Long non-coding RNA PVT1 promotes the proliferation, migration and EMT process of ovarian cancer cells by regulating CTGF

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Abstract. Ovarian cancer remains one of the most common gynecological malignancies with a poor prognosis. The present study investigated the roles of long non-coding RNA plasmacytoma variant translocation 1 (lncRNA PVT1) in the regulation of the malignant phenotype of ovarian cancer cells, including cell proliferation, migration, invasion and epithelial-mesenchymal transition (EMT). SKOV3 and CAOV3 cells were transfected with small interfering RNA (siRNA) targeting lncRNA PVT1 (si-PVT1) or control siRNA and the si-PCT1 transfected cells were co-cultured with recombinant human connective tissue growth factor (rhCTGF). The proliferation, migration and invasion abilities of the cells were examined via Cell Counting Kit-8, colony formation, wound-healing and Transwell assays. The relative expression levels of lncRNA PVT1, CTGF, E-cadherin and vimentin were analyzed using reverse transfection-quantitative polymerase chain reaction, and western blotting was employed to detect the protein levels of CTGF, E-cadherin and vimentin. The expression of lncRNA PVT1 was significantly reduced in SKOV3 and CAOV3 cells following transfection with si-PVT1. In addition, the proliferation, migration and invasion abilities of SKOV3 and CAOV3 cells were repressed following lncRNA PVT1 knockdown. The knockdown of lncRNA PVT1 also reduced the expression of CTGF and vimentin, and increased the expression of E-cadherin. The changes in the proliferation, migration and invasion of the cells induced by transfection with si-PVT1 were partially attenuated in the presence of rhCTGF. Furthermore, co-culture with rhCTGF reversed the si-PVT1-induced changes in the expression of EMT-associated proteins. In conclusion, lncRNA PVT1 promotes the proliferation, migration, invasiveness and EMT process of ovarian cancer cells, and CTGF contributes to the effect of lncRNA PVT1.

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Introduction

Ovarian cancer is one of the most common gynecologic malignancies and advanced ovarian cancer has a very low 5-year survival rate, despite improvements in medical strategies in recent years (1,2). The high mortality is partially due to the lack of effective diagnostic markers for ovarian cancer at an early stage and the prevalence of diffuse intra-abdominal metastasis (3).

Long non-coding RNA plasmacytoma variant translocation 1 (LncRNA PVT1) is a non-coding RNA of >200 bp, which is located in the well-known cancer-associated chromosomal region 8q24 (4). It has been implicated in the biological processes of several cancers, including ovarian epithelial cancer (4). In addition, PVT1 has been suggested to be a marker of poor prognosis in several types of cancer, which can promote malignancy by modulating various biological processes, including epithelial-mesenchymal transition (EMT) (5,6). A previous study demonstrated that PVT1 is upregulated in ovarian cancer, and that a high level of PVT1 expression is associated with a poor prognosis in patients with ovarian cancer (7). However, the biological role and underlying mechanism of lncRNA PVT1 in ovarian cancer cells remain unclear.

Connective tissue growth factor (CTGF) is a secreted protein belonging to the cellular communication network (CCN) family (8). It plays an important role in the remolding of the extracellular matrix and the development of connective tissues such as those constituting the skeleton (8,9). The dysregulation of CTGF is implicated in the development of pathological conditions such as diabetic retinopathy and the progression of cancer (10,11). However, the regulatory

mechanisms controlling the expression of CTGF under pathological conditions require clarification.

In the present study, the functional role of lncRNA PVT1 in the proliferation, migration, invasion and EMT of the SKOV3 and CAOV3 human ovarian cancer cell lines was explored. In addition, the potential involvement of CTGF in the biological role of lncRNA PVT1 as a regulator of the malignant phenotype of ovarian cancer cells was also investigated.

Materials and methods

Cell culture and transfection. The SKOV3 and CAOV3 human ovarian cancer cell lines were obtained from Qilu Medical College of Shandong University. The cells were maintained in DMEM (Hyclone; Cytiva) supplemented with 10% fetal bovine serum (Hyclone; Cytiva), 100 U/ml penicillin and 100 mg/ml streptomycin (Biosharp Life Sciences) in a humidified incubator at 37˚C with 5% CO_2. Recombinant human CTGF (rhCTGF; PeproTech, Inc.; 500 mg/l) was added to the culture medium to examine its role in the cell phenotype.

