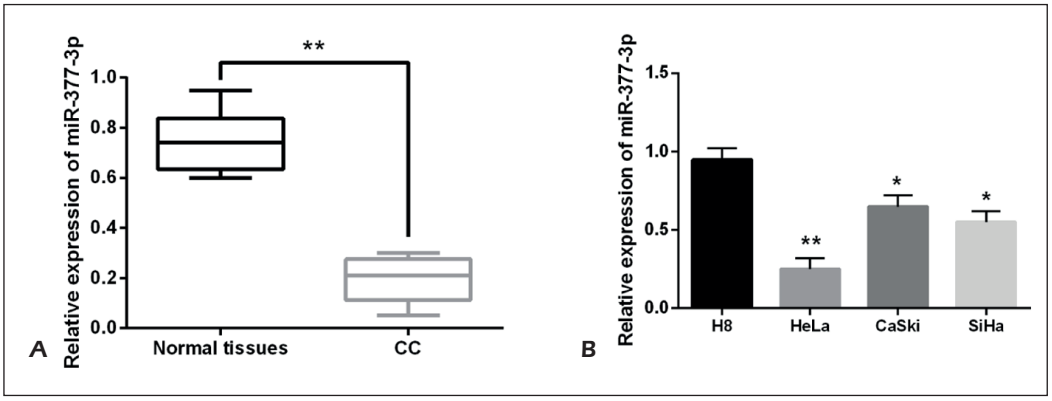

Figure 1. Decreased miR-377-3p expression in CC **A**, miR-377-3p expression in CC tissues **B**, miR-377-3p expression in HeLa, CaSki, SiHa, and H8 cells *p<0.05, **p<0.01.

were applied to analyze data. It is considered as a significant difference when p<0.05.

Results

Decreased MiR-377-3p Expression Was Identified in CC

MiR-377-3p expression in CC tissues was initially investigated. The miR-377-3p expression was found to be lower in CC tissues than in normal tissues (Figure 1A). Additionally, miR-377-3p expression was detected in HeLa, CaSki, SiHa, and H8 cell lines. And we found that miR-377-3p expression was distinctly declined in HeLa, CaSki, SiHa cell lines in comparison with H8 cells (Figure 1B). Those results reflected that the aberrant expression of miR-377-3p might be related to the tumorigenesis of CC.

The Association Between MiR-377-3p Expression and Clinical Features Was Found in CC

As shown in Table II, low miR-377-3p expression was significantly correlated with LNM (lymph node metastasis; p=0.006) and LVSI (lymph vascular space invasion; p=0.039). In addition, low miR-377-3p expression was associated with shorter overall survival in CC patients (p=0.0147; Figure 2), indicating that miR-377-3p could predict prognosis in CC patients. Based on the above results, we considered that the dysregulation of miR-377-3p may participate in the CC development.

MiR-377-3p Overexpression Repressed Migration and Invasion of CC Cells

To investigate the function of miR-377-3p in CC, HeLa cells with miR-377-3p mimics or inhibitor were prepared. MiR-377-3p mimic was found to remarkably enhance its expression (p<0.01; Figure 3A), when miR-377-3p inhibitor decreased its expression in HeLa cells (p<0.01; Figure 3B). The transwell assays showed that the upregulation of miR-377-3p was examined to inhibit cell migration and invasion, whereas the downregulation of miR-377-3p enhanced the abilities of HeLa cell migration and invasion (p<0.01; Figures 3C, 3D). In short, miR-377-3p overexpression restrained CC cell migration and invasion.

MiR-377-3p Overexpression Inhibited EMT in CC Cells

To further explain the effect of miR-377-3p on CC metastasis, the expressions of EMT markers were measured. We found that miR-377-3p upregulation promoted E-cadherin expression and repressed Vimentin and N-cadherin expressions (p<0.01; Figure 4A). On the contrary, the knockout of miR-377-3p declined the E-cadherin level and enhanced the Vimentin and N-cadherin levels (p<0.01; Figure 4B). Briefly, miR-377-3p overexpression inhibited the EMT of CC cells.

