

# YAP promotes gastric cancer cell survival and migration/invasion via the ERK/endoplasmic reticulum stress pathway

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**Abstract.** Yes-associated protein (YAP) has been reported to serve an important role in gastric cancer cell survival and migration. However, the underlying mechanism remains unclear. The aim of present study was to identify the underlying mechanism through which Yap sustains gastric cancer viability and migration. The results of the present study demonstrated that YAP expression was upregulated in gastric cancer MKN-28/74 cells compared with normal gastric GES-1 cells. Functional studies revealed that silencing of YAP inhibited gastric cancer MKN-28/74 cell viability and invasion. Mechanistically, YAP may promote gastric cancer cell survival and migration/invasion by inhibiting the endoplasmic reticulum (ER) stress pathway. In addition, YAP may regulate ER stress by activating the ERK signaling pathway. The results of the present study suggested that YAP may be a tumor promoter in gastric cancer and act through the ERK/ER stress pathway; therefore, YAP may have potential implications for new approaches to gastric cancer therapy.

## Introduction

Gastric cancer is one of the most common malignant tumors worldwide with an occurrence rate of 10.79% (1). Gastric cancer is the fifth leading cause of cancer-associated mortality in both the male and female population worldwide with a mortality rate of 8.8% (2). Despite the continuous development of comprehensive diagnosis and treatment technologies in recent years, the 5-year survival rate for patients with advanced gastric cancer is still >30% (3-5). The reasons for this are complex, and one of the most important issues is that gastric cancer cells are prone to survival and migration/invasion (6-8). Therefore,

it is worthwhile to explore the mechanism of gastric cancer cell survival and migration/invasion for early intervention, late treatment and improvement of treatment outcomes.

Endoplasmic reticulum (ER) is the primary site of protein folding, modification and assembly, as well as intracellular Ca<sup>2+</sup> storage in eukaryotic cells (9,10). Under stressed conditions, misfolded or unfolded protein aggregation and imbalances in Ca<sup>2+</sup> levels in the ER lumen occur, and the cell enters a state termed ER stress (11-13). If the stress persists or the stress damage exceeds the ability of cell survival and protection, the ER stress-dependent apoptosis pathway is activated, leading to apoptosis (14-16). Recent studies have suggested that ER stress-mediated cell migration/invasion is closely associated with the occurrence and development of gastric cancer (17-20). However, the initiator of ER stress that regulates gastric cancer cell survival and migration/invasion remains unknown.

Yes-associated protein (YAP) is involved in the regulation of cell proliferation, organ development and the occurrence of tumors (21-23). Previous studies have demonstrated that YAP is abnormally expressed in breast, ovarian and other types of cancer, and its expression levels are associated with stage and prognosis of patients with tumors (24-27). Upregulation of YAP has been observed in gastric cancer and is associated with the clinicopathological characteristics of patients with gastric cancer (28,29). In addition, YAP integrates ER stress to control liver size and tumorigenesis, suggesting a potential connection between YAP and ER stress (29,30). Therefore, the present study hypothesized that YAP may reduce gastric cancer cell survival and migration through the activation of ER stress.

## Materials and methods

*Cell culture and treatments.* The gastric cancer MKN-28/74 cells and normal gastric GES-1 cells were purchased from the American Type Culture Collection. The MKN28 cell line has been reported as cross-contaminated with MKN74; thus, it is referred to as MKN-28/74 throughout the present study (31). MKN-28/74 cells were cultured in RPMI-1640 medium (Nacalai Tesque, Inc.) supplemented with 10% fetal bovine serum (FBS; HyClone; GE Healthcare Life Sciences) at 37°C in a 5% CO<sub>2</sub> humidified incubator; GES-1 cells were cultured in DMEM (HyClone; GE Healthcare Life Sciences)

