

RESEARCH ARTICLE



# MicroRNA-377-3p inhibits growth and invasion through sponging JAG1 in ovarian cancer

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## Abstract

**Background** Ovarian cancer is the one of the most deadly gynecologic malignancy among cancer related death in women. However, the treatment for ovarian cancer is still limited. In this study, we aimed to explore the inhibition potential of miR-377-3p in ovarian cancer and explore the mechanism of this effect.

**Methods** Quantitative real-time PCR was used to detect the mRNA or microRNA (miRNA) levels. CCK-8, wound-healing, transwell assay were used to detect cell proliferation, migration and invasion. The protein levels were examined by western blot. The dual luciferase reporter assay was conducted to examine the luciferase activity. Tumor volume was measured and Ki67 was detected via immunohistochemistry.

**Results** qRT-PCR results showed that miR-377-3p was downregulated in ovarian cancer patients. MiR-377-3p mimics suppressed cell proliferation, migration, invasion and decreased the JAG1 level. However, miR-377-3p inhibitor promoted these appearances. Interestingly, we found JAG1 was a target gene of miR-377-3p. JAG1 overexpression reversed the miR-377-3p-induced inhibition of proliferation and invasion. In addition, miR-377-3p inhibited ovarian cancer tumorigenesis in vivo, indicating by decreased tumor volume and staining of Ki67.

**Conclusion** The results showed that miR-377-3p inhibited growth and invasion of ovarian cancer cells by targeting JAG1.

**Keywords** MiR-377-3p · Growth · Invasion · JAG1 · Ovarian cancer

## Introduction

Ovarian cancer is reported to be the most deadly gynecologic malignancy with the relatively asymptomatic nature (Jayson et al. 2014; Siegel et al. 2018). In 2018, there are 14,070 deaths among 22,240 new cases in ovarian cancer (Siegel et al. 2018). In ovarian cancer, 75% of patients are in advanced-stage, as defined by the International Federation of Gynecology and Obstetrics (FIGO), and the tumors present widespread peritoneal cavity metastasis (Heintz et al. 2006; Lengyel 2010). Currently, the combination of chemotherapy and surgery is reported to be the primary

therapeutic strategy for ovarian cancer. The main surgeries used for ovarian cancer include removal of patient's uterus, omentum, pathologically enlarged lymph nodes, bilateral tubes and ovaries, as well as peritoneal surfaces involving disease (Pearre and Tewari 2018). Nevertheless, the molecular mechanism involved in ovarian cancer development and progression remains unclear.

MicroRNAs (miRNAs), which comprised 21–24 nucleotides, are highly conserved endogenous and small non-coding RNAs (Bartel 2004; Shen et al. 2016; Wu et al. 2014). They are reported to be involved in regulation of cellular processes in tumor and the aberrant expression of miRNAs may lead to tumor formation (Iorio et al. 2005; Zhang et al. 2008). Recently, more and more studies have focused on the relationship between miRNAs and tumors, including ovarian cancer. For example, Liu et al. (2018a) found that miR-665 inhibits the growth and migration in ovarian cancer cells. In addition, Jiang et al. (2018) showed that miR-383-5p had an inhibitory effect on proliferation, and it could enhance chemosensitivity of ovarian cancer cells. Interestingly, miR-377-3p displayed the inhibition for proliferation as well as

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invasion in cervical cancer (Ye et al. 2018). Furthermore, in osteosarcoma, miR-377-3p was downregulated to increase cisplatin resistance (Liu et al. 2018b). However, there are no reports on the function of miR-377-3p in ovarian cancer.

Jagged1 (JAG1), a Notch ligand, was found in ovarian carcinoma (Chen et al. 2010). Previous studies showed that JAG1 was frequently overexpressed in ovarian cancer cells and JAG1/Notch3 interaction can enhance cell proliferation and dissemination in ovarian cancer (Choi et al. 2008). Moreover, interference of JAG1 reduced ovarian cancer cell growth and increased the tumor inhibition rate in xenograft tumor (Liu et al. 2016). Interestingly, miRNAs may be involved in progression of certain tumors through regulation of JAG1. For instance, miR-199b inhibited proliferation of porcine muscle satellite cells by targeting JAG1 (Zhu et al. 2019). In addition, miR-26b-5p showed its suppressive role on proliferation of multiple myeloma cells via targeting JAG1 (Jia et al. 2018). However, whether miR-377-3p is associated with ovarian cancer through targeting JAG1 is still unknown.

