



Expression of *YAP* in endometrial carcinoma tissues and its effect on epithelial to mesenchymal transition

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Background: Yes-associated protein (*YAP*) can function as a cancer suppressor or a cancer promoter. Studies have proved that *YAP* can collaborate with other genes to accelerate cancerous epithelial to mesenchymal transition (EMT), but little is known about how *YAP* performs in endometrial carcinoma (EC).

Methods: Real time-polymerase chain reaction (RT-PCR) and western blot (WB) were used to quantify the relative mRNA and protein levels of *YAP* in 50 EC tissue samples and 20 normal endometrial tissues in the proliferative phase. The association between *YAP* expression level and EC index (clinical stage, histologic grade, and lymphatic metastasis) was analyzed. *YAP* interference and overexpression vectors were constructed. RT-PCR and WB were used to quantify the mRNA and protein levels of *YAP* and EMT markers in the normal control group (N), the negative control group (NC), and the *YAP* interference and overexpression group. Cell counting kit-8 (CCK8) assay and scratch test were performed to evaluate the proliferation, invasion, and migration of EC cells after *YAP* interference and overexpression.

Results: The mRNA and protein levels of *YAP* increased in EC tissues ($P < 0.01$) and showed differences associated with histologic grade and lymphatic metastasis, not with the clinical stage ($P > 0.01$). CCK8 assay showed that the proliferation of EC cells was inhibited after *YAP* interference and increased after *YAP* overexpression. The cell wound healing test displayed that the migration of EC cells was inhibited after *YAP* interference and increased after *YAP* overexpression. RT-PCR and WB found the mRNA and protein levels of E-cadherin (an EMT marker) increased ($P < 0.01$), but those of other markers (N-cadherin, Vimentin) dropped ($P < 0.01$) after *YAP* interference; however, these trends were inverted after *YAP* overexpression ($P < 0.01$).

Conclusions: *YAP* serves as an EC-promoting gene that may regulate the EMT and other EC-related processes via promoting the proliferation, invasion, and migration of EC cells.

Keywords: Yes-associated protein (*YAP*); expression; endometrial carcinoma (EC); epithelial to mesenchymal transition (EMT)

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Introduction

Annually and globally, endometrial carcinoma (EC), a common gynecological epithelial malignancy, victimizes over 200,000 females, a population that makes up 6% of all females with malignancies (1). EC has complex pathogenesis co-regulated by genetic and environmental factors. Among them, genetic mutation plays a vital role. The mutation and polymorphism of protooncogenes, cancer suppressor genes, estrogen-related genes, estrogen/progesterone receptor genes can increase the risk of EC (2). The cancer cells invade the myometrium in the early stages of EC, but the recurrence, mortality, and prognosis of patients are mainly decided by the cancer cells' direct extension/penetration, lymphatic metastasis, or migration to distal organs (3). Therefore, genetically clarifying the regulatory mechanism hiding behind EC development may supply a therapeutic target for EC.

Human yes-associated protein (*YAP*) was first found as researchers were screening the genetic mutants in fruit flies in 1994, located in 11q22 amplicon (4). *YAP* has no DNA-binding sites, but its structural domains and specific amino acid sequences (5) enable *YAP* to interact with various proteins (like transcriptional factors in the TEAD family, cyclin E) in the regulation of signaling pathways. Recent studies have evaluated the aberrantly high expression of *YAP* that facilitates the development of pancreatic ductal adenocarcinoma, serous ovarian carcinoma, pulmonary small cell carcinoma, urinary bladder carcinoma (6-9). Wang *et al.* found that *YAP* promoted the malignancy of endometrial cancer cells via regulation of IL-6 and IL-11 (10). In addition, Konno *et al.* confirmed that ASPP2 suppression promoted malignancy via LSR and *YAP* in human endometrial cancer (11). However, Yuan *et al.* (12) discovered that the *YAP* gene was deficiently expressed in invasive breast carcinoma, showing its role as a suppressor, which was consequently confirmed by the immunohistochemical analysis performed by Jaramillo-Rodríguez *et al.* (13).

YAP acts as a powerful regulator in epithelial to mesenchymal transition (EMT), even cancerous invasion and migration (14). During EMT, epithelial cells lose their original morphological characteristics and differentiate into mesenchymal cells that have already gained a spindle shape and motility. Biochemically, epithelial cell markers are expressed and transformed into mesenchymal markers, like E-cadherin and its counterpart N-cadherin. Meanwhile, Vimentin is also abnormally expressed. The present

study verified that *YAP* regulates the EMT and other biological processes involved in EC through promoting the proliferation, invasion, and migration of EC cells. We present the following article in accordance with the MDAR reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-3155>).