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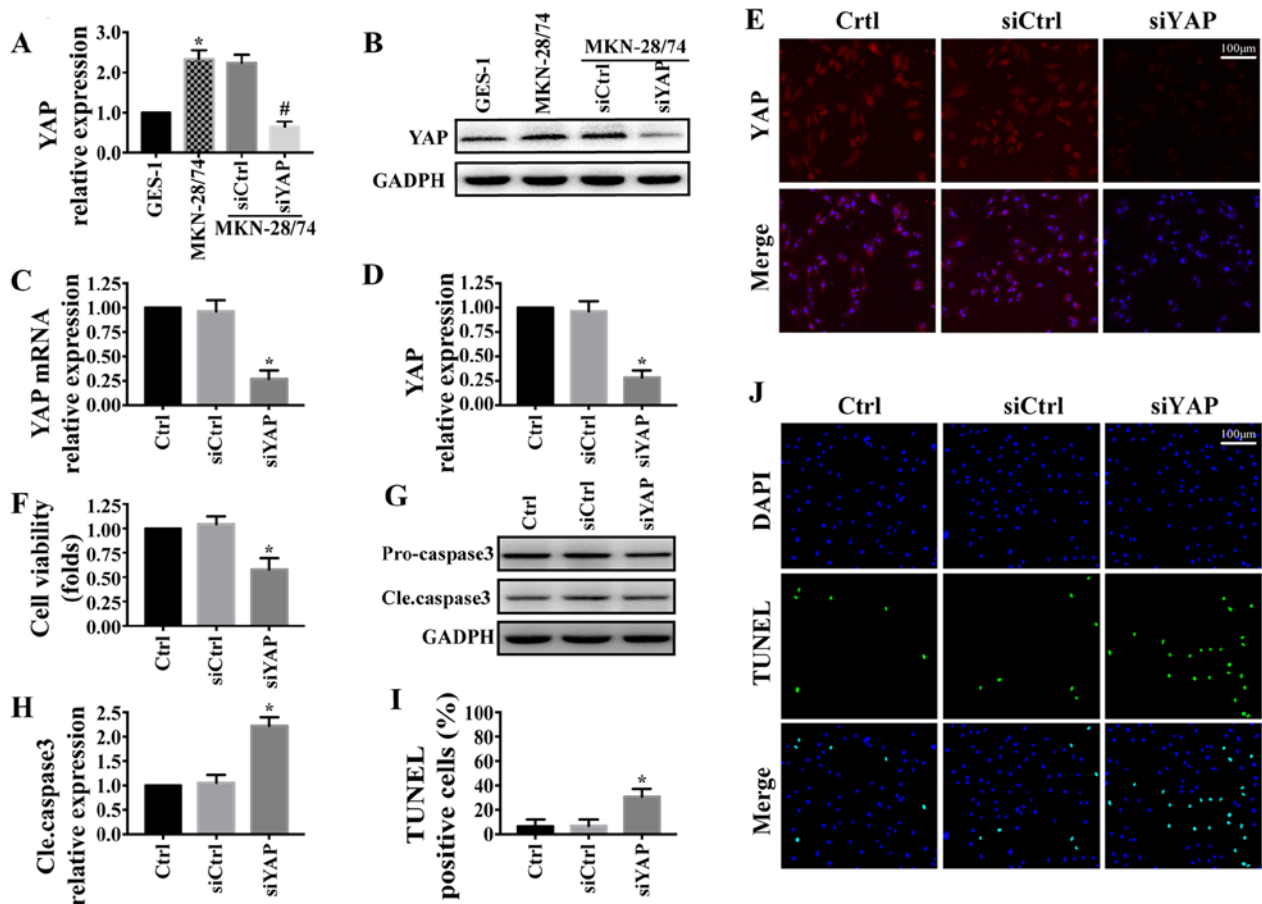


Figure 1. YAP affects viability and apoptosis in gastric cancer MKN-28/74 cells. (A and B) The protein level of YAP was measured in gastric cancer MKN-28/74 cell and normal gastric GES-1 cells. (C-E) siYAP transfection efficiency was confirmed by (C) reverse transcription-quantitative PCR and (D and E) immunofluorescence assays. (F) MTT assay was used to measure MKN-28/74 cell viability following YAP knockdown. (G and H) Western blotting was used to detect the expression of caspase-3 and cleaved caspase-3. (I and J) TUNEL staining was performed to determine the effect of YAP on apoptosis in MKN-28/74 cells. \* $P < 0.05$  vs. GES-1 or Ctrl. # $P < 0.05$  vs. MKN-28/74. YAP, yes-associated protein; siYAP, small interfering RNA targeting YAP; siCtrl, control small interfering RNA; cle, cleaved; Ctrl, untransfected control.

containing 10% FBS (HyClone; GE Healthcare Life Sciences) at 37°C in a 5% CO<sub>2</sub> humidified incubator (32). Tunicamycin (TM; 100 nM; Sigma-Aldrich; Merck KGaA) and 4-phenylbutyrate (10 mM; Sigma-Aldrich; Merck KGaA), the agonist and antagonist for ER stress, respectively, were added to the medium for 12 h. MKN-28/74 cell were pre-treated with PD98059 (10 μM) for 24 h at 37°C.