Therefore, in this study, we explored the role of miR-377-3p in ovarian cancer and investigated the molecular mechanisms by which miR-377-3p regulates the growth and migration of ovarian cancer are investigated. Our findings will provide us additional evidence that miR-377-3p plays a key role in the progression of ovarian cancer.

## Materials and methods

### Patient samples

Total of 60 cancer and para-cancer ovarian tissue samples were collected from Affiliated Hospital of Guilin Medical University. The patients received and signed the informed consents prior to the study. In addition, all patients were primary cases and they did not received radiotherapy, chemotherapy or any other treatments prior to surgery. The tissues were immediately snap-frozen in liquid nitrogen following surgical resection and stored until use. The experimental protocol was obeyed by World Medical Association Declaration of Helsinki.

### Animals

All animal experiments were approved by Guide for the Care and Use of Laboratory Animals. The 5-week-old male BALB/c nude mice were randomly divided into two groups (n = 5/group). In the control group, the mice were injected by negative control (NC) vector. In the experimental group, the mice were injected with miR-377-3p lentivirus. They were placed on a 12h artificial dark–light cycle and provided with standard food pellets and tap water for 21 days. The tumor

growth and tumor size was calculated as following: tumor volume =  $0.5 \times (\text{length} \times \text{width}^2)$ .

### Cell culture

The ovarian cancer cell lines SKOV-3, OVCAR3, A2780 and CAOV3 were purchased from CRC/PUMC (Cell Resource Center, IBMS, CAMS/PUMC). They were cultured in RPMI medium 1640 with 10% fetal bovine serum (FBS) at 37 °C containing 5% CO<sub>2</sub>. 293T cells were obtained from ATCC and maintained in DMEM supplemented with 10% FBS at 37 °C in 5% CO<sub>2</sub>.

### Quantitative real-time PCR

Total RNAs were extracted from the tissues and cells using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) and reversely transcribed into cDNA by PrimeScript RT reagent kit (Promega, Madison, WI, USA). The relative expression level of miR-377-3p and JAG1 were detected using quantitative real-time PCR (qRT-PCR) by SYBR Premix EX Taq™ (TaKaRa, Dalian, Liaoning, China). The relative quantitation was analyzed by the  $2^{-\Delta\Delta C_t}$  method and U6 and GAPDH were used as the internal controls. The primers used for qRT-PCR in this study were listed as following:

Gene	Forward	Reverse
MiR-377-3p	GAGCAGAGGTTG CCCTTG	ACAAAAGTTGCC TTTGTGTGA
JAG1	ATCGTGCTGCCT TTCAGTTT	GGTCACGCGGAT CTGATACT
GAPDH	GCAGGGGGGAGC CAAAA GGGT	TGGGTGGCAGTG ATGGCATGG

### Western blot assay

Proteins were obtained from cells or tissue from mice. RIPA lysis buffer containing protease inhibitors (Beyotime, Jiangsu, China) was used to lyse the proteins. Then BCA Kit (Wuhan Boster Biological Technology, Co. Ltd., Wuhan, China) was used to quantify the protein concentration. Protein samples were loaded into SDS-PAGE to separate and then wet-transferred onto PVDF membrane. Subsequently, blocking buffer containing 5% non-fat milk was used to block the membrane for 1 h. The primary antibodies, such as JAG1 (1:400, Santa Cruz Biotechnology, Dallas, TX, USA), GAPDH (1:1000, Cell Signaling Technology, Leiden, Netherlands) were then applied to incubate the membrane for overnight at 4 °C. After membranes were washed with

TBST for 3 times, they were continuously incubated with the secondary antibody for 1 h at room temperature. Finally, the bands were visualized and analyzed.