Methods

Samples

A total of 52 EC tissue samples and 20 normal endometrial tissue samples were prepared. The EC tissues were obtained from patients (ages 38–55 years, mean 45.3 years) having undergone comprehensive staging laparotomy at the First Affiliated Hospital of Anhui Medical University. The first treatment the patients received was surgery: extra fascial abdominal radical/extensive hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy. The patients did not receive chemotherapy, radiotherapy, and hormone therapy before the surgery. The ECs were staged according to the staging system released by the International Federation of Gynecology and Obstetrics (FIGO): stage I, 22 cases; stage II, 20 cases, stage III, 10 cases. Of these 52 cases, 43 showed no lymphatic metastasis. The EC was histologically graded according to the WHO classification system [2003]: grade 1, 21 cases; grade 2, 7 cases; grade 3, 24 cases. The patients aged 38–55 years (average of 45.3 years).

A normal control group was constructed with 20 normal endometrial tissue samples provided by the Hysteroscopy Department of the hospital. These tissues were obtained from the proliferative-phase endometrium of outpatient-hysteroscopy-treated patients (ages 38–54 years, mean 43.4 years) for subserous hysteromyoma (12 cases) or lodged contraceptive rings (8 cases). Intraoperative and postoperative pathological examination confirms the normality of all the tissues.

The ethics committee approved the sampling procedures of the Affiliated Hospital of Anhui Medical University. All the patients presented their informed consent. All procedures performed in studies involving human participants were in accordance with the Helsinki Declaration (as revised in 2013).

Cell culture and plasmid transfection

HEC-1-A and Ishikawa cells (BeNa Culture Collection,

China) were allowed to thaw and then cultured with DMEM medium (Gibico, USA) containing 10% fetal bovine serum in an incubator (37 °C, 5% CO₂). Cell passage was allowed once every 3–4 days. From the information on *YAP* (NM_1130145) in GenBank, three *YAP*-specific shRNA sequences (GV102) and Shanghai Genechem Co. Ltd constructed one eukaryotic expression vector (Shanghai, China).

Lipofectamine 2000 was used to transfect *YAP*-shRNAI, *YAP*-shRNAII, and *YAP*-shRNAIII into Ishikawa cells. The normal control group and *YAP*-shRNA transfection group were set up. GV230/*YAP* was transfected into HEC-1-A cells. The normal control group and GV230 transfection group were set up. A standard protocol was performed in triplicate.

RT-PCR

Total RNA was extracted from the cells using the DP430 kits and the tissues using DP431 kits provided by (Tiangen Biotech Co. Ltd., Beijing, China). The ultraviolet spectrophotometer was used for RNA-seq analysis. The RNA was reverse transcribed into cDNA using reverse transcription kits (Thermo Fish, USA). The RT-PCR kit was used to detect the expression of the *YAP* gene, E-cadherin, and Vimentin. (Glyceraldehydes phosphate dehydrogenase) GAPDH was used as an internal control. Primers of *YAP* gene (forward: 5'-TGACCCTCGTTTTGCCATGA-3; reverse: 5'-GTTGCTGCTGGTTGGAGTTG-3'), GAPDH (forward: 5'-CTTCTTTTGGCTCGCCAGCC-3'; reverse: 5'-GCCCAATACGACCAAATCCGT-3'); E-cadherin (forward: 5'-TCGCTTACACCATCCTCAGC-3'; reverse: 5'-GGAAACTCTCTCGGTCCAGC-3'); N-cadherin (forward: 5'-AACAGCAACGACGGGTTAGT-3'; reverse: 5'-CAGACACGGTTGCAGTTGAC-3'); Vimentin (forward: 5'-AGGCGAGGAGAGCAGGATTT-3'; reverse: 5'-AGTGGGTATCAACCAGAGGGA-3').

RT-PCR was performed (95 °C for 30 s, 95 °C for 5 s, 60 °C for 34 s; 40 cycles). The gene expression was calculated with the $\Delta\Delta$ Ct method in each group. Relative quantification = $2^{-\Delta\Delta Ct}$. A standard protocol was performed in triplicate for all primers.

Western blot (WB)

Total protein was extracted with radio-immunoprecipitation

assay (RIPA), quantified with bicinchoninic acid (BCA), injected into the well (50 mcg/well) on a sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) gel. After electrophoretic separation, the protein was moved to the PVDF membrane. Then, the protein was stored at room temperature for 1.5 hours, incubated with primary antibodies at 4 °C overnight, and with secondary antibodies at room temperature for 1 hour. At last, enhanced electrochemiluminescence (ECL) plus developer was applied to develop X-ray films. Quantity One software was used to analyze the grey value (pixel density) of each protein band. The expression level of the protein of interest = grey value of protein of interest/grey value of GAPDH of interest.

