Original Research

ARID1A-*mutated* cervical cancer depends on the activation of YAP signaling

Fei Gao[1], Peiling Li[1,*], Xianchao Kong[1], Tiefang Song[1], Qi Han[1], Suiyang Zhou[1]

[1]*Department of Obstetrics and Gynecology, The 2nd Affiliated Hospital of Harbin Medical University, 150081 Harbin, Heilongjiang, China*

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1. Abstract

Background: Cervical cancer is a prevalent female malignancy with poor survival rates. ARID1A is frequently mutated or deleted in a variety of tumors and YAP signaling is widely activated in human malignancies. Nevertheless, the mechanism of YAP signaling in *ARID1A*-mutated cervical cancer remains unknown. **Methods**: The cell viability was determined by MTT assay. The expression of ARID1A, YAP1 and CTGF were evaluated by western blot. The cell proliferation was detected by colony formation. **Results**: The bioinformatics analysis suggested that mutation of ARID1A was associated with the activation of YAP1 signaling. In addition, knockdown of YAP1 inhibited ARID1A-mutated cervical cancer cells growth. Verteporfin is an inhibition of YAP1 signaling. Interestingly, knockdown of ARID1A decreased ARID1A-wildtype cervical cancer cells resistance to verteporfin. Meanwhile, overexpression of ARID1A increased ARID1A-mutated cervical cancer cells resistance to verteporfin. Similarly, blocking YAP1 signaling inhibited the tumor formation caused by ARID1A-mutated cervical cancer cells *in vivo*. **Conclusion**: Inhibition of YAP1 signaling suppresses *ARID1A*-mutated-induced tumorigenesis of cervical cancer, providing a novel therapeutic strategy for cervical cancer.

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2. Introduction

Cervical cancer is a prevalent female malignancy with the highest mortality rate among all female malignant tumors [1, 2], and second highest in term of incidence among gynecological malignant tumors [3]. In 2012, a total of 528,000 new cases and 266,000 deaths caused by cervical cancer were reported [4]. In particular, more than 80 percent of new cases are diagnosed in developing countries [5]. Due to advances in screening technologies and therapeutic strategies, the incidence and mortality of cervical cancer are declining [6]. Nevertheless, the survival of cervical cancer patients is still poor [7]. Thus, it is urgent to uncover efficient diagnostic markers for cervical cancer.

As a member of the SWI/SNF complex, ARID1A is a tumor suppressor gene, which is frequently mutated or deleted in a variety of tumors [8]. Given that tumor suppressor gene inactivation cannot be directly interfered, synthetic lethality in *ARID1A*-mutated cancers, such as targeting EZH2 has been proposed to be an effective therapeutic strategy [9]. It has been reported that the SWI/SNF complex can inhibit YAP1. Therefore, inactivation of the SWI/SNF complex (such as deletion of ARID1A) leads to YAP1 activation, suggesting that YAP1 is a potential synthetic lethality target in *ARID1A*-mutated tumors [10].

YAP is a transcriptional coactivator that is localized in cytoplasm or nucleus. YAP regulates gene expression by interacting with other transcription factors (such as TEAD) to identify homologous cis-acting elements [11]. YAP is widely activated in human malignancies and is essential for tumorigenesis or tumor growth in most cancers [12]. Activation of YAP induces characterization, proliferation, chemotherapeutic resistance and metastasis of cancer stem cells [12]. Thus, addiction to YAP may represent a cancer susceptibility, which can be used for therapeutic strategies in clinic.

Cervical cancer patients often have ARID1A gene mutations or YAP1 gene amplification, and the genomic changes in these two genes are mutually exclusive events [13]. Here, we showed that the effect of YAP signaling on *ARID1A*-mutated cervical cancer *in vivo* and *in vitro*. Taken together, our results defined a YAP-dependent mechanism in *ARID1A*-mutated cervical cancer. Moreover, by using YAP signaling inhibitor, we described a novel tool to interfere with *ARID1A*-mutated cervical cancer and identify a promising new treatment strategy for cervical cancer.

3. Methods and materials

The animal experiments in the present study were in accordance with the Guide for the Care and Use of Laboratory Animals and approved by the 2nd Affiliated Hospital of Harbin Medical University.

3.1 Cell culture and transfection

Four human cervical cancer cell lines (HeLa, C33A, CaSki and ME180) from the American Type Culture Collection (ATCC, USA) were cultured in Minimum Essential Medium, Eagle's Minimum Essential Medium, RPMI-1640 Medium, and McCoy's 5a (Gibco/Thermo Fisher Scientific, USA), respectively, with 10% fetal bovine serum (FBS, Gibco) at 37 °C in a humidified atmosphere of 5% CO_2.

To knockdown the expression of YAP *in vitro*, si-NC, si-YAP#1, or si-YAP#2 were purchased from GenePharma (China), and transfected into ME180, CaSki, HeLa, C33A cells by using Lipofectamine 3000 (Thermo Fisher Scientific, USA). Besides, si-NC (negative control), si-ARID1A#1, or si-ARID1A#2 (GenePharma; China) was transfected into ME180 and HeLa cells by Lipofectamine 3000. Similarly, the pcDNA3 (vector control) and pcDNA-ARID1A plasmids were also transfected into CaSki and C33A cells by using Lipofectamine 3000. After transfection, cells were treated with 0.625, 1.25, 2.5, 5 or 10 μM of verteporfin for 48 h and cell viability was detected with MTT assay.

3.2 YAP1-tead promoter reporter assay

Human YAP1 gene promoter was cloned into pGL2 reporter plasmid (Promega, USA), and the recombinant plasmid pGL2-YAP1 promoter was transfected into C33A, CaSki, ME180 or HeLa cells. pRL-SV40 reporter plasmid with Renilla luciferase activity (Promega, USA) was used to normalize the transfection efficiency. After 24 h, the firefly and Renilla luciferase activities were measured by a Dual-Luciferase Reporter Assay Kit (Promega, USA).