### Cell migration and invasion assays

For cell migration assay, we performed the wound-healing. Briefly, the 6-well plates were seeded with transfected cells ( $5 \times 10^4$  cells/well). Then they were scratched using 200  $\mu$ l pipette tip to create wound at cell surface. They were cultured in serum-free medium for 48 h. At 0 and 48 h, images were captured with an X71 inverted microscope (Olympus, Tokyo, Japan).

For invasion assay, we carried out the Matrigel invasion assays. Briefly, the transfected cells ( $1 \times 10^5$  cells) mixed with 100  $\mu$ l serum-free medium were placed into the upper chamber with Matrigel (BD Biosciences, Franklin Lakes, NJ, USA). In addition, 600  $\mu$ l medium containing 20% FBS was transferred into lower chamber. SKOV3 or OVCAR3 cells were then grown for 48 h, the cells harvested from membrane were then fixed and stained. The photographs and cell numbers were taken and counted, respectively.

### Cell proliferation assay

Cell proliferation was measured using CCK-8 assays. The cells (3000 cells/well) were cultured in 96-well plate at 37 °C. At 0, 24, 48 and 72 h, 10  $\mu$ l CCK-8 solution was added to each well and incubated for 4 h. Then at each analyzed time point, the cell viability was determined using a plate reader at 490 nm (BioRad Laboratories, Hercules, CA, USA).

### Dual luciferase reporter assay

Targeted sequences of JAG1 3'-UTR were amplified by PCR using 293T genomic DNA as a template. Then, the isolated PCR product were inserted into luciferase reporter vector pmirGLO to generate the pmirGLO-JAG1-wild type (WT) or pmirGLO-JAG1-mutant type (MUT). The 293T cells were co-transfected with pmirGLO-JAG1-WT or pmirGLO-JAG1-MUT and miR-377-3p mimics or NC using Lipofectamine 2000 for 48 h. Subsequently, the cells were harvested and dual luciferase reporter assay kit (BioTek, Winooski, VT, USA) was used to detect the luciferase activity.

### Immunohistochemistry

Tumor tissues were obtained from miR-377-3p lentivirus- and NC vector-treated mice and the tissues were dissected and fixed in 4% paraformaldehyde. Then the tissues were embedded in paraffin. Specimens were sectioned at 4  $\mu$ m

thickness. Subsequently, the sections were deparaffinized and hydrated. After blocking the sections were incubated with primary antibodies Ki67 (1:100, Abcam, Cambridge, MA, USA) for overnight at 4 °C. The secondary antibody was then continually incubated the sections for 30 min. Finally, the diaminobenzidine was used to visualize immunoreactive signals.

### Statistical analysis

Statistical differences were assayed using GraphPad Prism 5.0. Statistical comparisons were conducted by Student's *t* test or an ANOVA test followed by Turkey. In this study, all experiments were conducted in triplicate. *p* values below 0.05 indicated statistically significant. In addition, all data were expressed as mean  $\pm$  SEM.