Cell wound healing assay

The cells were seeded into a 6-well dish. A 10 µm razor blade in a vertical line was used on the dish surface to create the scratch. Three eye-piece fields were randomly selected to capture images at 0 hours, 24 hours, and 48 hours during the assay. The migration rate of cells was measured. The migration rate = (scratch width at 0 hours – width of the scratch at 24 hours/48 hours)/scratch width at 0 hours.

CCK8 cell proliferation assay

The cells were seeded in a 96-well plate (2×10^5 cells/well), put in an incubator for 24 hours at 37 °C, and 5% CO₂. The same standard protocol was duplicated eight times. According to the CCK8 kit (Bestbio Co. Ltd., Shanghai, China), 10 µL of CCK8 solution was injected into each well and incubated for 2 hours at 37 °C and 5% CO₂. Absorbance was detected at a wavelength of 450 nm. The rate of proliferation = $(OD_{\text{control group}} - OD_{\text{untreated group}}) - (OD_{\text{treatment group}} - OD_{\text{untreated group}}) / (OD_{\text{control group}} - OD_{\text{untreated group}}) \times 100\%$.

Statistical analysis

PSS 13.0 was used to analyze data presented as mean ± SD. The enumerated data were described with percent. Chi-square was performed for comparison. Measurement data were presented as mean ± SD. One-way ANOVA was performed to compare multiple groups; the LSD *t*-test was done for the between-group comparison. P < 0.01 was considered significantly different.

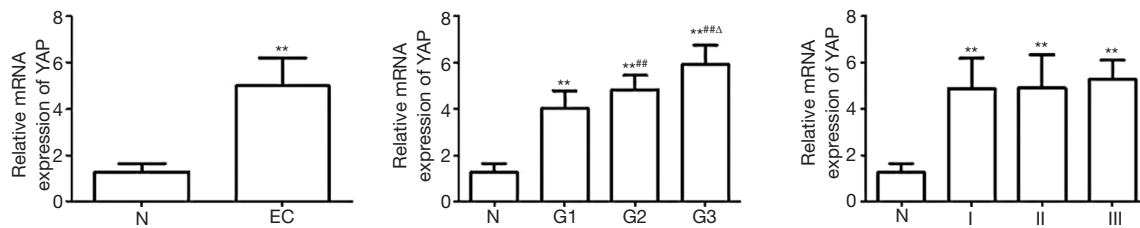


Figure 1 mRNA expression of *YAP* in EC tissues and normal endometrial tissues. **, compared with normal tissues, $P < 0.01$; ##, compared with G1 tissues, $P < 0.01$; ^, compared with G2 tissues, $P < 0.05$. The mRNA expression level of *YAP* rose in EC tissue and was positively correlated with pathologic grade. However, this difference was not stage-dependent. N, normal endometrium; G1, G1 endometrium; G2, G2 endometrium; G3, G3 endometrium; I, stage I endometrium; II, stage II endometrium; III, stage II endometrium. *YAP*, yes-associated protein; EC, endometrial carcinoma.

