YAP promotes the malignancy of endometrial cancer cells via regulation of IL-6 and IL-11

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Abstract

Background: Emerging evidence shows that Hippo signal pathways can regulate the progression of various cancer. While the roles of Yes-associated protein (YAP), the key transducer of Hippo signals, in the development of endometrial cancer (EC) are rarely investigated.

Methods: The expression of YAP in endometrial cancer cells and tissues was measured. Its roles in proliferation and expression of interleukins (ILs) were investigated by use of its specific siRNA or inhibitor (verteporfin, VP).

Results: YAP was upregulated in endometrial cancer cells and tissues. Knockdown of YAP or VP can suppress the proliferation while increase its chemo-sensitivity of EC cells. We found that targeted inhibition of YAP can decrease the expression of interleukin-6 (IL-6) and IL-11 in EC cells. Recombinant IL-6 or IL-11 can attenuate si-YAP suppressed proliferation of EC cells. Chromatin immunoprecipitation (ChIP) assay suggested that YAP can directly bind with the promoter of IL-6 and induce its transcription. As to IL-11, inhibitor of NF-κB (BAY 11–7082) can significantly down regulate the mRNA expression of IL-11. Over expression of p65 abolished si-YAP suppressed transcription of IL-11. It suggested that NF-κB was involved in the YAP regulated expression of IL-11.

Conclusions: YAP can regulate the proliferation and progression of EC cells. It suggested that targeted inhibition of YAP might be a potent potential approach for EC therapy.

Keywords: YAP, Endometrial Cancer, IL-6, IL-11, Proliferation

Introduction

Endometrial cancer (EC) is the most common gynecological cancer in developed countries (Dizon, 2010), with about 50,327 deaths occurring worldwide each year (Siegel et al., 2016). Further, the incidence and mortality rate are still increasing in the developed and developing countries (Rauh-Hain and Del Carmen, 2010). The 5-year overall survival ranges from 74 to 91% in patients without metastatic disease (Colombo et al., 2013). However, for EC patients with metastasis, treatment failure is still high due to the loss of opportunity for surgery. In advance stages of EC patients, the growth and systemic metastasis lead to patient morbidity and mortality (Huang et al., 2014). Previous studies indicated that some proteins are variated in the EC tissues and cells such as PTEN, KRAS, CTNNB1, PIK3CA and FGFR2 (Tsujura et al., 2014). Therefore, one major challenge for EC treatment is to develop efficiency approaches to block the signals essential for the progression of EC cells.

As the key downstream effector in the Hippo signaling cascade, the Yes-associated protein (YAP) is a major contributor to cancer pathophysiology (Pan, 2010; Zhao et al., 2007). The Hippo signals are composed of mammalian Ste20-like kinases 1/2 (MST1/2) and large tumor suppressor 1/2 (LATS1/2), YAP and its paralog TAZ (Liu et al., 2010). After activation of Hippo signals, MST1/2 is phosphorylated and then activates LATS1/2 (Real et al., 2018). The activation of Lats1/2 can phosphorylate YAP and subsequent
promote proteasome mediated degradation (Zhao et al., 2010). Dephosphorylation of YAP can allow YAP to translocate into the nucleus, bind with its transcriptional co-activator TEAD, and increase the transcription of many oncogenes (Zhao et al., 2008). Although many studies indicated that YAP functions as an oncogene in most cancers (Zhao et al., 2010), the roles and related mechanisms of YAP on the progression of EC remain unclear. Recently studies revealed that increased nuclear YAP expression was significantly associated with higher grade, stage, lympho-vascular space invasion, postoperative recurrence/metastasis and overall survival in estrogen mediated EC patients (Tsujura et al., 2014). It suggested that YAP may also trigger the progression of EC via unknown mechanisms.

The present study investigated the potential roles and related mechanisms of YAP in the progression of EC. Our data showed that YAP is upregulated in EC cells and tissues. Knockdown of YAP or its inhibitor verteporfin can suppress the proliferation and increase the chemo-sensitivity of endometrial cancer cells. The upregulation of interleukin-6 (IL-6) and IL-11 is essential for YAP induced malignancy of EC cells.

Materials and methods

Chemicals and reagents

The doxorubicin (Dox) and other chemicals/inhibitors were purchased from Sigma-Aldrich (St. Louis, MO, USA). Human recombinant IL-6 and IL11 were obtained from R&D Systems (Sydney, Australia). Human recombinant IL-6 and IL11 were purchased from Invitrogen (Life Technologies, Grand Island, NY, USA). Primary antibodies and horseradish peroxidase (HRP)-conjugated secondary antibody were purchased from the Cells Signaling Technology (Danvers, MA, USA).