**Transfection.** To evaluate the functional role of YAP, small interfering (si)RNA was used to knockdown its expression. siYAP (5'-GCGACATTCAGGGUGACUAUU-3') and non-targeting sequences (siCtrl; 5'-UUCUCCGAACGUGUCACGU-3') were purchased from GenePharma Co., Ltd. (33). A total of 20 nM siYAP or siCtrl was used to transfect MKN-28/74 cells (2x10<sup>6</sup> cells/well) with Lipofectamine® 2000 (Thermo Fisher Scientific, Inc.) for 48 h in 6-well plates, and the transfection efficiency was determined by western blotting.

**Reverse transcription-quantitative PCR (RT-qPCR).** Total RNA was extracted from the MKN-28/74 cells using an RNeasy kit (Beyotime Institute of Biotechnology) and reverse transcribed using One-step RT-PCR kit (cat. no., AE311-02;

Beijing Transgen Biotech Co., Ltd.) at 37°C for 30 min according to the manufacturer's protocol (34). qPCR was performed using the SYBR Green RT-PCR kit (Takara Bio, Inc.) according to the manufacturer's protocol. The thermocycling conditions were as follows: 95°C for 5 min; followed by 40 cycles of 95°C for 40 sec, 60°C for 30 sec and 72°C for 30 sec. GAPDH was selected as an internal control. The following primers were used for PCR: YAP forward, 5'-AAG GCTTGACCCTCGTTT-3' and reverse, 5'-CTGCTGCTG CTGGTTTGA-3'; and GAPDH forward, 5'-GTCAACGGA TTTGGTCGTATTG-3' and reverse, 5'-CATGGGTGGAAT CATATTGGAA-3'. Fold-changes in mRNA expression were calculated using the 2<sup>-ΔΔC<sub>q</sub></sup> method (35).

**Western blotting.** The MKN28/74 cells (5x10<sup>6</sup>) was homogenized and sonicated in a lysis buffer (Beyotime Institute of Biotechnology). Protein concentrations were detected using a BCA Protein Quantification kit, according to the manufacturer's protocol. The proteins (50 μg) were separated by 10% SDS-PAGE and then transferred onto polyvinylidene difluoride membranes. The membrane was blocked with 5% non-fat dry milk for 1 h at room temperature and incubated with specific primary antibodies overnight at 4°C. The

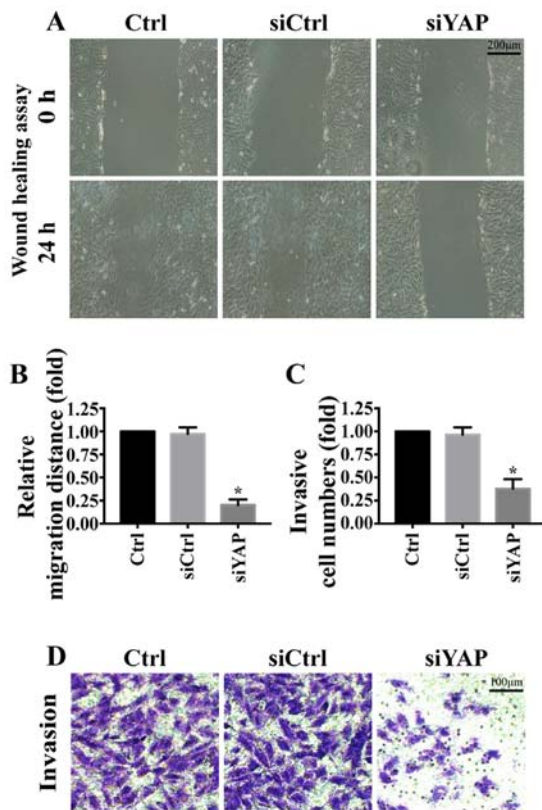


Figure 2. YAP inhibition is associated with cell migration and invasion. (A) Knockdown of YAP significantly reduced wound closure rates in gastric cancer MKN-28/74 cells compared with those in the Ctrl group. (B) Relative migration distance. (C) Knockdown of YAP reduced the numbers of migrated gastric cancer MKN-28/74 cells compared with those in the Ctrl group. (D) Transwell chamber assay. \* $P < 0.05$  vs. Ctrl. YAP, yes-associated protein; siYAP, small interfering RNA targeting YAP; siCtrl, control small interfering RNA; Ctrl, untransfected control.