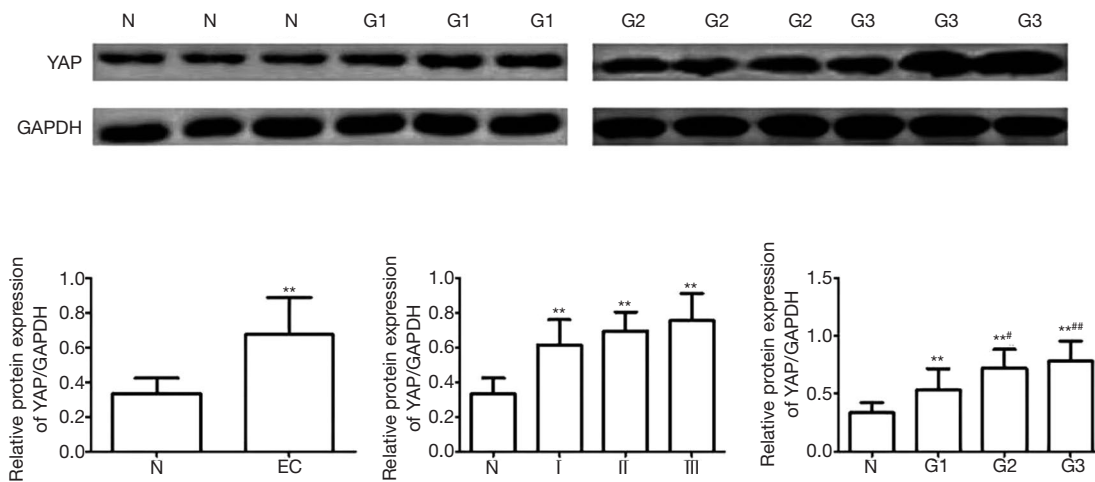


Figure 2 Protein expression of *YAP* gene in endometrial cancer and normal endometrial tissues. The protein expression level of *YAP* rises in EC tissues and is positively correlated with pathologic grade. However, this difference was not stage-dependent. **, compared with normal tissues, $P < 0.01$; ##, compared with G1 tissues, $P < 0.01$; #, compared with G1 tissues, $P < 0.05$. N, normal endometrium; G1, G1 endometrium; G2, G2 endometrium; G3, G3 endometrium; I, stage I endometrium; II, stage II endometrium; III, stage II endometrium. *YAP*, yes-associated protein; EC, endometrial carcinoma.

Results

Expression of *YAP* in EC tissues

The expression level of *YAP* in EC tissues was significantly higher than that in normal tissues in the proliferative phase (4.998 ± 1.173 vs. 0.841 ± 0.222 ; $P < 0.01$) (Figures 1,2). As shown by the pathological examination, the mRNA and protein expression levels of *YAP* increased in all three grades of tissues (G1, G2, G3). As shown by the between-group comparison, the mRNA expression level of *YAP* shows between-group differences ($P < 0.01$). Considering the clinical stages of EC, the *YAP* expression on both levels

significantly increased in three stages (stage I, stage II, stage III), but no between-group difference showed up ($P > 0.01$). The expression of *YAP* on both levels in the lymphatic metastasis group and none lymphatic metastasis group was quantified as 5.582 ± 0.633 vs. 3.582 ± 0.533 , 0.826 ± 0.346 vs. 0.396 ± 0.157 ($P < 0.01$) (Table 1).

Proliferation, invasion, and migration of EC cells promoted by *PAP* in vitro

YAP interference and overexpression vectors were constructed. *YAP*-shRNAII with high interference efficacy

Table 1 Expression of *YAP* in EC tissues of different clinical stages and pathologic grades

Stages and grades	Groups	Cases	YAP protein expression			YAP mRNA expression		
			$\bar{x}\pm SD$	F	P	$\bar{x}\pm SD$	F	P
Pathologic grades	G1	21	0.534±0.184	10.68	0.00	4.021±0.766	30.660	0.000
	G2	7	0.720±0.162			4.839±0.602		
	G3	24	0.781±0.172			5.900±0.840		
FIGO stages	I	22	0.615±0.242	1.718	0.19	4.868±1.318	0.341	0.713
	II	20	0.696±0.109			4.912±1.426		
	III	10	0.755±0.251			5.275±0.832		
Lymphatic metastasis	Present	9	0.826±0.346		0.00	5.582±0.633		0.000
	Absent	43	0.396±0.157			3.582±0.533		

The mRNA expression level of *YAP* peaked in G3 and showed a difference between groups of different grades ($P<0.01$). Nevertheless, its expression on both levels showed no grade- or stage-related difference ($P=0.713, 0.19$). *YAP*, yes-associated protein; EC, endometrial carcinoma.