Cell culture and transfection

The human EC Ishikawa, RL95–2, HEC1A, AN3CA and KLE cells and the human endometrial cell line endometrial stromal cell (ESC) were purchased from the Cell Bank of the Chinese Academy of Sciences, Shanghai, China. After confirmed by short tandem repeat profiling, cells were cultured in medium containing 10% (v/v) FBS (Scientix, Cheltenham, VIC, Australia) and 1% (V/V) penicillin-streptomycin solution (Sigma, St Louis, MO, USA). All cells were routinely tested as free from mycoplasma contamination. In order to knock down the expression of YAP, siRNA specific for YAP (5’GCCAGUA-CUGAUGACAGGUATT3’, Shanghai GenePharma Co. Ltd., Shanghai, China) was used to transfect cells by using Lipofectamine 2000 (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer’s instruction. Similarly, the pcDNA (vector control) and pcDNA/p65 plasmids were also transfected by use of Lipofectamine 2000.

RNA preparation and quantitative real time RT-PCR (qRT-PCR)

Total RNAs were isolated by use of TriReagent (Sigma-Aldrich) and further purified by use of the DNA free kit (Ambion) according to the manufacturer’s instructions. The cDNA was synthesized using Superscript III reverse transcriptase (Invitrogen) and 500 ng of total RNA. Then, qRT-PCR was performed on the Bio-Rad System (Bio-Rad Laboratories Inc., Hercules, CA, USA) using 2× Fast-Start SYBR green master and the following primers: YAP forward: 5’- TAGCCCTGCGTAGCAGTGA –3’, reverse: 5’- TCATGCTTAGTCACCTGCTGTGTG -3’; IL-1β, forward: 5’- ATGATGGCTTATCTACAGTGCGC3 –3’, reverse: 5’- GTCCGAGATTCGTA GCTGGA -3’; IL-6, forward: 5’- ACTCACCTCTTCA GAAAGATTG -3’, reverse: 5’- CCATCTTTTGAAGGTTAGGTGTT -3’; IL-8, forward: 5’- GAG AGT GAT TGA GAG TGG ACC AC –3’, reverse: 5’- CAC CAC CCT CTG CAC CCA GTT T-3’; IL-10, forward: 5’- TCT CCG AGA TGC CTT CAG CAG A –3’, reverse: 5’- TCA GAC AAG GCT TGG CAA CCC A -3’; IL-11, forward: 5’- GGGCTGTTCCTCTAACC CGCG-3’, reverse: 5’- GAGTCAGACTGTGATCTCCG-3’; TNF-α, forward: 5’- CTC TTC TGC CTG CTG CAC TTT G –3’, reverse: 5’- ATG GGC TAC AGG CTT GTC ACT C –3’; p65, forward: 5’- GTGGGGACTACG ACCTGAATG –3’, reverse: 5’- GGGGCACGGATTGTC AAAGATG -3’; GAPDH, forward: 5’- GGAGCGAG ATCCCCCTAAAAAT-3’, reverse: 5’- GGCTGTGGTCAT ACTTTCTCATGG-3’. GAPDH was used as the internal control for normalization. The 2−ΔΔCT method was used to quantify gene expression.

Western blot analysis

Cells or tissues were lysed by use of lysis buffer containing the protease inhibitor (2 μl/ml; ThermoScientific, Waltham, MA, USA). Then total 20 μg proteins were separated by use of a 10% SDS-PAGE gel. The proteins were transferred to polyvinylidene fluoride (PVDF) membranes and incubated with the primary antibodies overnight at 4°C. After washed three times, membranes were incubated with the secondary antibody, exposed to an enhanced chemiluminescence (ECL) western blot by use of ECL system (GE Healthcare Life Sciences), and quantified using Bio-Rad Quantity One 1-D software.

Patient samples

According to the permission of Ethical Committee in our hospital, seven paired tumor tissues and adjacent normal tissues were collected during July 2015 to June
2017. Informed consent was obtained from each patient. The samples were stored at −80°C immediately after surgery. The expression of YAP was measured by use of western blot analysis.