primary antibodies used were as follows: YAP (1:1,000; Cell Signaling Technology, Inc.; cat. no. 14074), pro-caspase-3 (1:1,000; Abcam; cat. no. ab13847), cleaved caspase-3 (1:1,000; Abcam; cat. no. ab49822), glucose-regulated protein 78 kDa (GRP78; 1:1,000; Abcam; cat. no. ab21685), GADPH (1:1,000; Abcam; cat. no. ab8245), pro-caspase-12 (1:1,000; Abcam; cat. no. ab8117), cleaved caspase-12 (1:1,000; Cell Signaling Technology, Inc.; cat. no. 2202), C/EBP homologous protein (CHOP; 1:1,000; Abcam; cat. no. ab11419), ERK (1:1,000; Cell Signaling Technology, Inc.; cat. no. 4695), phosphorylated (p-) ERK (1:1,000; Cell Signaling Technology, Inc.; cat. no. 4370). The blots were detected with an enhanced chemiluminescence substrate kit (Thermo Fisher Scientific, Inc.), according to the manufacturer's protocol. The bands were scanned and quantified by ImageJ version 1.47 software (National Institutes of Health) (36).

**Immunofluorescence staining.** Following transfection treatment, the MKN28/74 cell ( $0.5 \times 10^6$  cells/well) were fixed with 3.7% paraformaldehyde for 10 min at room temperature and subsequently blocked with 5% bovine serum albumin (Sigma-Aldrich; Merck KGaA) in PBS for 1 h at room temperature. Cells were incubated with primary antibodies for 4 h at room temperature. The primary antibodies used were YAP (1:500; Cell Signaling Technology, Inc.; cat. no. 14074)

and CHOP (1:500; Abcam; cat. no. ab11419). DAPI (5 mg/ml; Sigma-Aldrich; Merck KGaA) was used to stain the nuclei at room temperature for 3 min. A total of 5 randomly selected fields of view were used per sample and images were captured with a laser confocal microscope (magnification,  $\times 600$ ; TcS SP5; Leica Microsystems, Inc.).

**Cell invasion and migration.** Following transfection treatment, cell invasion was analyzed using a Transwell chamber assay as previously described (37). Briefly, cells ( $1 \times 10^6$  cells/well) were suspended in RPMI-1640 medium containing 10% FBS and seeded into the upper chambers.

Cell migration was analyzed using a wound-healing assay and cells were cultured with RPMI-1640 medium in 12-well plates. Once cells reached  $>80\%$  confluency, a sterile pipette tip was used to evenly scratch the 12-well plate. Following cell attachment, a straight line was gently scratched in the cell layer with a  $200 \mu\text{l}$  pipette tip, and the cells were washed with PBS (pH 7.4) three times. The relative wound closure was imaged under a light microscope (magnification,  $\times 100$ ; Leica Microsystems, Inc.) at 0 and 24 h. The wound was measured using ImageJ 1.74v software (National Institutes of Health).

**MTT assay and terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL).** The MKN-28/74 cells were seeded into 96-well plates at  $8 \times 10^3$  cells/well and incubated overnight. Following transfection treatment, MTT (5 mg/ml) was added to each well and incubated for 4 h. The insoluble formazan was collected and dissolved in dimethylsulfoxide, and the optical density value was measured with a scanning spectrophotometer at a wavelength of 570 nm.

The TUNEL assay was used for the detection of apoptosis. A one-step TUNEL kit (Beyotime Institute of Biotechnology) was used for TUNEL staining. The MKN-28/74 cells ( $1 \times 10^6$  cells) were incubated with fluorescein-dUTP (Invitrogen; Thermo Fisher Scientific, Inc.) to stain the apoptotic cell nuclei and with DAPI (5 mg/ml) to stain all cell nuclei at room temperature for 3 min. Images were captured with a laser confocal microscope (magnification,  $\times 600$ ; TcS SP5; Leica Microsystems, Inc.). The number of TUNEL-positive cells was calculated by counting at least five random fields of view as the ratio of the experimental samples to the control samples (untransfected cells).