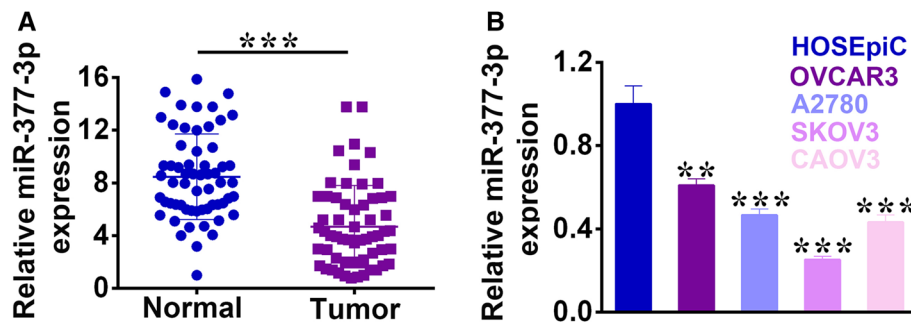
## Results

### MiR-377-3p is downregulated in ovarian cancer tissues and ovarian cancer cell lines

In order to examine the role of miR-377-3p in ovarian cancer, we measured the level of miR-377-3p in ovarian cancer tissues. The result from qRT-PCR assay revealed that miR-377-3p level was lower in ovarian cancer tissues compared with normal ovarian tissues (Fig. 1a). Subsequently, we measured the miR-377-3p level in ovarian epithelial cell lines (HOSEpiC) and ovarian cancer cell lines (OVCAR3, A2780, SKOV3 and CAOV3). qRT-PCR assay indicated that miR-377-3p was lower in ovarian cancer cell lines than in ovarian epithelial cell lines (Fig. 1b). In conclusion, these results suggest that miR-377-3p was downregulated in ovarian cancer tissues and ovarian cancer cell lines, indicating that miR-377-3p may serve an important role in ovarian cancer.

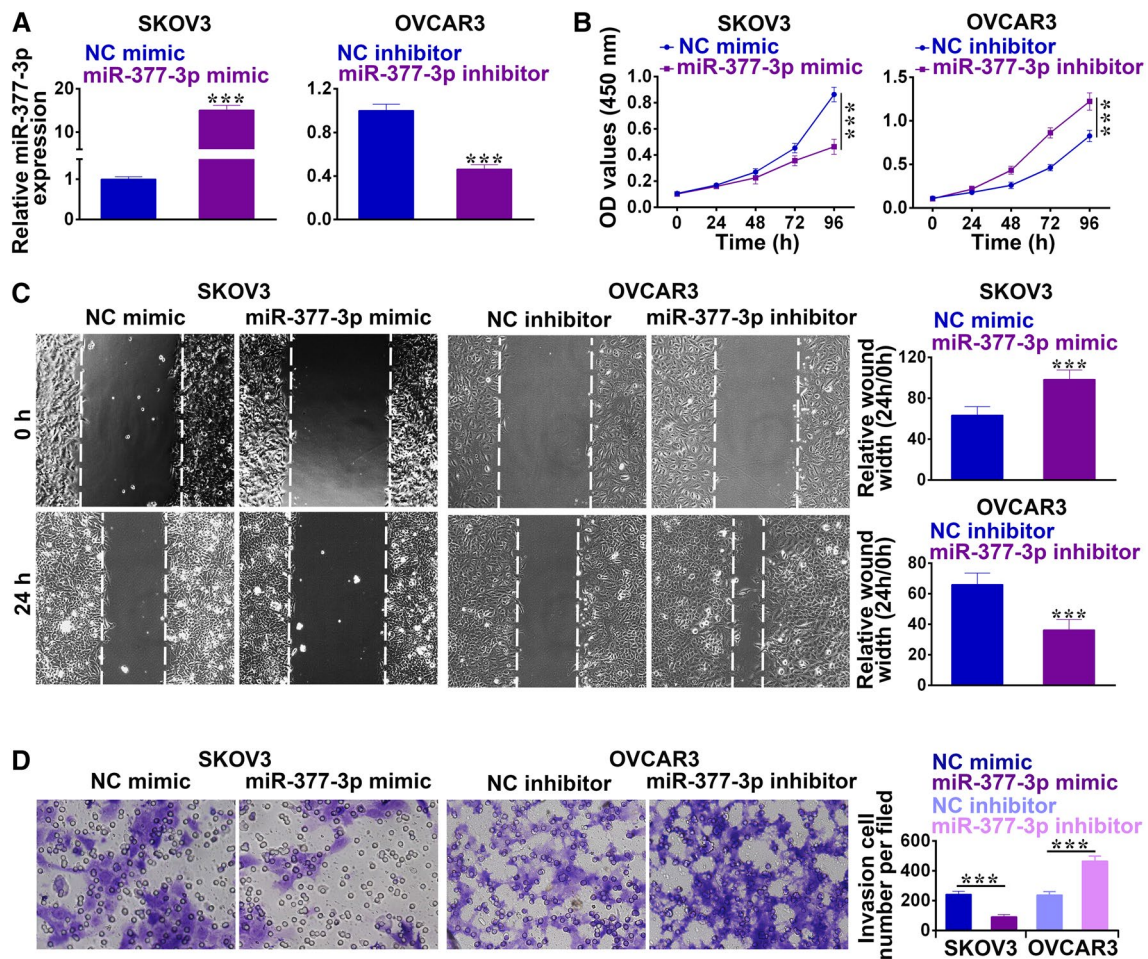
### MiR-377-3p inhibits the proliferation and invasion of ovarian cancer cells