Cell proliferation assay
The cell proliferation was analyzed by use of the Wst-1 assay according to the previous study (Lay et al., 2012). Briefly, cells (5,000 per well) were seeded into 96-well plates. After treatment, cells were incubated with Wst-1 dye (1:10; Roche Applied Science) for 4 h at 37°C. The absorbance at 450 nm was measured with a Wallac Envision 2103 plate reader (Perkin Elmer).

Enzyme-linked immunoassays (ELISAs)
The expression of IL-6 and IL-11 in medium was measured by ELISA by use of kits according to the manufacturer’s protocol (eBioscience, USA). The absorbance at 450 nm was measured with a Wallac Envision 2103 plate reader (Perkin Elmer).

Chromatin immunoprecipitation (ChIP) PCR
ChIP assays were performed with an Agarose ChIP Kit (Thermo Scientific) according to the manufacturer’s instructions. Briefly, after treatment as indicated conditions, cells were crosslinked and lysed. The DNA was extracted and sonicated to shear DNA into fragments of 500–1000 bp in length. The DNA/protein complexes were precipitated by antibody of YAP or IgG (ab171870, Abcam), and then incubated with Protein A/ G agarose beads for 2 h. The abundance of IL-6 or IL-11 promoter was analyzed by qPCR using primers as follows: IL-6, 5′-ACCCTCACCCCTCAACAAAG-3′ and 5′-GAGAATGAGCCTCAGACATC-3′; IL-11, 5′-CTTTGCTTCTCTGGTGTT-GT GC-3′ and 5′-CATGGTGGTTCATTGGCGT-3′.

Statistical analysis
All results were stated as mean ± standard deviation (SD). The data analysis was performed by use of GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA) for Windows. Statistical comparison was performed using the Student’s t test for two groups.

**Fig. 1** The expression of YAP is upregulated in EC cells and tissues. (a) The mRNA expression of YAP in human EC, ESC, and non-transformed endometrial cell line of epithelial origin such as MEF-280 and HEC-265 cells were measured by qRT-PCR. (b) The protein expression of YAP in human EC and ESC cells was measured by western blot analysis (left) and quantitatively analyzed (right); (c) The protein expression of YAP in seven cases of EC tissue and paired adjacent normal tissues was measured by western blot analysis (left) and quantitatively analyzed (right). Data are presented as means ± SD of three independent experiments. **p < 0.01 compared with control.
ANOVA analysis with Tukey’s multiple comparison test was also used to compare three or more groups. A p-value of < 0.05 was considered statistically significantly different between groups.

Results
The expression of YAP is upregulated in EC cells and tissues
Firstly, the expression of YAP was measured in various EC cells and the human endometrial cell line endometrial stromal cell (ESC). Our data showed that the mRNA expression of YAP in all tested EC cell lines including Ishikawa, RL95–2, HEC1A, AN3CA, and KLE and non-transformed endometrial cell line of epithelial origin such as MEF-280 and HEC-265 cells were significantly greater than that in the ESC (Fig. 1 a). This was confirmed by western blot analysis that protein expression of YAP in EC cells was greater than that in ESC (Fig. 1 b). We further evaluated the expression of YAP in seven collected human EC tissues and the paired normal adjacent tissues. Western blot analysis showed that the expression of YAP was increased in 85.7% (6/7) human EC tissues (Fig. 1 c). These data showed that the expression of YAP is upregulated in EC cells and tissues.

Targeted inhibition of YAP can suppress the proliferation and increase the chemosensitivity of EC cells
Ishikawa and AN3CA cells were used for the next studies due to the relative high levels of YAP and they have been widely used for EC study. To investigate the potential roles of YAP in cancer progression, we knocked down the expression of YAP by use of its specific siRNA (Fig. 2 a). Our data showed that knockdown of YAP can significantly decrease the proliferation of both Ishikawa (Fig. 2 b) and AN3CA (Fig. 2 C) cells. Further, verteporfin (VP), an inhibitor of the interaction of YAP with TEAD, can also significantly inhibit the proliferation of both Ishikawa and AN3CA cells via a concentration dependent manner (Fig. 2 d). Further, 1 μM of VP, which had no significant effect on the cell proliferation according to Fig. 2 d, colonization assay (data not shown), and previous studies (Hsu et al., 2016; Ma et al., 2016; Wang et al., 2016), can increase the sensitivity of Ishikawa cells to the treatment of Doxorubicin (Dox) (Fig. 2 e). Consistently,
si-YAP also increased the Dox sensitivity of Ishikawa cells (Fig. 2 F). These data suggested that targeted inhibition of YAP can suppress the proliferation and increase the chemosensitivity of EC cells.