For transfection, SKOV-3 and CAOV3 cells were seeded in 24-well plates at a density of $2x10^5$ cells/well. Then, 50 nM small interfering RNA (siRNA) targeting PVT1 (si-PVT1) or negative control siRNA (si-NC) was respectively transfected into cells at ambient temperature using Lipofectamine® 2000 (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions. Cells were subjected to further experiments 48 h after transfection. The sequence of the PVT1-specific siRNA was 5'-GGCACCTTCCAGTGGATT T-3'. The si-NC was scrambled siRNA with the following sequences: Sense, UGCUGACUCCAAAGCUCUGdTdT and anti-sense, CAGAGCUUUGGAGUCAGCAdTdT. The si-PVT1 and si-NC were purchased from Guangzhou Ruibo Biotechnology Co., Ltd.

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Total RNA was extracted from cells using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.). RT was performed to generate cDNA using a ReverTra Ace™ qPCR RT kit (Toyobo Life Science) at 42˚C for 1 h on a PCR machine. The relative expression level of each gene was measured using Thunderbird SYBR qPCR Mix (Toyobo Life Science) on a 7500 Real-Time PCR System (Applied Biosystems; Thermo Fisher Scientific, Inc.). The following thermocycling conditions were applied: 40 cycles of denaturation at 95˚C for 15 sec, primer annealing at 58˚C for 20 sec and extension at 72˚C for 20 sec. The relative expression levels of the target genes were normalized to GAPDH using the $2^{-\Delta\Delta Cq}$ method (12). The primer sequences used are shown in Table I.

Cell Counting Kit-8 (CCK-8) proliferation assay. The transfected cells ($5x10^3$ cells/well) were seeded in 96-well plates. The cells were cultured for 0, 24, 48, 72, 96 and 120 h, respectively. After culture, 10 μl CCK-8 solution (Dojindo Laboratories, Inc.) was added to each well and the cells were further incubated for 1 h. The absorbance at 450 nm was measured using a microplate reader (Thermo Fisher Scientific, Inc.).

Table I. Quantitative polymerase chain reaction primer sequences.

Genes		Primer sequences (5'-3')
PVT1	F	TCTGGGGAATAACGCTGGTG
	R	CTTCACCAGGAAGAGTCGGG
CTGF	F	ACCGACTGGAAGACACGTTTG
	R	CCAGGTCAGCTTCGCAAGG
E-cadherin	F	TGAAAACAGCAAAGGGCTTGGA
	R	GCAGTGTCTCTCCAAATCCGA
Vimentin	F	CTGGATTCACTCCCTCTGGT
	R	CGTGATGCTGAGAAGTTTCG
GAPDH	F	GGAGCGAGATCCCTCCAAAAT
	R	GGCTGTTGTCATACTTCTCATGG

PVT1, plasmacytoma variant translocation 1; CTGF, connective tissue growth factor; F, forward; R, reverse.

Colony formation assay. The transfected cells ($5x10^2$ cells/well) were seeded in 6-well plates and co-cultured with or without rhCTGF for 14 days. The cell medium was refreshed every 3 days. On day 14, the cells were fixed with 4% paraformaldehyde at room temperature for 10 min and then stained with 0.5% crystal violet (Beyotime Institute of Biotechnology) for 20 min at ambient temperature. Subsequently, the number of colonies (with >50 cells considered to be a colony) was counted manually under a Leica AM6000 microscope (Leica Microsystems GmbH).

Wound-healing assay. Transfected SKOV-3 and CAOV3 cells with or without rhCTGF were seeded into 6-well plates at a density of $5.0x10^5$ cells/well. Cells were serum-starved for 18 h. When the degree of confluence reached ~90%, a scratch wound was created in the cell layer using a sterile 200-μl pipette tip in the central region of each well. The wounded cells were incubated at 37˚C for 48 h. Cell images were then captured using an inverted light microscope (Leica AM6000). The distance that the cells migrated was analyzed using ImageJ software (version 1.8.0) (National Institutes of Health). The migration rate was calculated as ratio of the wound distance at 48 h to the wound distance at 0 h.