In order to further investigate the function of miR-377-3p in ovarian cancer, miR-377-3p overexpression or knockdown was employed in SKOV3 or OVCAR3 cell lines. The transfection efficiency of miR-377-3p mimics or inhibitor was analyzed by qRT-PCR in SKOV3 or OVCAR3 cells, respectively (Fig. 2a). The proliferation of SKOV3 or OVCAR3 cells was then measured by CCK-8 assay. The results demonstrated that the proliferation of OVCAR3 cells was suppressed by miR-377-3p mimics, whereas it was enhanced by miR-377-3p inhibitor (Fig. 2b). Subsequently, wound-healing assays demonstrated that miR-377-3p mimics decreased the migration and miR-377-3p inhibitor increased the migration (Fig. 2c) of the OVCAR3 cell. In addition, miR-377-3p



**Fig. 1** MiR-377-3p is decreased in ovarian cancer tissues and ovarian cancer cell lines. **a** qRT-PCR assay was performed to detect the miR-377-3p level in both ovarian cancer tissues and normal ovar-

ian tissues. **b** MiR-377-3p level was assayed using qRT-PCR assay in HOSEpiC, OVCAR3, A2780, SKOV3 and CAO3 cells. Note: \*\* $p < 0.01$  and \*\*\* $p < 0.001$



**Fig. 2** MiR-377-3p inhibits the proliferation and invasion of ovarian cancer cells. **a** miR-377-3p level was measured with qRT-PCR assay in SKOV3 and OVCAR3, respectively. **b** CCK-8 assay was conducted

to detect the cell proliferation. **c** Wound-healing assay was performed to examine the cell migration. **d** Transwell assay was used to determine the cell invasion. Note: \*\*\* $p < 0.001$

mimics inhibited the cell invasion, whereas miR-377-3p inhibitor promoted the cell invasion, indicating by transwell assay (Fig. 2d). Therefore, miR-377-3p suppressed the proliferation and invasion of ovarian cancer cells.

### JAG1 is a target gene of miR-377-3p

To elucidate the regulation mechanisms of miR-377-3p involved in proliferation, migration and invasion in ovarian cancer, the related molecule was detected. We found that JAG1 was predicted to be a target gene of miR-377-3p (Fig. 3a). The dual luciferase reporter assay demonstrated that miR-377-3p mimics restrained the luciferase activity from the WT 3'-UTR of JAG1, whereas it had no effect on that from the MUT 3'-UTR of JAG1 (Fig. 3b). Afterwards, the JAG1 level was examined in the cells transfected with miR-377-3p mimics or inhibitor. qRT-PCR assay results showed that miR-377-3p mimics downregulated the JAG1 level, whereas miR-377-3p inhibitor upregulated the JAG1 level (Fig. 3c). Similarly, western blot assay also revealed that the JAG1 level was reduced in SKOV3 cells with miR-377-3p mimics, while JAG1 level was enhanced in OVCAR3 cells with miR-377-3p inhibitor (Fig. 3d). These results suggest that JAG1 was verified to be a target gene of miR-377-3p.

### JAG1 overexpression reverses the inhibition of proliferation and invasion induced by miR-377-3p in ovarian cancer cells

To gain more insight into the detailed role of miR-377-3p/JAG1 axis in ovarian cancer cells, the proliferation, migration and invasion assays were conducted again. qRT-PCR assay indicated that JAG1 was augmented in the cell co-transfected with miR-377-3p mimics and JAG1 (Fig. 4a). As presented in Fig. 4b, the proliferation was enhanced in the cells co-transfected with miR-377-3p mimics and JAG1 than that in the cells transfected with miR-377-3p mimics

alone. Western blot assay also showed the increased JAG1 level in these cells (Fig. 4c). Furthermore, we continually measured the migration and invasion of SKOV3 cells. The results demonstrated that the enhanced migration and invasion were found in the cells co-transfected with miR-377-3p mimics and JAG1 (Fig. 4d, e). Altogether, these findings indicated that JAG1 overexpression reversed the suppression of proliferation and invasion induced by miR-377-3p in ovarian cancer cells.