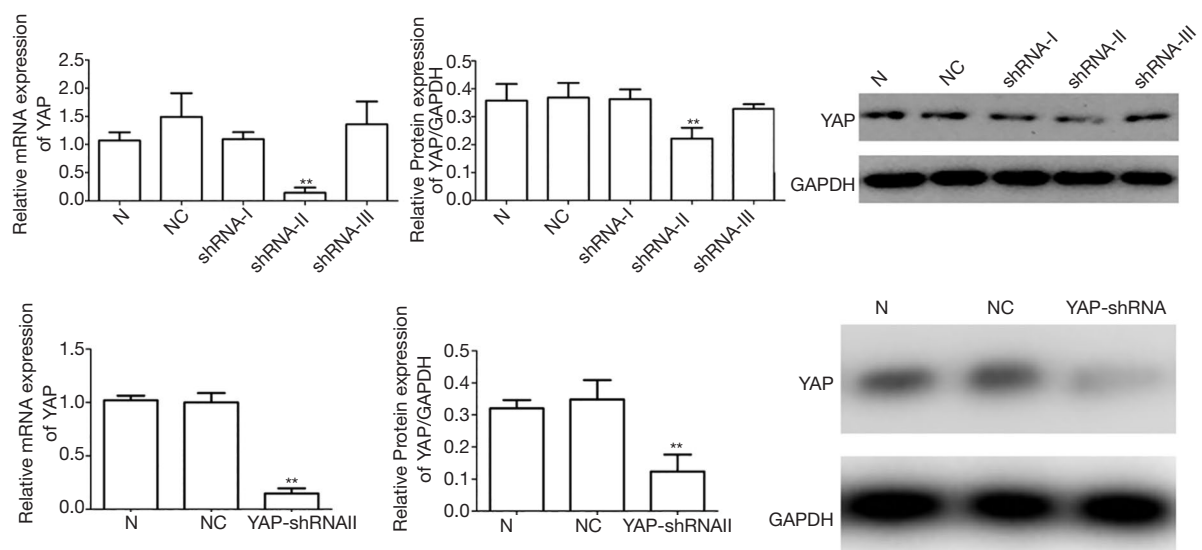


Figure 3 Selection of interference vector for downregulating *YAP* expression and construction of stable cell line. Ishikawa cells are transfected with three strains of *YAP*-shRNAII. *YAP*-shRNAII that showed the highest inference efficacy was used to construct a stable cell line. N, normal endometrium. *, compared with normal group, $P<0.05$; **, compared with normal group, $P<0.01$. *YAP*, yes-associated protein.

was selected for functional assays (Figure 3). Ishikawa and HEC-1A cell lines were transfected (transfection efficiency $>75\%$). Overexpressed *YAP* was stably transfected into HEC-1A cell lines (Figure 4). As shown by the results of CCK8 assay, compared to the normal control group, at 12 after downregulating *YAP* expression, the proliferative ability of Ishikawa cells began to drop. However, at

24 hours after upregulating *YAP* expression, this ability of HEC-1A cells began to rise (Figure 5). As shown by the cell wound healing assay, compared to the normal control group, at 24 hours and 48 hours after downregulating *YAP* expression, the migratory ability of Ishikawa cells dropped by $7.23\% \pm 2.39\%$ and $22.04\% \pm 5.92\%$, respectively; simultaneously pointing after upregulating *YAP* expression,

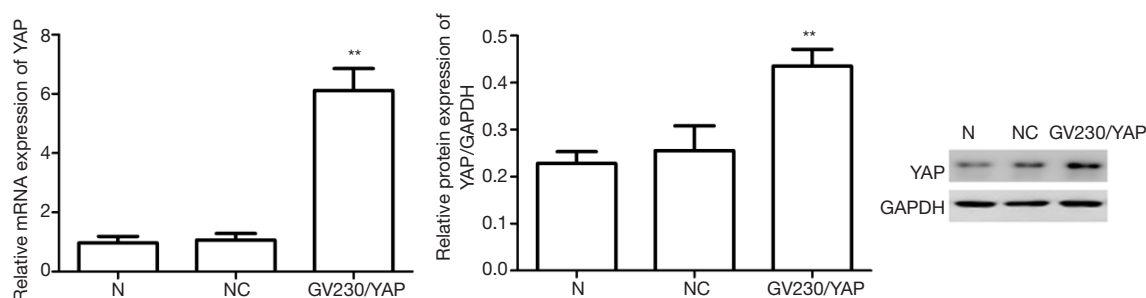


Figure 4 Construction of the stable cell line for upregulating *YAP* expression. The mRNA expression level of *YAP* in HEC-1A cells increases obviously. N, normal endometrium. **, compared with normal group, $P < 0.01$. *YAP*, Yes-associated protein.

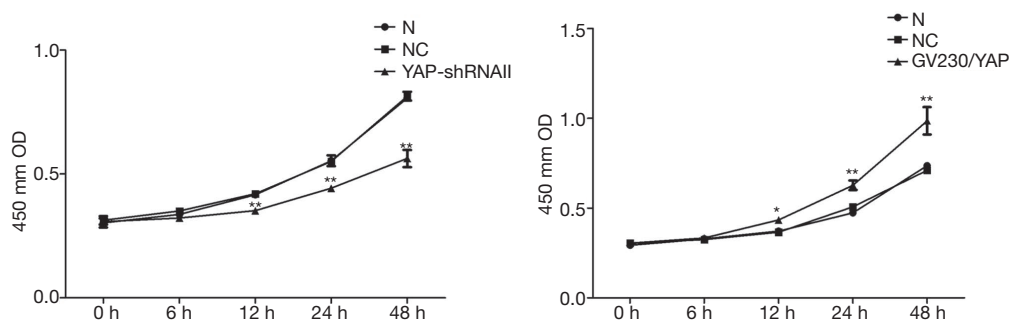


Figure 5 Effect of *YAP* gene on the proliferation of Ishikawa and HEC-1A cells. N, normal endometrium. *, compared with normal group, $P < 0.05$; **, compared with normal group, $P < 0.01$. *YAP*, yes-associated protein.

this ability of HEC-1A cells increased by $7.23\% \pm 2.39\%$ and $22.04\% \pm 5.92\%$, respectively. These findings suggested that the *YAP* gene could increase the proliferation, invasion, and migration of EC cells (Figures 6-8).