Transwell migration and invasion assays. The migration and invasion ability of the ovarian cancer cells was detected using a 24-well Transwell chamber (Costar; Corning, Inc.) with an 8.0-μm pore size. The transfected cells were suspended in serum-free DMEM and inoculated in the upper chamber at a density of $5.0x10^5$ cells/well. Matrigel-coated chambers (BD Biosciences) were used for the invasion assay, while chambers without Matrigel coating were used for the migration assay. The chamber coating was performed at 37˚C for 30 min. Medium containing 10% FBS was added to the lower chamber with or without rhCTGF. After 48 h of incubation at 37˚C, the migratory or invading cells on the membrane were fixed with methanol and stained with 0.1% crystal violet (Beyotime Institute of Biotechnology) at ambient temperature for 20 min. The number of migrating and invading

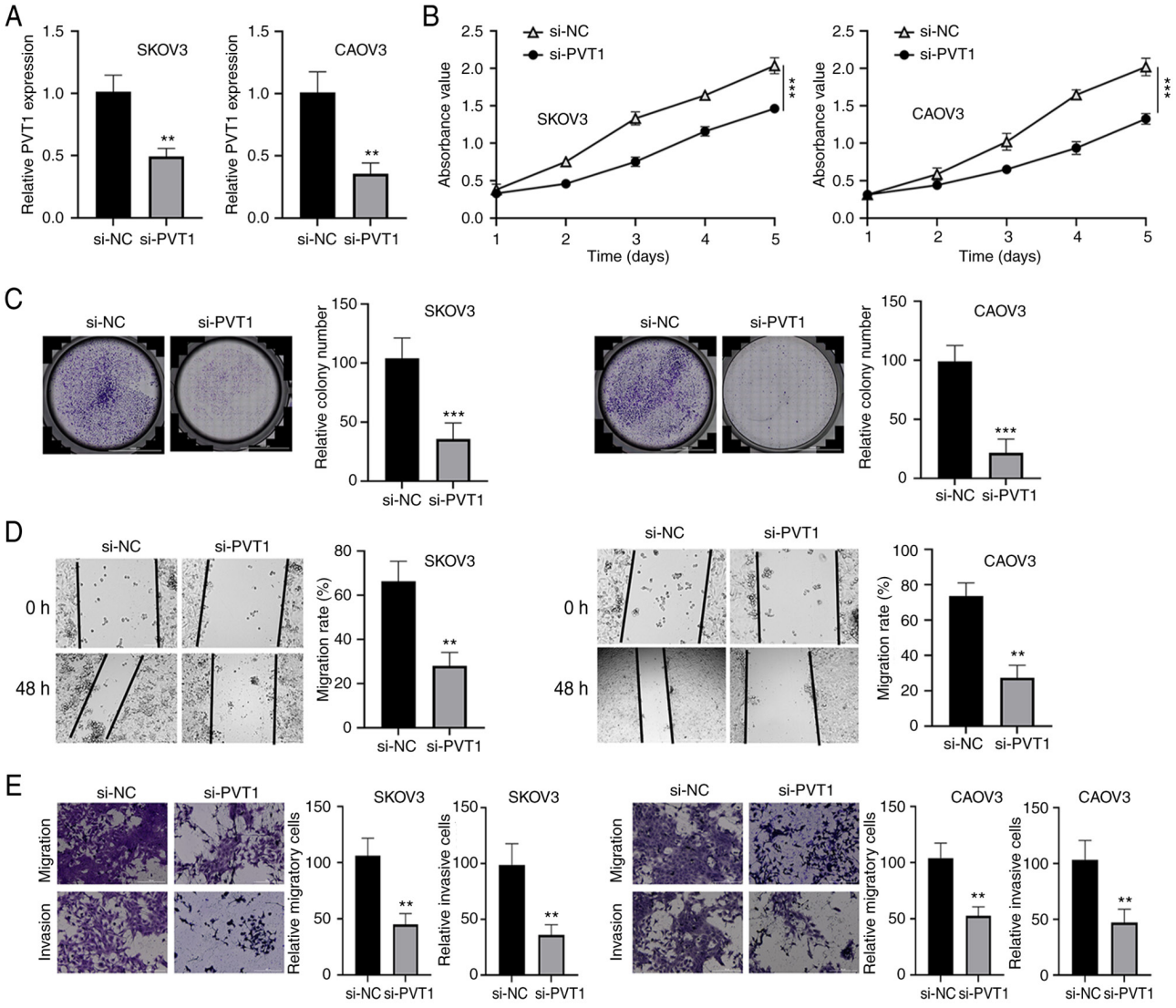

Figure 1. Knockdown of PVT1 suppresses the proliferation, migration and invasion ability of SKOV3 and CAOV3 cells. (A) The expression level of PVT1 in SKOV3 and CAOV3 cells transfected with si-NC or si-PVT1 was measured by reverse μtranscription-quantitative polymerase chain reaction. (B) Cell Counting Kit-8 and (C) colony formation assays were conducted to evaluate the cell proliferation of SKOV3 and CAOV3 cells transfected with si-NC or si-PVT1. (D) Wound-healing (scale bar, 80 μm) and (E) Transwell assays were employed to assess the migration and invasion abilities of SKOV3 and CAOV3 cells transfected with si-NC or si-PVT1 (scale bar, 200 μm). Two-way ANOVA was employed for the statistical analysis of the data in (B), and the significance level represents the total interaction of these two curves with regard to time points and treatments. Data are presented as the mean ± standard deviation. **P<0.01, ***P<0.001. PVT1, plasmacytoma variant translocation 1; si, small interfering siRNA; NC, negative control.