**Statistical analysis.** All analyses were performed with SPSS 20.0 software (IBM Corp.). Experiments were repeated three times and data are presented as the means  $\pm$  standard error of the mean. Statistical analyses were performed using one-way analysis of variance with the Bonferroni test for post hoc comparisons.  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**YAP is upregulated in gastric cancer MKN-28/74 cells and promotes cell survival.** The expression levels of YAP were detected by western blotting in MKN-28/74 gastric cancer cells and GES-1 normal gastric cells. The results demonstrated that YAP was significantly upregulated in gastric cancer MKN-28/74 cells compared with GES-1 cells (Fig. 1A and B).

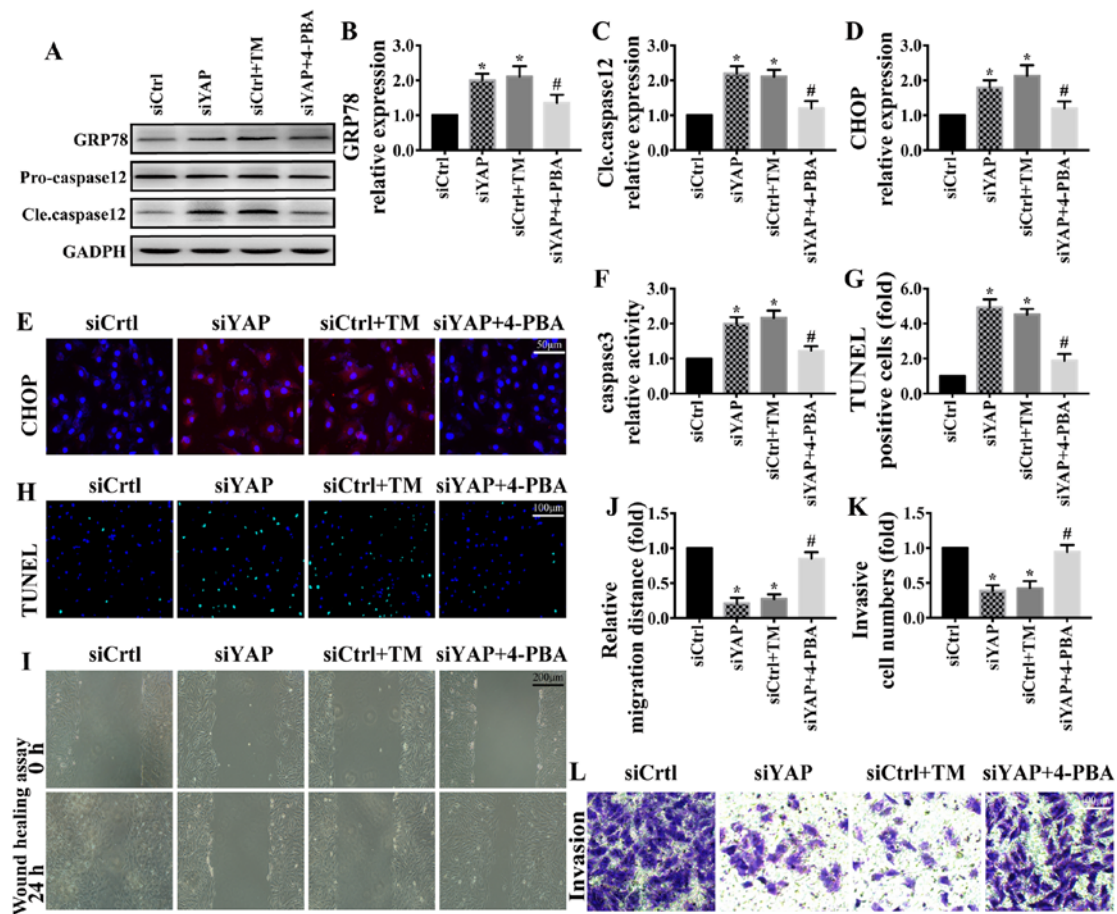


Figure 3. YAP promotes MKN-28/74 cell survival and migration through the inhibition of ER stress. (A) Protein levels of (B) GRP-78 and (C) Cle.caspase12 were evaluated via western blotting. (D) Knockdown of YAP also reduced expression of CHOP. (E) Expression of CHOP was measured by immunofluorescence assay. (F) Caspase3 activity assay and (G) TUNEL staining were performed to determine the effects of ER stress on MKN-28/74 cell apoptosis. (H) TUNEL staining. (I) Wound-healing assay. (J) ER stress reduced the wound closure rates in gastric cancer MKN-28/74 cells. (K and L) Transwell assay was used to detect the invasive ability of MKN-28/74 cells. \* $P < 0.05$  vs. siCtrl; # $P < 0.05$  vs. siYAP. YAP, yes-associated protein; siYAP, small interfering RNA targeting YAP; siCtrl, control small interfering RNA; Ctrl, control; ER, endoplasmic reticulum.