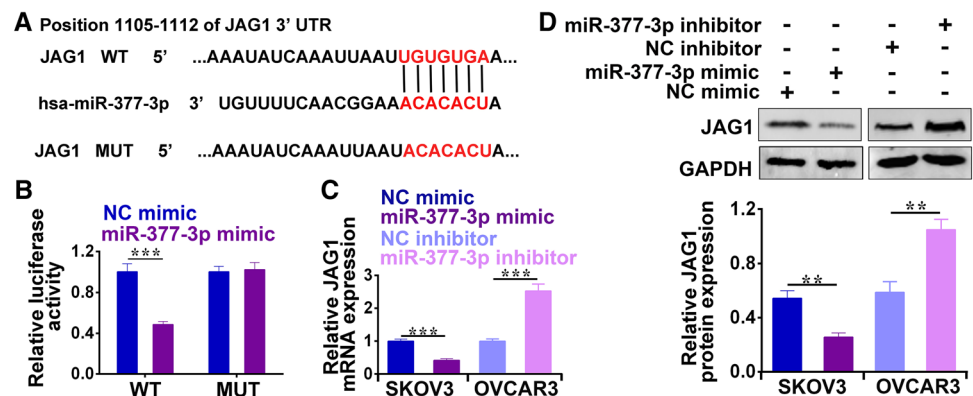
### MiR-377-3p inhibits ovarian cancer tumorigenesis in vivo

To examine whether miR-377-3p could function as tumor suppressor in ovarian cancer, we used a nude mice model in vivo. qRT-PCR assay revealed that miR-377-3p was upregulated in mice treated with miR-377-3p lentivirus (Fig. 5a). In addition, in these mice, the tumor volume was decreased (Fig. 5b), and Ki67, the marker of proliferation, was inhibited (Fig. 5c). Western blot assay further detected that miR-377-3p caused the decrease of JAG1 protein level in tumor tissues (Fig. 5d). The findings suggest that miR-377-3p repressed ovarian cancer tumorigenesis in vivo.