EMT accelerated by *YAP* in EC cell lines

Given the performances of *YAP* mentioned above, we detected the mRNA and protein expression of EMT markers after *YAP* interference and overexpression. As shown by the RT-PCR and WB results, compared to the normal control group, both mRNA and protein expression levels of E-cadherin increased obviously ($P < 0.01$), but all those of N-cadherin and Vimentin fell obviously in the *YAP*-shRNAII transfection group ($P < 0.01$) (Figures 9,10). Besides, an inversed trend was observed in the GV230/*YAP* overexpression group (Figures 11,12). These findings suggested that *YAP* could promote the invasion and migration of EC through accelerating EMT.

Discussion

Previously known as a protein playing a central role in the Hippo signaling pathway, *YAP* can promote the growth, inhibit the apoptosis, abolish the contact inhibition, exacerbate the malignancy of cancer cells (15). In this experiment, we found the mRNA and protein expression levels of *YAP* rose in EC tissues, indicating the cancer-promoting role of *YAP* in EC. Tsujiura *et al.* (16) investigated 120 cases of type I and 30 cases of type II endometrioid adenocarcinoma, finding that the *YAP* gene was expressed in both nuclei cytoplasm. Among type I cases, 55.0% (66/120) showed high *YAP* expression in nuclei and 68.3% (82/120) in the cytoplasm; among type II cases, these two percentages climbed to 90.0% (27/30) and 63.3% (19/30). This finding is consistent with ours. Tsujiura also verified the tight association between *YAP* expression level and the cell differentiation, pathologic grade, lymphovascular space invasion, recurrence, and metastasis of type I EC, but this association did not occur to



Figure 6 Migration of Ishikawa cells after *YAP* gene downregulation. Compared with the normal control and negative control group, the migration rate of Ishikawa cells dropped obviously in *YAP*-shRNAII group at 24 and 48 hours after *YAP* expression was downregulated (magnification, $\times 100$). N, normal endometrium; *YAP*, yes-associated protein.

type II EC.

Our statistical results proved that the *YAP* expression level was linked with pathologic grade and metastasis, not with the clinical stage. Opinions conflict with each about the role of *YAP* (promotor or suppressor) in cancer development. Recent studies (4,17,18) hypothesize this conflict may arise because *YAP* bears various phosphorylation sites and can bind various activators. *YAP* has no DNA-binding sites, so the transcriptional co-activators binding *YAP* maneuvers its functions. It acts as a cancer promoter once bound to TEAD, and a cancer suppressor once bound to P73/P63. Nevertheless, the hiding mechanism is still to be dug out.

The present experiment verified that high *YAP* expression promoted the development of EC despite its pathologic grade and lymphatic metastasis. That high *YAP* expression can benefit tumorigenesis, and EMT has been validated

by researching hepatocellular carcinoma, oral squamous cell carcinoma, colon cancer, and ovarian cancer (19-23). In this *in vitro* experiment, downregulating *YAP* expression inhibited the proliferation, invasion, and migration of Ishikawa cells, a process that curbed the progression of EMT. Together, upregulating *YAP* expression powered the proliferation, invasion, and migration of HEC-1A cells, a process that fueled the progression of EMT. These suggest that *YAP* can regulate the invasion and migration of EC cells, and the EMT or other biological processes in EC.

We demonstrated that up-regulation and down-regulation of *YAP* could increase and decrease the proliferation and differentiation of EC cells. Although further mechanisms and *in vivo* evidence have not been fully demonstrated, our data suggest targeted inhibition. *YAP* may be a potential treatment for EC patients.