cells was counted in 5 random fields using a Leica AM6000 microscope.

Western blotting. The protein levels of CTGF, E-cadherin and vimentin were examined by western blotting. Total protein was extracted ovarian cancer cells using RIPA lysis buffer containing protease inhibitor cocktail (Thermo Fisher Scientific, Inc.). Cells suspended in the RIPA buffer were lysed on ice for 10 min and then centrifuged at 13,200 x g for 10 min. The supernatant containing total protein lysate was quantified using a BCA Protein assay kit (Beyotime Institute of Biotechnology,). Then, 10 μg protein sample per lane was loaded for separation on 12% gels by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). The separated proteins on the SDS-PAGE gel were transferred onto polyvinylidene fluoride membranes (Bio-Rad Laboratories, Inc.). After blocking with 5% skimmed milk for 1 h at ambient temperature, the membrane was incubated with the following primary antibodies at 4˚C overnight: Anti-CTGF (ab5097; dilution 1:1,000; Abcam,), E-cadherin (ab231303; dilution 1:1,500; Abcam), vimentin (ab92547; dilution 1:1,000; Abcam) and anti-GAPDH (BM1985; dilution 1:2,500; Boster Biological Technology) The membranes were washed three times with TBS with 2.5% Tween 20 (TBST) buffer and then incubated with HRP-conjugated secondary antibody (#7074; dilution 1:3,000; Cell Signaling Technology, Inc.) at room temperature for 1 h. After further washes with TBST buffer, the protein signals were developed using Super ECL Plus Detection Reagent (Tanon Science and Technology Co., Ltd.) and images captured using a gel imager system (Bio-Rad Laboratories, Inc.). The western blot experiment was performed once for each condition.

Statistical analysis. SPSS 25.0 (IBM Corp.), ImageJ and GraphPad Prism 8 (GraphPad Software, Inc.) were used for data