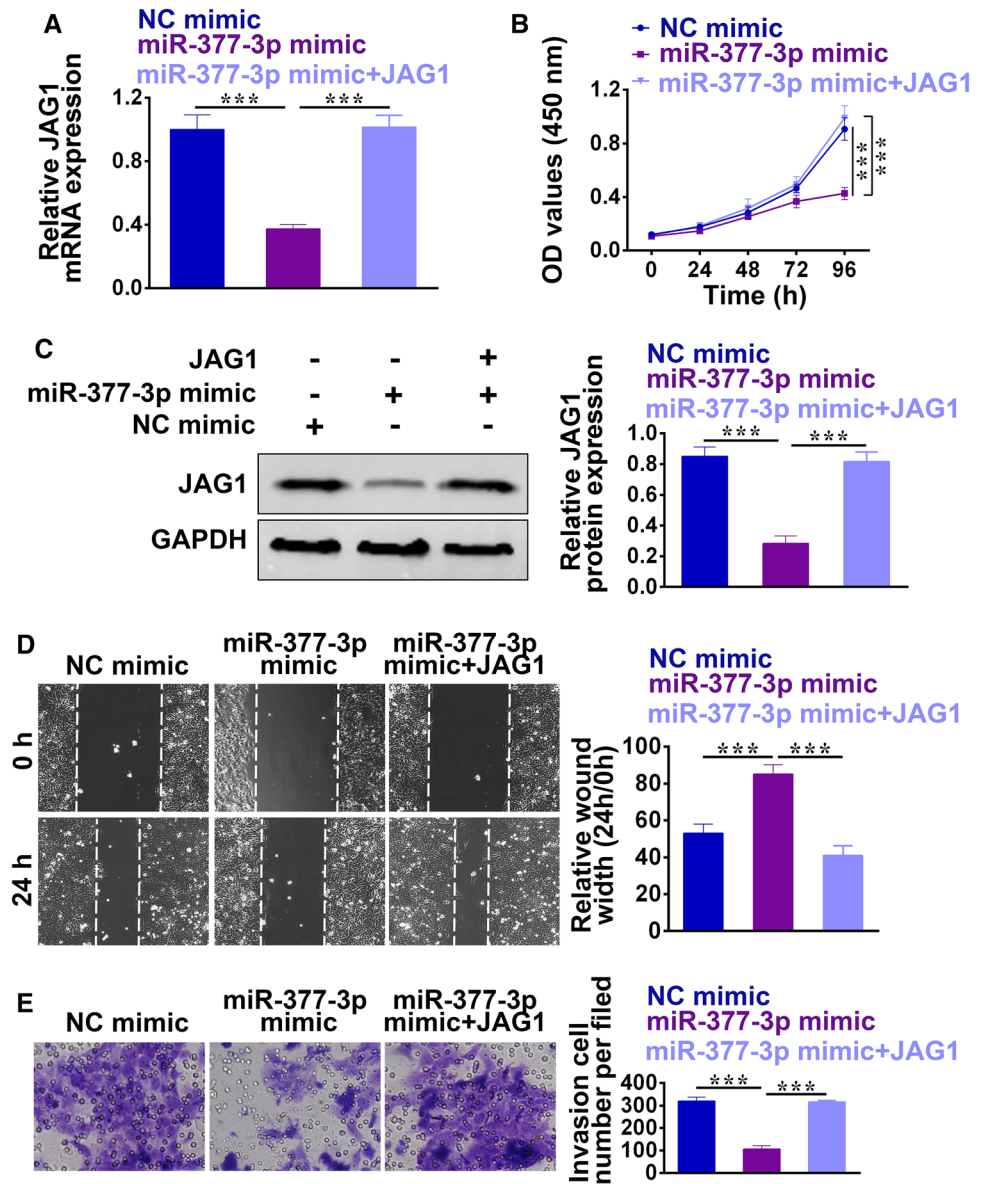
### Discussion

Here, the downregulation of miR-377-3p was first revealed in ovarian cancer tissues compared with normal ovarian tissues, suggesting miR-377-3p may act as a tumor suppressor in ovarian cancer. Subsequently, to explore the role of miR-377-3p, we transfected the miR-377-3p mimics and inhibitor in ovarian cancer cells. The results indicated that miR-377-3p inhibited the proliferation, migration and invasion of ovarian cancer cells. Furthermore, JAG1 was indicated to be the potential target gene of miR-377-3p in this study. The enhanced JAG1 could alleviate the reduction of migration

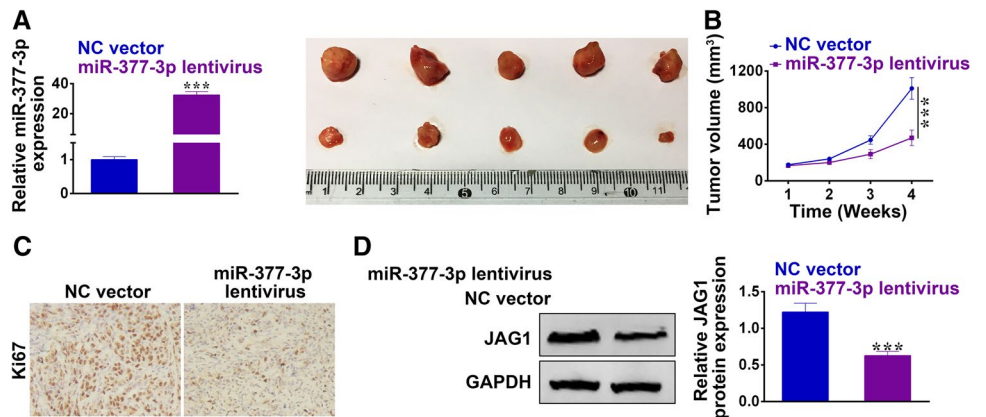
**Fig. 3** JAG1 is a target gene of miR-377-3p. **a** The binding site was predicted. **b** The luciferase activity was measured through dual luciferase reporter assay. QRT-PCR assay (c) and western blot assay (d) was performed to examine JAG1 level in SKOV3 and OVCAR3 cells, respectively. Note: \*\* $p < 0.01$  and \*\*\* $p < 0.001$