MiR-377-3p Directly Targeted SGK3 in CC Cells

In addition, we searched the targets of miR-377-3p in TargetScan database (http://www.targetscan.org/vert_71/). Especially, SGK3 was selected as a candidate target of miR-377-3p, which has binding sites with miR-377-3p (Figure 5A). Then, the Luciferase reporter assay was performed to testify the prediction. MiR-377-3p mimics were found to apparently block the Luciferase activity of wt-SGK3, whereas it

Table II. Relationship between miR-377-3p expression and their clinicopathological characteristics of CC patients.

Characteristics	Cases	miR-377-3p		*p*-value
		High	Low	
Age (years)				0.179
≥ 45	50	21	29	
< 45	27	10	17	
FIGO stage				0.164
I	47	19	28	
II	30	12	18	
Tumor size (cm)				0.395
<4	60	25	35	
≥4	17	6	11	
LNM				0.006*
Negative	62	26	36	
Positive	15	5	10	
LVSI				0.039*
Negative	61	25	36	
Positive	16	6	10	
Histology				0.633
Squamous	52	20	32	
Adenocarcinoma	25	11	14	
Parametrail extension				0.973
Negative	53	21	32	
Positive	24	10	14	

Statistical analyses were performed by the χ^2-test. CC, cervical cancer; FIGO, International Federation of Gynecology and Obstetrics; LNM, lymph node metastasis; LVSI, lymphovascular space invasion. *p<0.05 was considered significant.

did not affect mut-SGK3 (p<0.01; Figure 5B). Moreover, the expression of SGK3 in CC tissues was demonstrated to be negatively associated with miR-377-3p expression (R^2=0.8382, p<0.0001, Figure 5C). Additionally, the upregulation of miR-377-3p significantly inhibited the SGK3 expressions, when the downregulation of miR-377-3p promoted its expression in HeLa cells (p<0.01; Figures 5D, 5E). Collectively, miR-377-3p directly targeted SGK3 and inversely regulated its expression in CC cells.

The function of SGK3 Was Identified in CC

Then, the SGK3 expression was impeded by si-SGK3 in HeLa cells to investigate the role of SGK3 for EMT and metastasis in CC (p<0.01; Figure 6A). As for EMT, si-SGK3 enhanced the level of E-cadherin and reduced the Vimentin and N-cadherin expressions (p<0.01; Figure 6B). Moreover, the transwell assay revealed that si-SGK3 restrained cell invasion and migration (p<0.01; Figure 6C, 6D). In conclusion, SGK3 had the same effect of miR-377 overexpression in CC.

Upregulation of SGK3 Abolished the Inhibitory Action of MiR-377-3p in CC

Finally, SGK3 vector was transfected into HeLa cells, and miR-377-3p was overexpressed to further explore their interaction. We found that the upregulation of SGK3 repaired the reduction

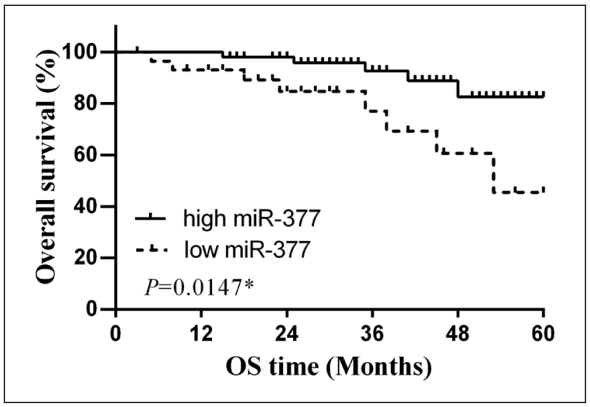

Figure 2. MiR-377-3p could predict prognosis in CC patients. High miR-377-3p expression patients showed longer OS. **p<0.01.