To confirm the role of YAP in the progression gastric cancer, siYAP was transfected into MKN-28/74 cells to knockdown the expression of YAP. The transfection efficiency was detected by western blotting (Fig. 1A and B), RT-qPCR (Fig. 1C) and immunofluorescence (Fig. 1D and E). The results demonstrated that siYAP, but not siCtrl, significantly inhibited the expression of YAP in gastric cancer MKN-28/74 cells compared with untransfected cells. The effect of YAP on MKN-28/74 cell viability was investigated. The results of the MTT assay demonstrated that YAP knockdown significantly reduced the viability of MKN-28/74 cells (Fig. 1F). In addition, the inhibition of YAP expression increased the expression of cleaved caspase-3 (Fig. 1G and H) and the number of TUNEL-positive cells (Fig. 1I and J) in gastric cancer MKN-28/74 cells. These results suggested that YAP was upregulated in gastric cancer MKN-28/74 cells and promoted cell survival by inhibiting apoptosis.

*YAP is associated with MKN-28/74 cell migration and invasion.* The role of YAP in MKN-28/74 cell migration and invasion was further investigated. Knockdown of YAP significantly reduced wound closure rates in the wound-healing assay (Fig. 2A and B). In addition, compared with the control

group, knockdown of YAP reduced the invasive ability of gastric cancer MKN-28/74 cells (Fig. 2C and D). These results suggested that YAP promoted MKN-28/74 cell migration and invasion.

*YAP promotes MKN-28/74 cell survival and migration/invasion through the inhibition of ER stress.* ER stress serves a critical role in the progression of cancer (38,39). To determine the underlying mechanism by which YAP may regulate gastric cancer MKN-28/74 cell survival and metastasis, the present study focused on ER stress. TM, the activator of ER stress, was used to induce ER stress in MKN-28/74 cells transfected with siCtrl. 4-phenylbutyrate (4-PBA), the inhibitor of ER stress, was used to inhibit ER stress in YAP-knockdown MKN-28/74 cells. Western blotting (Fig. 3A-C) and immunofluorescence (Fig. 3D and E) were used to determine the changes in ER stress markers. Compared with the siCtrl group, knockdown of YAP contributed to the upregulation of GRP78, CHOP and cleaved caspase-12; similar results were observed following TM treatment in the siCtrl group. However, the upregulation of ER stress markers was partially reversed by 4-PBA (Fig. 3A-E). These results suggested that YAP knockdown was associated with ER stress. In addition,

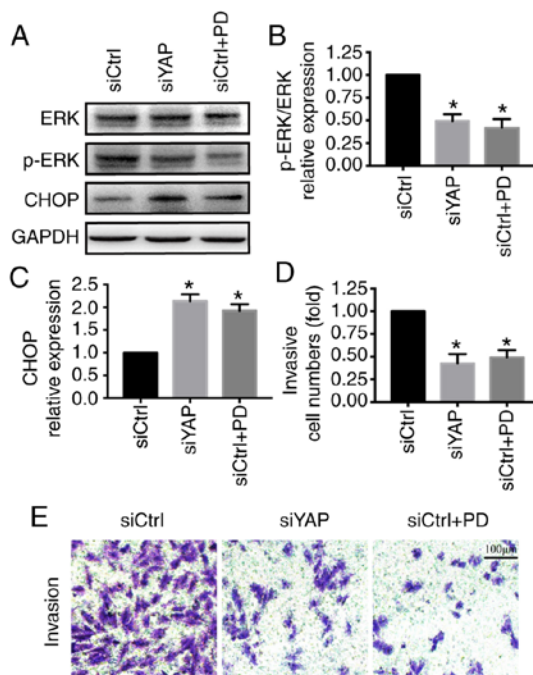


Figure 4. The ERK pathway is involved in YAP-mediated endoplasmic reticulum stress inhibition. (A-C) The protein levels of ERK, p-ERK and CHOP were evaluated by western blotting. PD98059 was used to inhibit the ERK pathway in MKN-28/74 cells transfected with siCtrl. (D and E) Transwell assay was used to detect the invasive ability of MKN-28/74 cells. \* $P < 0.05$  vs. siCtrl. YAP, yes-associated protein; siYAP, small interfering RNA targeting YAP; siCtrl, control small interfering RNA; Ctrl, control; p-, phosphorylated; PD, PD98059.