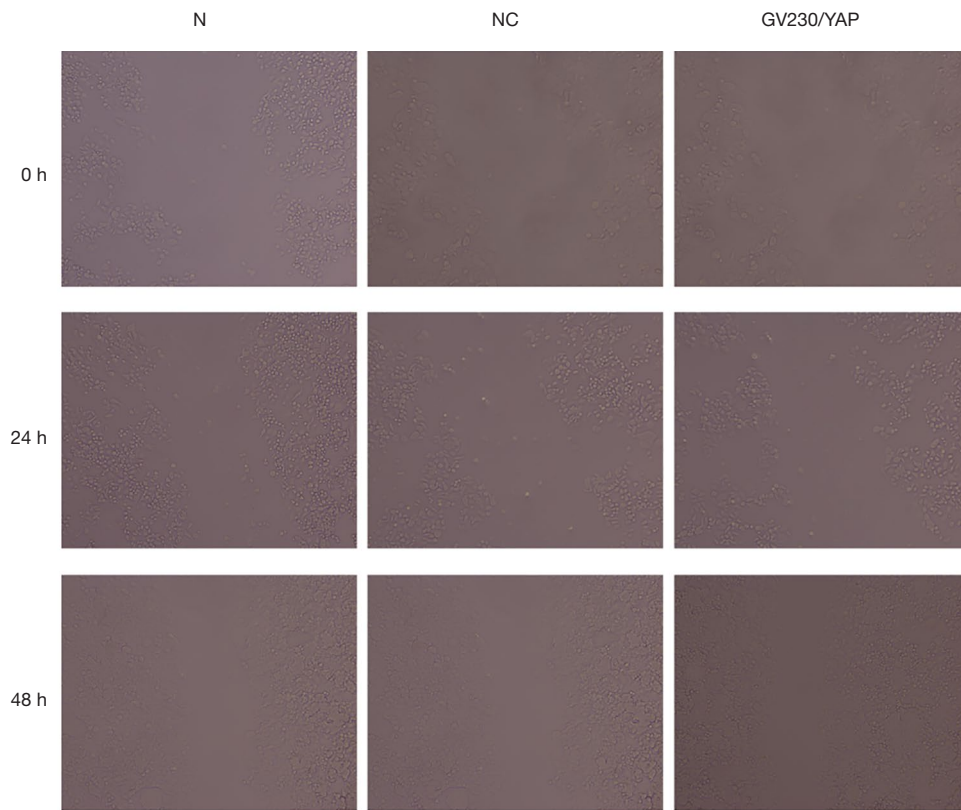


Figure 7 Migration of HEC-1A cells after the up-regulation of the *YAP* gene. Compared with the normal control and negative control group, the migration rate of HEC-1A cells dropped obviously at 24 and 48 hours after *YAP* was overexpressed (magnification, $\times 100$). N, normal endometrium; *YAP*, yes-associated protein.

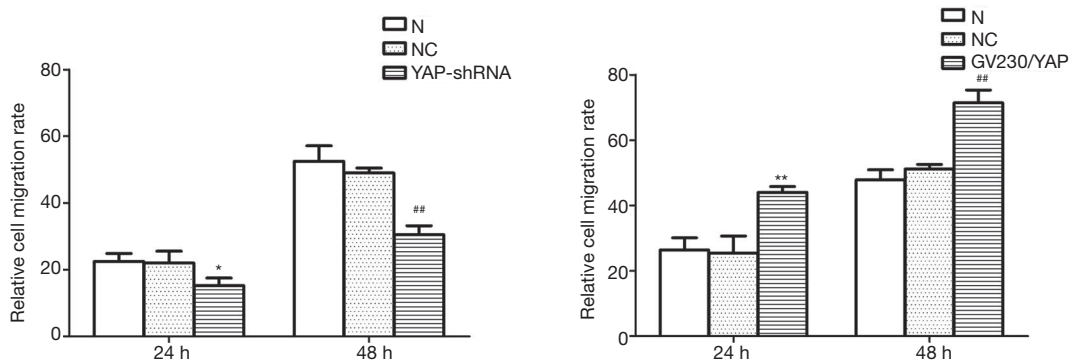


Figure 8 Effect of *YAP* downregulation and upregulation on cell migration rate. *YAP*, yes-associated protein. **, compared with normal group at 24 hours, $P < 0.01$; *, compared with normal group at 24 hours, $P < 0.05$; ##, compared with normal group at 48 hours, $P < 0.01$.

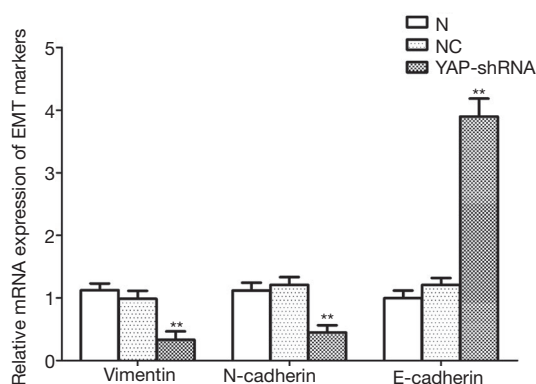


Figure 9 effect of downregulation of *YAP* on the mRNA expression of EMT markers. After *YAP* downregulation, the mRNA expression level of E-cadherin increased, but those of N-cadherin and Vimentin dropped obviously. **, compared with normal group, $P < 0.01$. *YAP*, yes-associated protein; EMT, epithelial mesenchymal transition.