**Fig. 4** MiR-377-3p reverses the inhibition of proliferation and invasion of ovarian cancer cells by overexpression of JAG1. **a** The JAG1 mRNA level was indicated using qRT-PCR assay. **b** The cell proliferation was analyzed using CCK-8 assay. The wound-healing (c) and transwell assays (**d**) were used to explore the cell migration and invasion, respectively. Note: \*\*\* $p < 0.001$



**Fig. 5** MiR-377-3p inhibits ovarian cancer tumorigenesis in vivo. **a** miR-377-3p mRNA level was detected by qRT-PCR assay. **b** The tumor volume from mice was measured. **c** Immunohistochemistry was used to examine the proliferation. **d** Western blot assay was used to detect the JAG1 protein level. Note: \*\*\* $p < 0.001$



and invasion induced by overexpression of miR-377-3p in ovarian cancer cells. In addition, miR-377-3p showed the inhibition on ovarian cancer tumorigenesis *in vivo*. Taken together, it suggests that miR-377-3p plays a tumor suppressor role through targeting JAG1 in ovarian cancer.

It is well known that miR-377-3p has been reported to be associated with tumors. For example, earlier studies showed that miR-377-3p had a suppressive effect on proliferation, migration and invasion of the gastric cancer (Wang et al. 2017). Furthermore, miR-377-3p could inhibit cell growth and decrease cell migration of the oral squamous cell carcinoma (Rastogi et al. 2017). Interestingly, in our study, lower expression of miR-377-3p was detected in ovarian cancer. In addition, miR-377-3p mimics suppressed the cell proliferation, reduced the migration and invasion of the ovarian cancer cell lines, whereas miR-377-3p inhibitor showed the converse effect. The data suggest that miR-377-3p may act as an inhibitor of cell migration and invasion to exert the anti-tumor effect in ovarian cancer.

In addition to the function of miR-377-3p in migration and invasion of ovarian cancer cells, the role of JAG1 was also explored. Previous studies have reported that JAG1 knockdown leads to the limitation of cell migration in transformed adult T cell leukemia (Bellon et al. 2018). Furthermore, the enforced JAG1 expression have been found to show the promotion effect on cell migration and invasion of lung cancer cells (Chang et al. 2016). Notably, JAG1 was indicated to be involved in migration or invasion as the target of miRNA in some cancers. For example, Guo et al. (2018) revealed that miR-634 could reduce the cell migration and invasion in gastric cancer via targeting JAG1. In addition, Chen et al. (2017) found that miR-598 has been reported to decrease the cell migration and epithelial mesenchymal transition through inhibition of JAG1 in colorectal cancer. Interestingly, in our study, JAG1 was also verified as a target of miR-377-3p. Besides, we also indicated that the suppression of migration and invasion induced by miR-377-3p was alleviated by the JAG1 overexpression in ovarian cancer cells. Together, these findings indicate that miR-377-3p may decrease the migration and invasion by downregulation of JAG1 in ovarian cancer.

In conclusion, this study demonstrates that miR-377-3p overexpression inhibits the migration and invasion of ovarian cancer cells by a mechanism that involves suppression of the JAG1. This study provides a potential diagnostic and therapeutic target for ovarian cancer. Although miR-377-3p played an important role in ovarian cancer cells in our study, the effect of miR-377-3p/JAG1 axis on growth and invasion in other cancer cells was not explored. Therefore, in order to confirm the function of miR-377-3p in other cancer cells, additional experiments will be conducted in the near future.

## Compliance with ethical standards

**Conflict of interest** Liulin Tang, Bin Yang, Xiaolan Cao, Qin Li, Li Jiang and Dan Wang declare that they have no competing interests, and all authors should confirm its accuracy.

**Ethical approval** The experimental protocol was obeyed by World Medical Association Declaration of Helsinki. Informed consent was obtained from all individual participants prior to the study.

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