ER stress activation was associated with apoptosis activation (Fig. 3F-H) and the inhibition of migration/invasion (Fig. 3I-L). By contrast, inhibiting ER stress with 4-PBA in YAP-knockdown cells promoted cell survival and invasion. These results indicated that YAP promoted gastric cancer MKN-28/74 cell survival and migration/invasion through the regulation of ER stress.

*YAP regulates ER stress via the ERK pathway.* Finally, experiments were performed to determine how YAP inhibited ER stress. The ERK pathway has been reported to be involved in YAP-associated functions and ER stress inhibition (40,41). PD98059, an inhibitor of the ERK pathway, was used to inhibit the ERK pathway in MKN-28/74 cells transfected with siCtrl. The activation of the ERK pathway was assessed by western blotting. Compared with the control group, YAP knockdown inhibited ERK phosphorylation, similar to PD98059 treatment (Fig. 4A). The inhibition of the ERK pathway by siYAP promoted the activation of ER stress as indicated by the upregulation of CHOP and reduced cell invasion (Fig. 4). These results suggested that the ERK pathway may contribute to the YAP-induced ER stress inhibition.

## Discussion

Previous studies have demonstrated that YAP is essential for gastric cancer cell survival and migration/invasion (42-44). However, the underlying mechanism remains unclear. The present study proposes a novel underlying mechanism

by which YAP regulates gastric cancer MKN-28/74 cell survival and metastasis. The results of the present study demonstrated that: i) YAP was upregulated in gastric cancer MKN-28/74 cells compared with normal gastric GES-1 cells; ii) YAP promoted gastric cancer MKN-28/74 cell survival and migration/invasion by inhibiting ER stress; iii) YAP may regulate ER stress by activating the ERK pathway. The present study provides a new target for the treatment of gastric cancer that may affect cancer cell survival and metastasis. A limitation of the present study was that only one gastric cancer cell line was used. Additional cell lines will be used in our future study, to confirm the results.

In eukaryotic cells, the ER is responsible for protein synthesis and calcium storage; perturbations in the ER function, a process termed ER stress, have been reported to be involved in cancer initiation, growth and metastasis in the majority of solid tumors (45,46). However, the role of ER stress in tumorigenesis and development is still controversial. Previous studies have demonstrated that ER stress is a tumor suppressor, and the activation of ER stress inhibits gastric cancer cell survival and migration (19,47,48). However, a number of studies have suggested that ER stress can promote tumor development (49,50). Induction of ER stress protects gastric cancer cell apoptosis during cisplatin and doxorubicin treatment via the p38 MAPK pathway (51).

Recent studies have identified an association between YAP and ER stress. The activated Hippo-YAP signaling pathway promoted neuron survival in the TNF $\alpha$ -induced microenvironment by inhibiting ER stress (52). In addition, downregulation of YAP evoked ER stress and contributed to myocyte death in isoproterenol-induced myocardial infarction (53). The results of the present study are consistent with previous studies. However, the exact mechanism by which YAP controls ER stress remains unknown. The results of the present study suggested that YAP may inhibit ER stress via the ERK pathway. Thus, these results provide valuable information on the role of YAP and ER stress in tumorigenesis.

In the present study, the critical role of YAP in the progression of gastric cancer was identified. A recent study demonstrated that YAP regulates gastric cancer survival and migration through SIRT1/Mfn2/mitophagy (42). The results of the present study demonstrated that YAP may function via the ERK/ER stress pathway in gastric cancer survival and metastasis. To the best of our knowledge, this is the first identification of YAP functions involved in ER stress and the ERK pathway in the development of gastric cancer. However, *in vivo* experiments and clinical data are required to support these results.

In conclusion, the results of the present study identified the important role of YAP in gastric cancer cell migration and survival. YAP promoted gastric cancer MKN-28/74 cell survival and migration/invasion via the ERK/ER stress pathway. These results suggested that the YAP/ERK/ER stress pathway may be a potential target for the treatment of gastric 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

HL and DM conceived and designed the study, performed the experiments, analyzed and interpreted the data and wrote the manuscript. PX, HW and YW were involved in data analysis and interpretation.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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