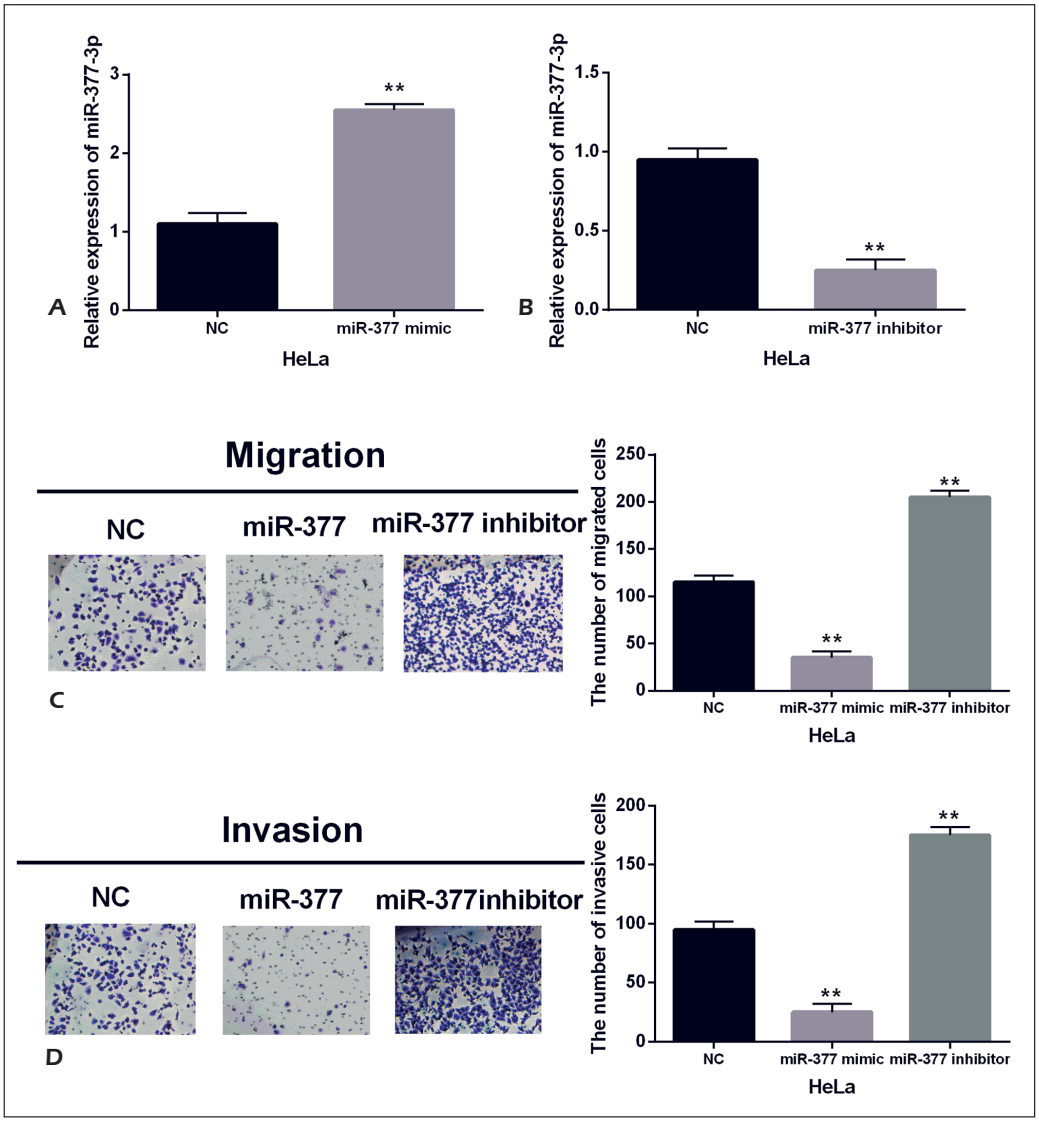

Figure 3. MiR-377-3p overexpression repressed CC cell migration and invasion. **A**-**B**, MiR-377-3p expression in HeLa cells containing miR-377-3p mimics or inhibitor. **C**-**D**, MiR-377-3p regulated cell migration and invasion in HeLa cells $^{**}p<0.01$ (magnification: 40X).

of SGK3 mRNA and the protein levels induced by miR-377-3p mimics ($p<0.01$; Figures 7A, 7B). As we expected, SGK3 overexpression also abolished the inhibitory action of miR-377-3p for cell migration and invasion in CC cells ($p<0.01$; Figures 7C, 7D). Taken together, the upregulation of SGK3 abolished miR-377-3p mediated inhibition of CC cell invasion and migration.