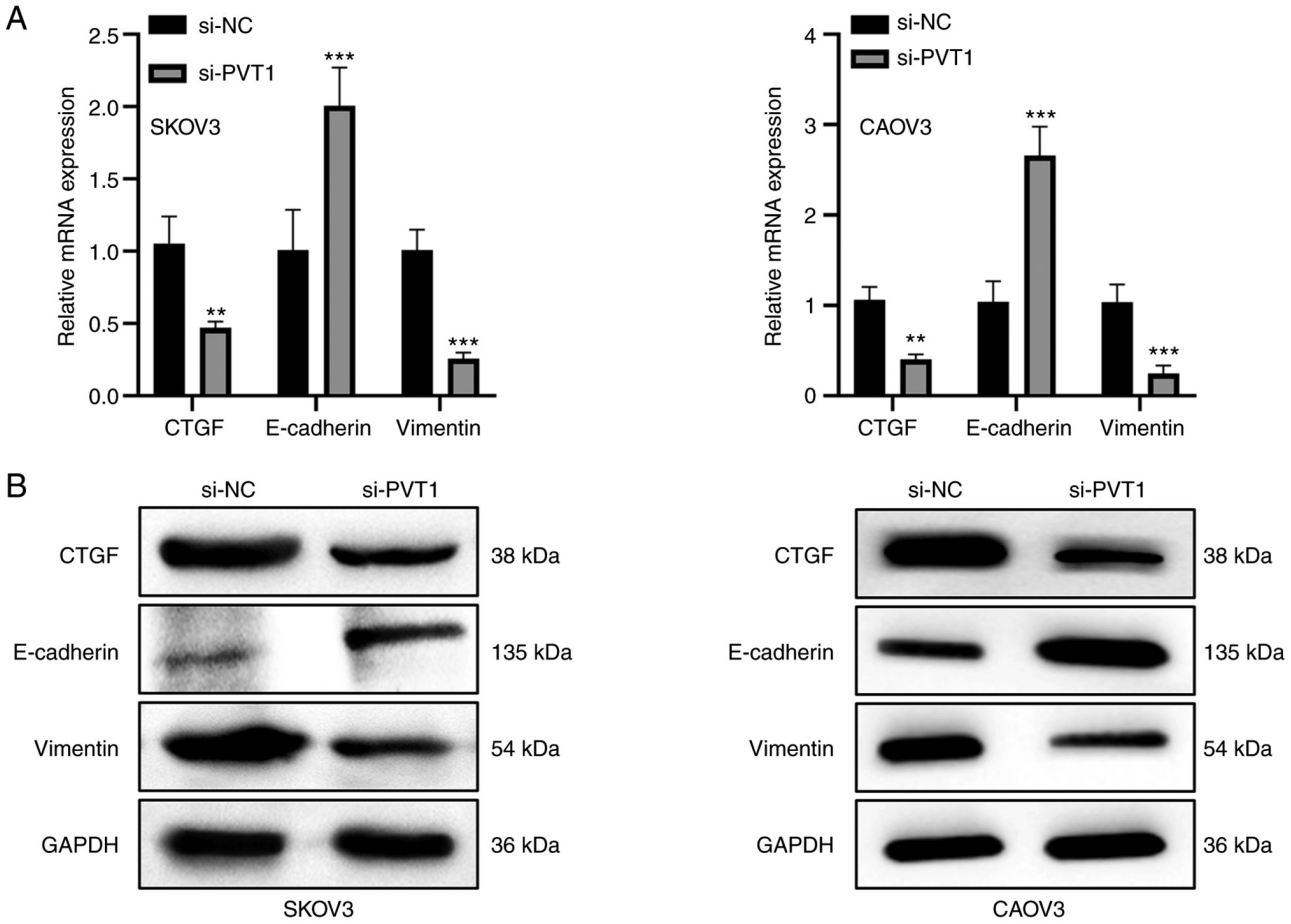

Figure 2. Knockdown of PVT1 regulates the expression of CTGF and EMT-related genes in SKOV3 and CAOV3 cells. The mRNA and protein levels of CTGF and EMT-related genes in SKOV3 and CAOV3 cells transfected with si-PVT1 or si-NC were examined by (A) RT-qPCR and (B) western blotting. RT-qPCR data are presented as the mean ± standard deviation. **P<0.01, ***P<0.001. PVT1, plasmacytoma variant translocation 1; CTGF, connective tissue growth factor; EMT, epithelial-mesenchymal transition; si, small interfering siRNA; NC, negative control; RT-qPCR, reverse transcription-quantitative polymerase chain reaction.

analysis. Data are presented as the mean ± standard deviation of three independent experiments. Unpaired Student's t-test was used for comparisons between two groups. Comparisons among multiple groups were analyzed using one-way analysis of variance (ANOVA) with Tukey's post hoc test for subsequent pairwise comparisons. Comparisons of data at multiple time points were examined using two-way ANOVA, with Bonferroni's post hoc test. P<0.05 was considered to indicate a statistically significant difference.

Results

Silencing PVT1 suppresses the proliferation, migration and invasion ability of ovarian cancer cells. To investigate the biological roles of lncRNA PVT1 in the phenotype of ovarian cancer cells, si-PVT1 and si-NC were transfected into SKOV3 and CAOV3 cells. The transfection of si-PVT1 significantly reduced the expression of PVT1 in SKOV3 and CAOV3 cells compared with that in cells transfected with si-NC (Fig. 1A). Comparison of the transfected cells in CCK-8, colony formation, wound healing and Transwell assays revealed that the proliferation, migration and invasion abilities of both cell lines were significantly impaired following PVT1 silencing (Fig. 1B-E). These results suggest that lncRNA PVT1 contributes to the malignant phenotype of ovarian cancer cells.