**YAP can regulate the expression of IL-6 and IL-11 in EC cells**

It has been reported that cytokines such as IL-1β, IL-6, IL-8, IL-10, IL-11 and tumor necrosis factor (TNF-α) are important for the proliferation and malignancy of EC cells (Eritja et al., 2017). We tested the effects of si-YAP on the expression of these cytokines in both Ishikawa and AN3CA cells. qRT-PCR showed that si-YAP can significantly decrease the expression of IL-6 and IL-11 in Ishikawa cells (Fig. 3 a). Consistently, si-YAP can also decrease the expression of IL-6 and IL-11 in AN3CA cells (Fig. 3 b). si-YAP decreased the expression of IL-1β in AN3CA cells while not in Ishikawa cells, which indicated that the effects of YAP on IL-1β are cell line dependent. In Ishikawa cells, VP can decrease the expression of IL-6 and IL-11 via a concentration dependent manner (Fig. 3 c). The down regulation of IL-6 and IL-11 in Ishikawa cells treated with VP (Fig. 3 d) or transfected with si-YAP (Fig. 3 e) was confirmed by ELISA. Consistently, overexpression of YAP (Fig. 3 f) can increase the expression of IL-6 and IL-11 in Ishikawa cells (Fig. 3 g). These results showed that YAP can regulate the expression of IL-6 and IL-11 in EC cells.

**Both IL-6 and IL-11 are involved in YAP regulated malignancy of EC cells**

We then investigated whether IL-6 and IL-11 are involved in YAP regulated malignancy of EC cells. Our data showed that recombinant IL-6 (rIL-6) and rIL-11 can increase the proliferation of Ishikawa cells, further, both rIL-6 and rIL-11 can attenuate the si-YAP suppressed proliferation of Ishikawa cells (Fig. 4 a). Similar results were also observed in AN3CA (Fig. 4 b). Further, rIL-6 and rIL-11 also reversed the suppression effects of VP (5 μM) on the proliferation of Ishikawa cells (Fig. 4 c). In the presence of rIL-6 and rIL-11, 1 μM of VP increased Dox sensitivity of Ishikawa cells was also significantly reversed (Fig. 4 d). These data showed that both IL-6 and IL-11 are involved in YAP regulated malignancy of EC cells.

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**Fig. 3** YAP can regulate the expression of IL-6 and IL-11 in EC cells. Ishikawa (a) or AN3CA (b) cells were transfected with si-NC or si-YAP for 24 h, the mRNA expression of cytokines was measured by qRT-PCR. (c) Ishikawa cells were treated with increasing concentrations of VP for 24 h, the mRNA expression of cytokines was measured by qRT-PCR. (d) Ishikawa cells were treated with or without 1 μM of VP for 24 h, the expression of cytokines was measured by ELISA; (e) Ishikawa cells were transfected with si-NC or si-YAP for 24 h, the expression of cytokine was measured by ELISA; Ishikawa cells were transfected with pcDNA vector or pcDNA/YAP for 24 h, (f) the protein expression of YAP was tested by western blot, (g) the mRNA expression of IL-6 and IL-11 was tested by qRT-PCR. *p < 0.05, **p < 0.01 compared with control.
YAP can directly regulate the transcription of IL-6, while not IL-11, in EC cells

We further investigated the mechanisms involved in YAP regulated expression of IL-6 and IL-11 in EC cells. Our data showed that VP can rapidly decrease the expression of IL-6 in Ishikawa cells after treatment for 1 h (Fig. 5 a). However, VP can only decrease the expression of IL-11 in Ishikawa cells after treatment for more than 8 h (Fig. 5 b). We then investigated whether YAP can directly bind to the promoter of IL-6 or IL-11 by ChIP assay. Our data showed that YAP can directly bind to the promoter of IL-6, while VP can decrease the binding between YAP and promoter of IL-6 in Ishikawa cells (Fig. 5 c). However, there was no enrichment of promoter of IL-11 in YAP antibody as compared to that of IgG, further, VP had no effect on the binding efficiency (Fig. 5 d). The dual luciferase assay indicated that VP can suppress the promoter activity of IL-6 in both Ishikawa and AN3CA cells (Fig. 5 e). These results suggested that YAP can directly regulate the transcription of IL-6, while not IL-11, in EC cells.