Discussion

In this study, miR-377-3p expression was declined in CC, which was related to LNM and LVSI. Moreover, miR-377-3p was observed to inhibit cell metastasis and EMT in CC by directly suppressing SGK3. Additionally, we also found that high miR-377-3p expression could predict a good prognosis for CC patients. According to these findings, we considered that miR-377-3p would be an important regulator in CC development.

In recent years, miR-377-3p had been reported[20-23] to be downregulated in some human cancers, such as gastric cancer, pancreatic cancer, and hepatocellular carcinoma. However, Wen et al[24] proposed that miR-377 was upregulated in gastric cancer and predicted poor clinical out-

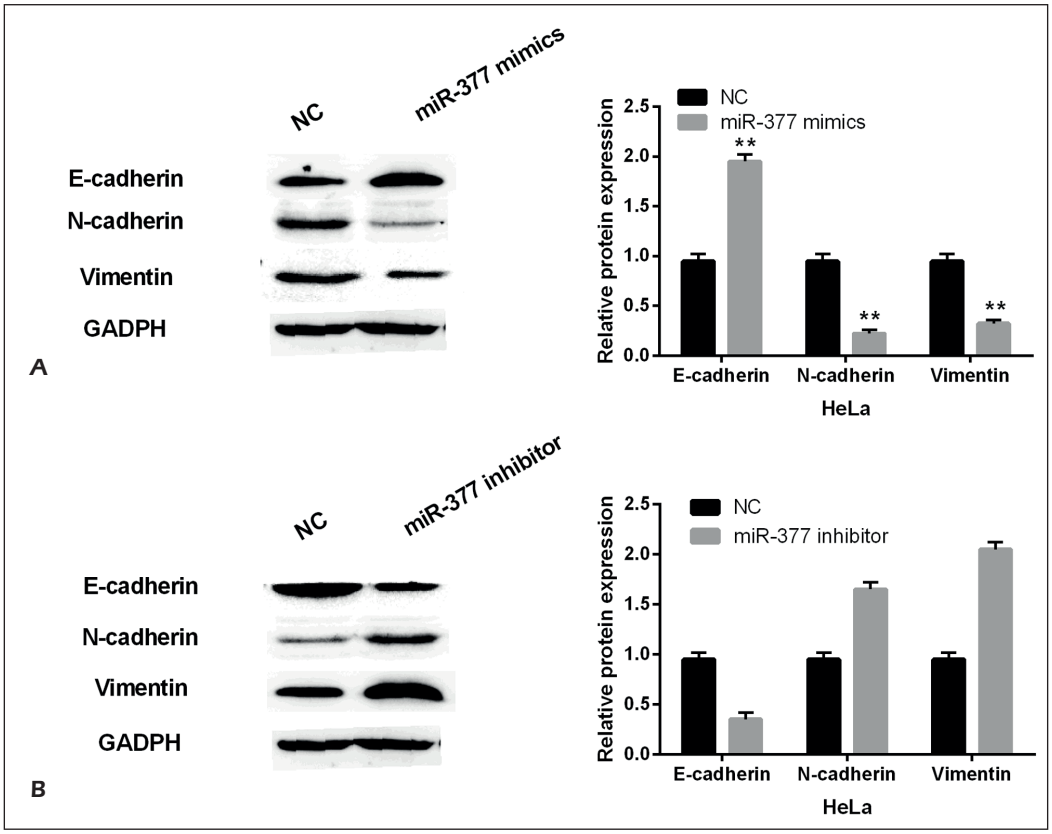

Figure 4. MiR-377-3p overexpression blocked EMT in CC cells. **A-B**, MiR-377-3p regulated Vimentin, N-cadherin, and E-cadherin expressions in HeLa cells.