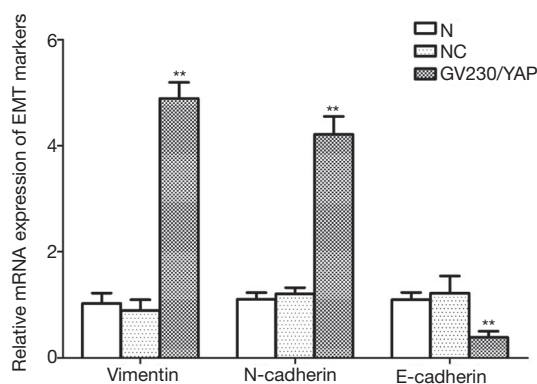


Figure 11 effect of upregulation of *YAP* gene on the mRNA expression of EMT markers. After *YAP* upregulation, the mRNA expression of E-cadherin decreased, but those of N-cadherin and Vimentin increased obviously. **, compared with normal group, $P < 0.01$. N, normal endometrium. *YAP*, yes-associated protein; EMT, epithelial mesenchymal transition.

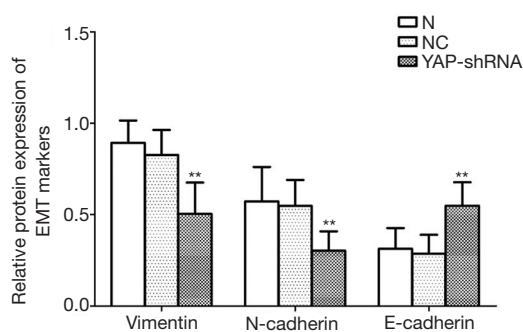
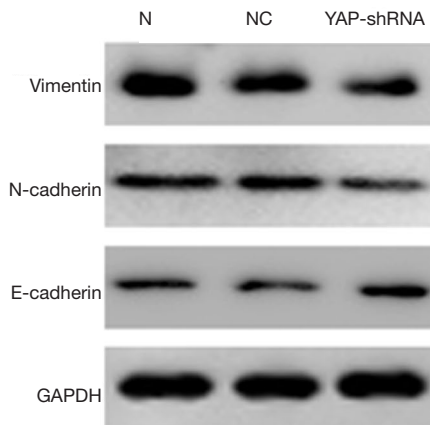


Figure 10 Effect of downregulation of *YAP* on the protein expression of EMT markers. After *YAP* downregulation, the protein expression level of E-cadherin increased, but those of N-cadherin and Vimentin dropped obviously. **, compared with normal group, $P < 0.01$. N, normal endometrium. *YAP*, yes-associated protein; EMT, epithelial mesenchymal transition.



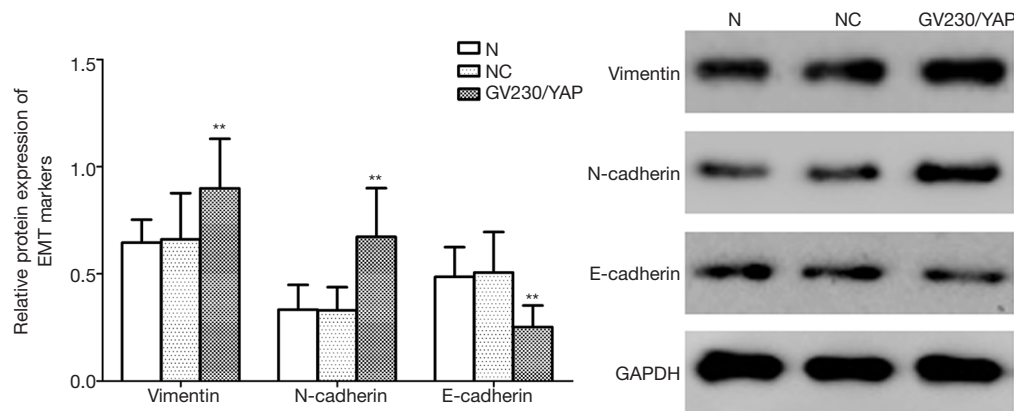


Figure 12 Upregulation of *YAP* gene on the protein expression of EMT markers. After *YAP* upregulation, the protein expression of E-cadherin decreased, but those of N-cadherin and Vimentin increased obviously. **, compared with normal group, $P < 0.01$. N, normal endometrium. *YAP*, yes-associated protein; EMT, epithelial mesenchymal transition.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-3155>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The Research Ethics Committee approved the present study of the First Affiliated Hospital of Anhui Medical University. All the patients presented their informed consent. All procedures performed in studies involving human participants were in accordance with the Helsinki Declaration (as revised in 2013).

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