PVT1 knockdown reduces CTGF expression and regulates the levels of EMT-related genes. To investigate whether PVT1 modulate the EMT process, the level of CTGF and EMT-associated genes, namely E-cadherin and vimentin, were examined using RT-qPCR and western blotting. In SKOV3 and CAOV3 cells, PVT1 silencing suppressed the expression of CTGF and vimentin but increased the expression of E-cadherin at the mRNA and protein levels (Fig. 2). These results indicate that the downregulation of PVT1 inhibits the expression of CTGF and suppresses the EMT process.

rhCTGF partially abrogates the inhibitory effects of PVT1 knockdown. As CTGF expression was found to be decreased by PVT1 knockdown, whether CTGF is a downstream mediator of PVT1 function was investigated via the addition of rhCTGF to the cell culture. Consistent with the previous results, the proliferation, migration and invasion abilities of SKOV3 and CAOV3 cells were repressed by PVT1 siRNA. However, the inhibitory effect was partially attenuated by treatment with rhCTGF (Fig. 3). In addition, the rhCTGF treatment also attenuated the reduction in the expression levels of CTGF

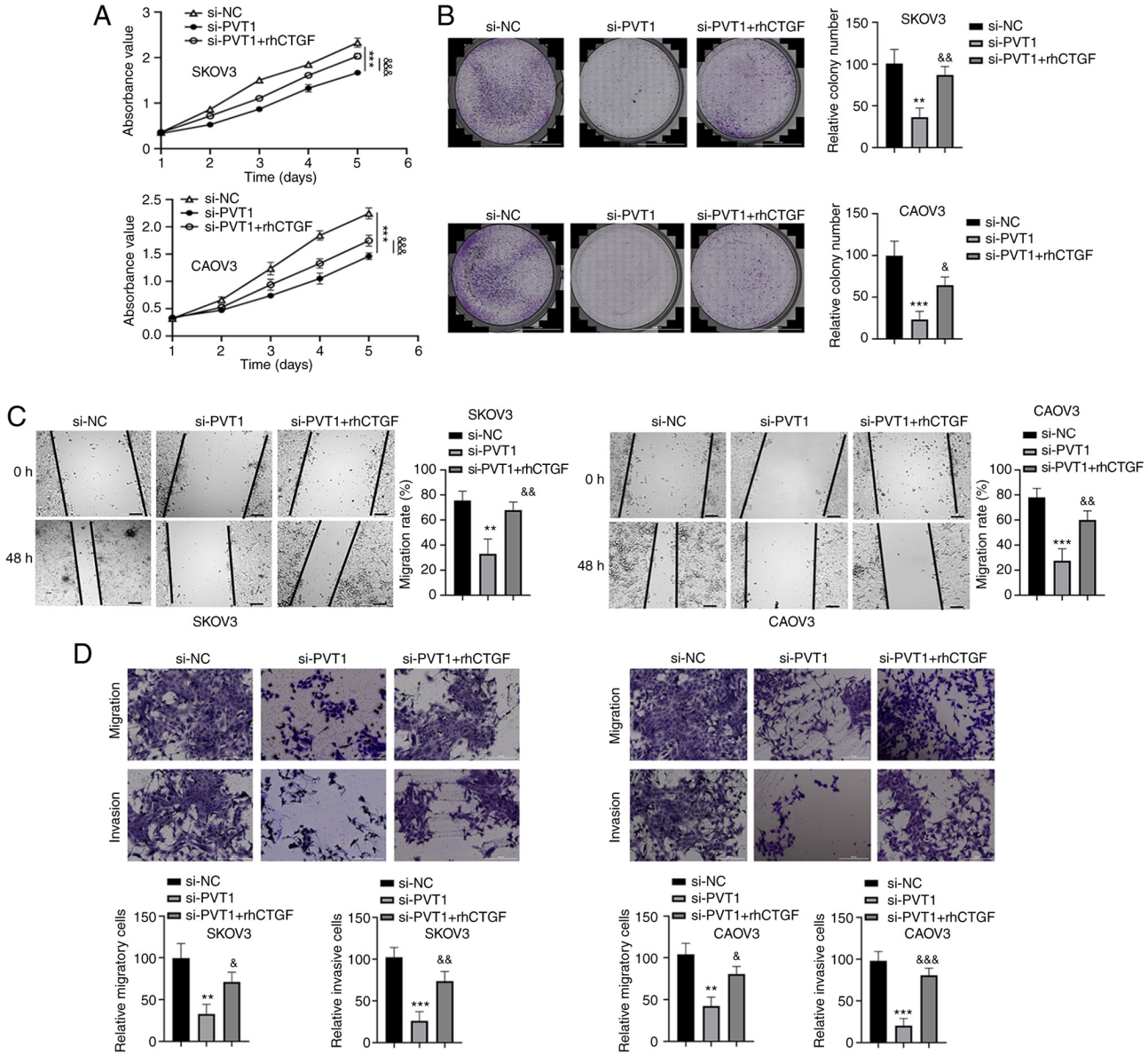

Figure 3. rhCTGF partially abrogates the inhibitory effects of PVT1 knockdown. (A) Cell Counting Kit-8 proliferation and (B) colony formation assays were used to evaluate the cell proliferation of SKOV3 and CAOV3 cells transfected with si-NC or si-PVT1, or si-PVT1 with rhCTGF treatment. (C) Wound-healing (scale bar, 80 μm) and (D) Transwell assays were performed to evaluate the migration and invasion abilities of SKOV3 and CAOV3 cells transfected with si-NC or si-PVT1, or si-PVT1 with rhCTGF treatment (scale bar, 80 μm). The data in (A) were analyzed by two-way ANOVA with Bonferroni post hoc