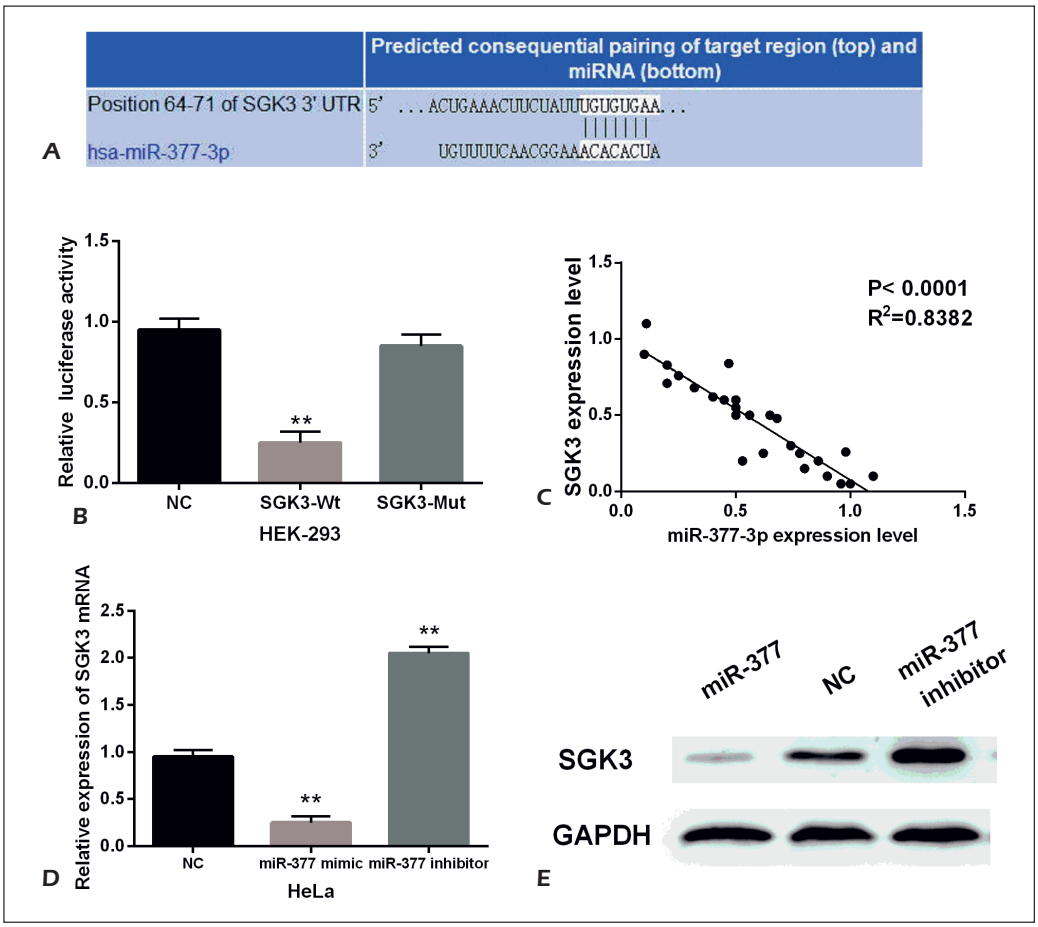

Figure 5. MiR-377-3p directly targeted SGK3 in CC cells. **A**, The binding sites between miR-377-3p and SGK3. **B**, Luciferase reporter assay. **C**, MiR-377-3p had negative association with SGK3 expression. **D-E**, SGK3 expressions in cells with miR-377-3p mimics or inhibitor **p<0.01.