NF-κB is involved in YAP regulated transcription of IL-11 in EC cells

IL-11 transcription is largely dependent upon transcription factors such as AP-1, SMADs, and p65NF-κB in cancer cells (Xu et al., 2016). EC cells were further treated with the inhibitors of AP-1 (SR 11302), SMAD2/3 (SB431542), and NF-κB (BAY 11–7082), respectively. Our data showed that only the inhibitor of NF-κB (BAY 11–7082) can significantly down regulate the mRNA expression of IL-11 in Ishikawa and AN3CA cells (Fig. 6a).
Further, over expression of p65 (Fig. 6 b), one key component of NF-κB complex (Tak and Firestein, 2001), can reverse si-YAP induced down regulation of IL-11 in both Ishikawa (Fig. 6c) and AN3CA (Fig. 6d) cells. This might be due that the inhibitor of YAP can rapidly decrease the transcription of p65 in both Ishikawa and AN3CA cells (Fig. 6 e). Collectively, these results showed that NF-κB is involved in YAP regulated transcription of IL-11 in EC cells.

Discussion

Although various studies indicated that YAP functions as an oncogene in most cancers (Zhao et al., 2010), the roles of YAP in the progression of EC remain unclear. Our present study revealed that the expression of YAP was upregulated in both EC cells and tissues as compared to their corresponding controls. Targeted inhibition of YAP by its siRNA or inhibitor can suppress the proliferation and increase the chemosensitivity of EC cells. Among the measured cytokines, YAP can directly bind with the promoter of IL-6 to increase its transcription. As to IL-11, the upregulation of p65 is involved in YAP regulated its expression. Collectively, our present study revealed that YAP can trigger the malignancy of EC cells via upregulation of IL-6 and IL-11.

Our study revealed that the upregulation of YAP in EC cells can trigger its proliferation and decrease its chemosensitivity. Tsujiura et al. (Tsujiura et al., 2014) reported that higher levels of nuclear YAP were associated with poor prognostic factors of EC patients. Consistently, YAP can promote the proliferation, anchorage independent growth, invasion and migration of human EC HEC-1-B cells (Tsujiura et al., 2014). The reasons responsible for upregulation of YAP in EC cells need further study.

Our data suggested that the upregulation of IL-6 and IL-11 was involved in YAP regulated proliferation and...
YAP can induce the expression of IL-6 in hepatocellular carcinoma cells and then recruit tumor-associated macrophages (Zhou et al., 2018). Further, IL-6 has been proved as the transcriptional target of YAP involved in basal-like breast cancer (Kim et al., 2015). Our data confirmed that YAP can directly bind with the promoter of IL-6 to regulate its transcription in EC cells. In addition, our data also showed that YAP can regulate the expression of IL-11 in EC cells but not directly bind with its promoter. This might be due to that YAP can upregulate p65 induced transcription of IL-11. Both IL-6 and IL-11 can promote the malignancy of EC cells via triggering cell proliferation, migration and invasion (Chu et al., 2018; Lay et al., 2012; Yap et al., 2010).

**Conclusions**

We demonstrated that the upregulation of YAP can increase the proliferation and decrease the chemosensitivity of EC cells via upregulation of IL-6 and IL-11. Although further mechanisms and in vivo evidences are needed, our data suggested that targeted inhibition of YAP might be a potential therapy approach for treatment of EC patients.

**Abbreviations**

ChIP: Chromatin immunoprecipitation; Dox: doxorubicin; EC: endometrial cancer; ECL: enhanced chemiluminescence; ELISA: Enzyme-linked immunosassays; ESC: endometrial stromal cell; HRP: horseradish peroxidase; ILS: interleukins; LATS1/2: large tumor suppressor 1/2; MST1/2: mammalian Ste20-like kinases 1/2; PVDF: polyvinylidene fluoride; SD: standard deviation; TNF: tumor necrosis factor; VP: verteporfin; YAP: Yes-associated protein

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**Authors’ contributions**

Data collecting: Jing Wang, Xianchao Kong. Writing: Jing Wang, Tiefang Song. Data analysis: Suiyang Zhou, Xianchao Kong. Design: Jing Wang, Tiefang Song, Suiyang Zhou, Xianchao Kong. All authors read and approved the final manuscript.

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**Availability of data and materials**

All data and material are available.

**Ethics approval and consent to participate**

All human related experiments have been conducted according to the approve of the Ethical Committee of our hospital according to the Chinese Ethical Regulations. Informed consent was obtained from all individual participants included in the study.

**Consent for publication**

All authors give the consent for the publish of this study.
Competing interests
The authors declare that they have no competing interests.

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