tests. Data are presented as the mean ± standard deviation. **P<0.01 and ***P<0.001 vs. si-NC; $^{\&}$P<0.05, $^{\&\&}$P<0.01 and $^{\&\&\&}$P<0.001 vs. si-PCT1. rhCTGF, recombinant human connective tissue growth factor; PVT1, plasmacytoma variant translocation 1; si, small interfering siRNA; NC, negative control.

and vimentin induced by PVT1 knockdown, and reduced the PVT1 knockdown-induced increase in the expression level of E-cadherin (Fig. 4). Together, these results suggest that CTGF mediates the biological effects of lncRNA PVT1 in ovarian cancer cells.

Discussion

The lncRNA PVT1 has been recognized as an oncogenic non-coding RNA and is a potential prognostic marker for various cancers. It has been implicated in the development and progression of various tumors, including ovarian cancer (13,14). However, its functional roles and regulatory mechanisms in ovarian cancer remain unclear. Previous studies suggest that lncRNA PVT1 is involved in the regulation of EMT processes in pancreatic, prostate and breast cancer (6,15,16). Chen *et al* (17) demonstrated that PVT1 contributes to regulation of the EMT process by silencing microRNA-214 in ovarian cancer. In addition, other studies have demonstrated that PVT1 regulates the expression of CTGF (18,19). The present study clarified the roles of lncRNA PVT1 and CTGF and their relationship in ovarian cancer.

CTGF is an extracellular factor of the CCN family, members of which are implicated in remodeling the extracellular matrix and signal transduction (11,20). The upregulation of CTGF has been reported to promote cancer initiation, progression and metastasis via the augmention of cell proliferation, migration, invasion, drug resistance and the EMT process (11,20). In addition, Yang *et al* (21) reported that