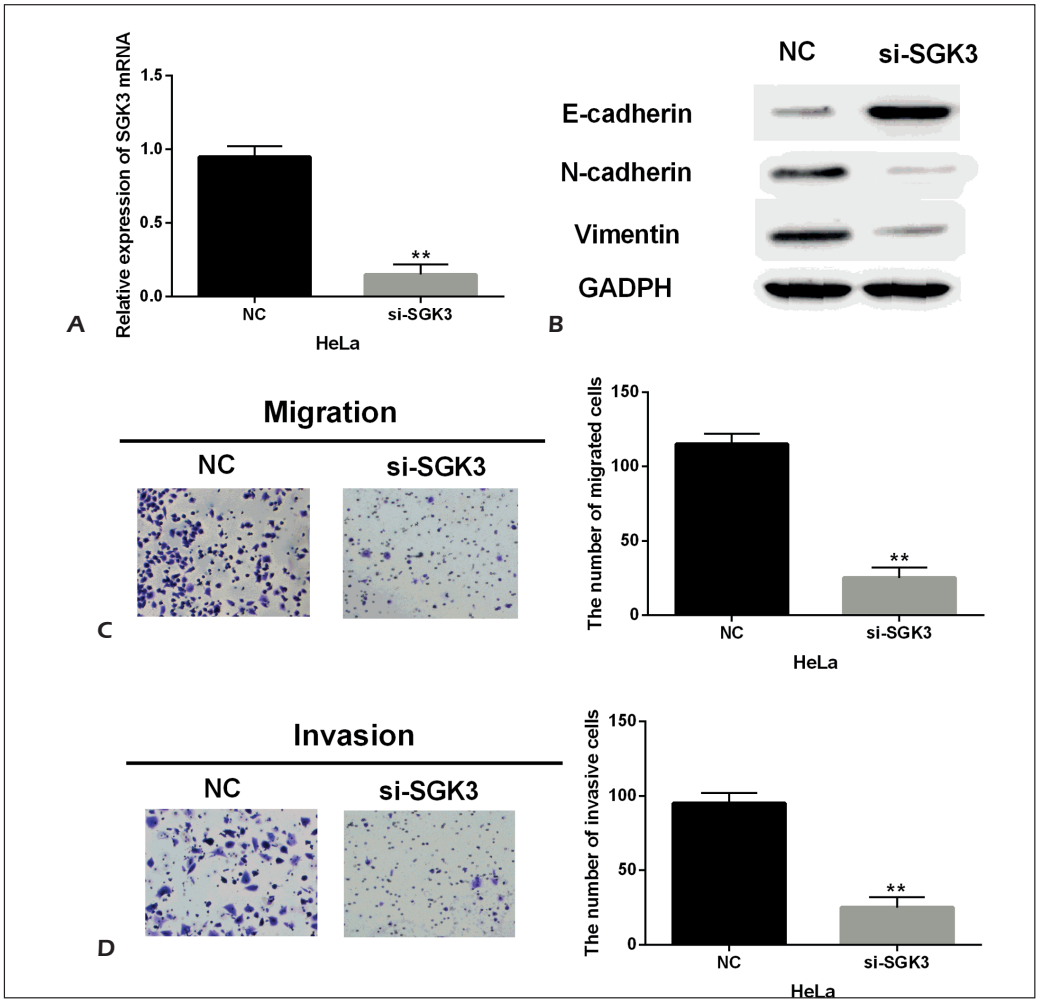

Figure 6. The function of SGK3 was identified in CC. **A**, SGK3 expression in cells with SGK3 siRNA. **B**, Protein expression of E-cadherin, N-cadherin, and Vimentin in HeLa cells containing si-SGK3. **C-D**, SGK3 siRNA regulated cell migration and invasion $^{**}p<0.01$ (magnification: 40X).

comes. In addition, Bo et al[25] also showed that the upregulation of miR-377-3p had carcinogenesis in the progression of gastric cancer by targeting RASSF8. These investigations suggested that the function of miR-377-3p was different in several cancers. Moreover, there was almost no research about the role of miR-377-3p in CC. Our research confirmed that miR-377-3p was downregulated in CC. Moreover, the overexpression of miR-377-3p functioned as an inhibitor in the formation of CC tumor.

Besides that, miR-377-3p was demonstrated to target directly SGK3 and to be inversely associated with its expression in this investigation. SGK3, belonging to the AGC protein kinase family, shares structural similarity with the Akt1-3 catalytic domains[26]. In addition, SGK3 has been reported[27-29] to obstruct the expressions of miR-212, miR-155, and miR-144 in glioblastoma and hepatocellular carcinoma. In the current research, miR-377-3p was found to directly target SGK3. Consistent with the above studies, SGK3 was also verified to contribute to the occurrence of CC. In addition, SGK3 has been revealed to affect breast cancer cell migration *via* mediating INPP4B[30], but no researches were found about the relationship between SGK3 and EMT. Moreover, we found that SGK3 could promote EMT in CC. Thus, we thought that SGK3 might offer a new avenue for the therapy of CC.