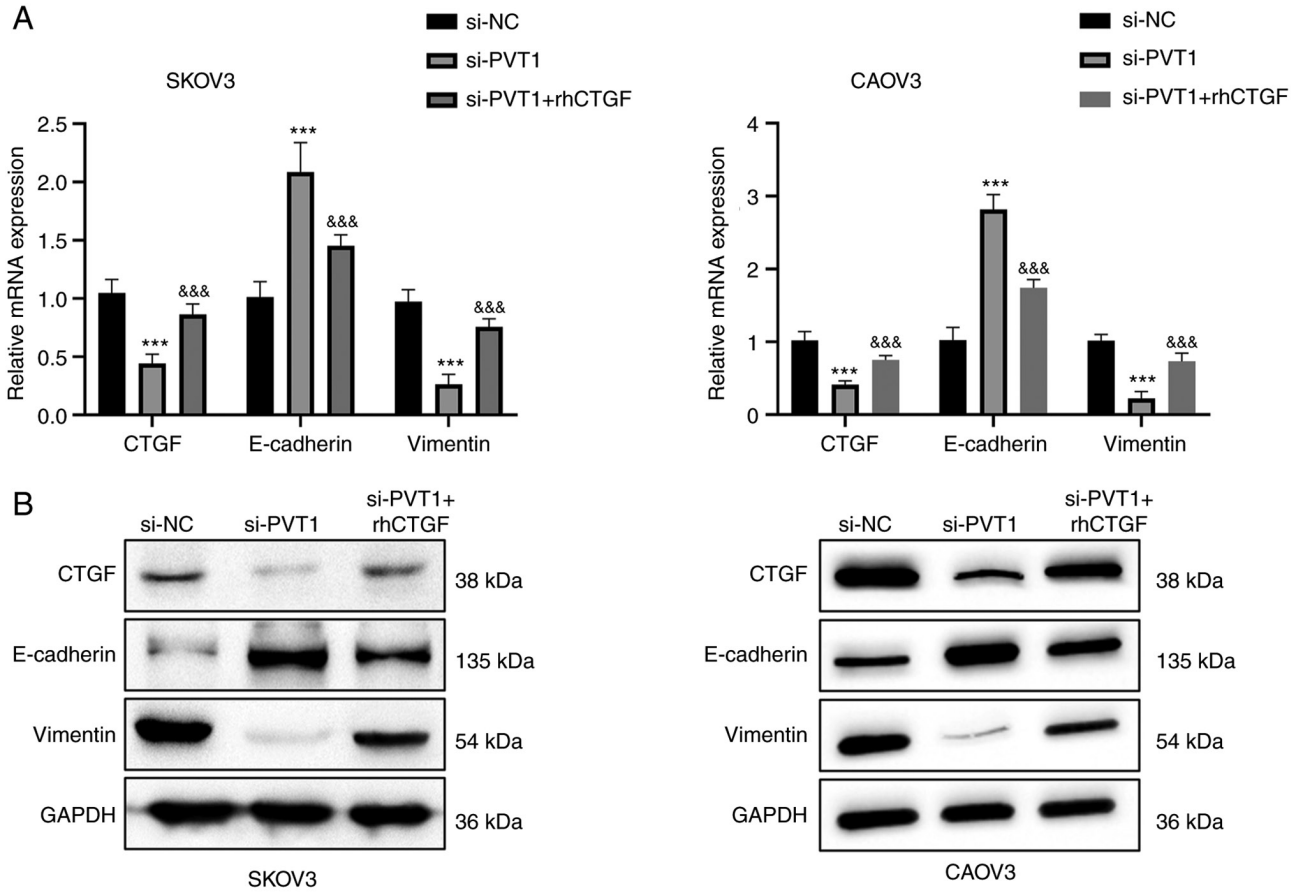

Figure 4. PVT1 regulates the expression of EMT-related proteins via CTGF. CTGF and EMT-related proteins were examined by (A) RT-qPCR and (B) western blotting in SKOV3 and CAOV3 cells. RT-qPCR data are presented as the mean ± standard deviation. ***P<0.001 vs. si-NC; $^{\&\&\&}$P<0.001 vs. si-PCT1. PVT1, plasmacytoma variant translocation 1; EMT, epithelial-mesenchymal transition; CTGF, connective tissue growth factor; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; si, small interfering siRNA; NC, negative control.

CTGF is a key factor dictating the malignancy and EMT processes in ovarian cancer cells. The EMT process has been proposed to be a key event in the invasion and metastatic dissemination of cancer cells, during which cells gradually gain enhanced mobility and invasive potential; the ability of ovarian cancer cells to invade and metastasize is enhanced through EMT (22,23).

In the present study, it was demonstrated that the proliferation, migration and invasion abilities of SKOV3 and CAOV3 cells were inhibited following PVT1 knockdown, which was consistent with previous studies (24-26). In addition, the present study showed that CTGF and the mesenchymal marker protein vimentin were downregulated in cells with PVT1 knockdown, while the epithelial marker E-cadherin was upregulated. Importantly, these effects were partially attenuated when the cells were treated with rhCTGF. These data indicate that lncRNA PVT1 promotes the proliferation and migratory abilities of ovarian cancer cells via the regulation of CTGF expression, which may also induce EMT in the progression of ovarian cancer.

However, the present study is limited by the lack of clinical samples to validate the regulation of CTGF by lncRNA PVT1 in ovarian cancer tissues. The regulation of CTGF by lncRNA PVT1 during the progression of ovarian cancer also merits evaluation in a xenograft mouse model. In addition, the mechanisms underlying the dysregulation effect of lncRNA PVT1 require further study in ovarian cancer tissues and cell lines.

In summary, lncRNA PVT1 serves as an oncogenic factor by facilitating the proliferation, migration, invasiveness and EMT process in ovarian cancer cells via the regulation of CTGF. Therefore, lncRNA PVT1 and CTGF may be considered as therapeutic targets to limit the progression of ovarian cancer.

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Availability of data and materials

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

Authors' contributions

LD, HW, YG, SW and WW contributed to manuscript drafting, writing and revision, as well as study concept and design. LD, HW, YG and SW were responsible for the collection, assembly and interpretation of the data and figure drawing. All authors read and approved the final manuscript. LD and WW confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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