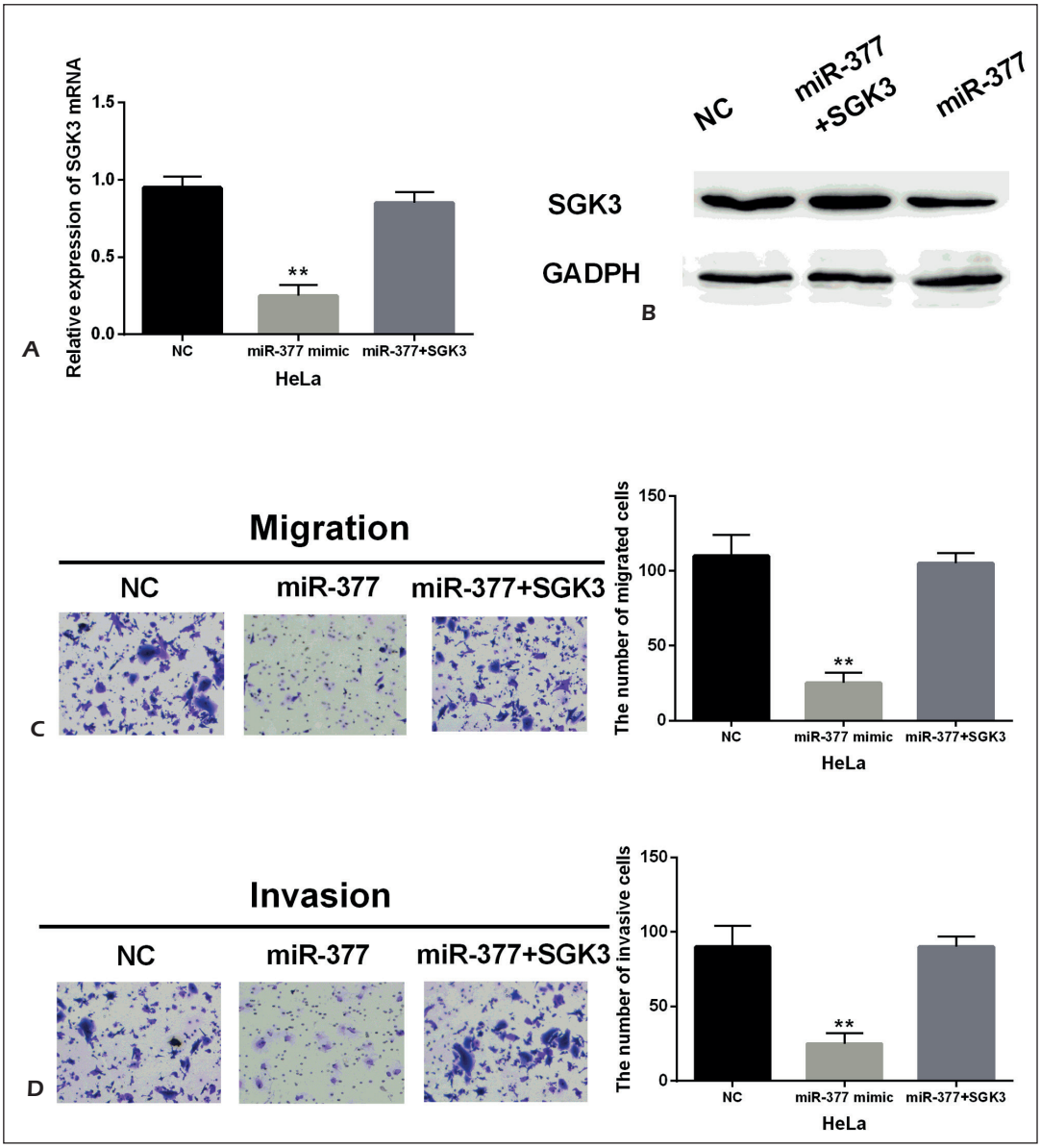

Figure 7. Upregulation of SGK3 abolished the inhibitory action of miR-377-3p in CC. **A**-**B**, The mRNA and protein expressions of SGK3 were measured in the cells containing SGK3 vector and miR-377-3p. **C**-**D**, Cell migration and invasion in the cells containing SGK3 vector and miR-377-3p was measured by the transwell assay. $^{**}p<0.01$ (Magnification: 40X).

Conclusions

In this study, the decreased miR-377-3p expression was identified in CC. Furthermore, miR-377-3p suppressed migration and invasion of CC cell, as well as to repress EMT in CC *via* directly regulating SGK3 expression. MiR-377-3p/SGK3 axis will be employed as a novel therapeutic target in CC.

Conflict of Interests

The authors declare that they have no conflict of interests.

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