3.3 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide (MTT) assay

Cell viability was determined using MTT assays in 96-well plates. Cells after transfection or incubation with verteporfin for 48 h were incubated with MTT solution for 4 h. Next, 100 μL of dimethyl sulfoxide (DMSO) was added to dissolve the formazan crystals for the MTT assay. The absorbance was read at 490 nm using a spectrophotometer (Tecan, Männedorf, Switzerland).

3.4 Colony formation assay

200 cells per well were seeded into a 12-well plate. The medium was changed every 3 days. After 10 days, the majority of the cell clones were more than 50 cells. The clones were washed with phosphate-buffered saline (PBS) and then stained with crystal violet (Beyotime, China) for 5 min.

3.5 Tumor xenograft assay

C33A cells (5×10^6) were resuspended in PBS and immediately subcutaneously injected into the flank of each nude mouse (female, 6 weeks old; Biotechnology Co Beijing zhongkezesheng, China). A total of 12 nude mice

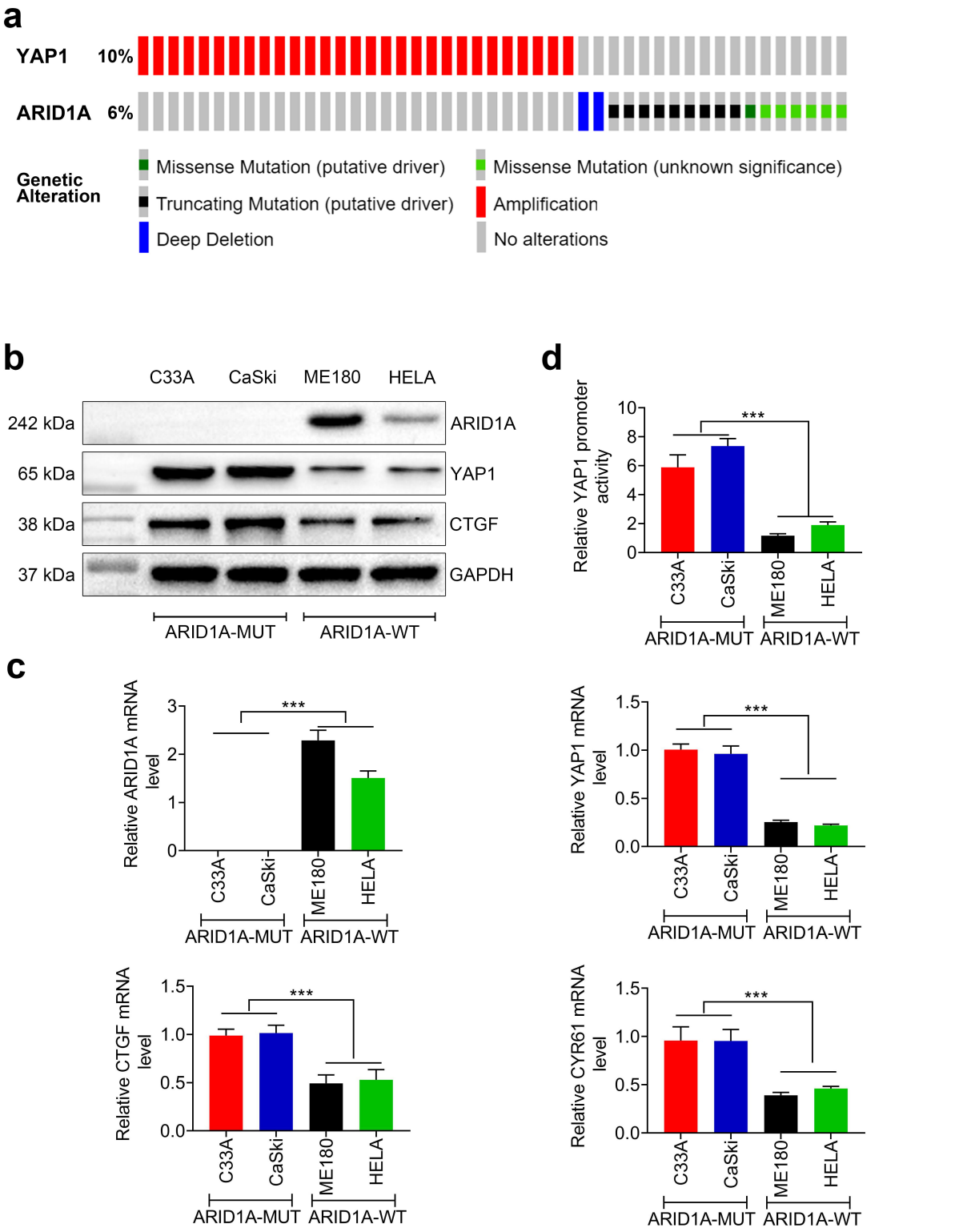

Fig. 1. Mutation of *ARID1A* is associated with the activation of YAP1 signaling. (a) *ARID1A* and *YAP* mutations in cervical cancer patients based on the cbioportal database. (b) C33A and CaSki cells served as *ARID1A*-mutated cells, whereas ME180 and HeLa cells were used as wildtype cell lines. Western blots indicate that ARID1A is barely detected but YAP1 and CTGF are enhanced in C33A and CaSki cells. (c) The transcript levels of *ARID1A*, *CTGF*, *YAP1* and *CYR61* were determined by qRT-PCR. (d) Luciferase activity assays indicate that depletion of *ARID1A* promotes *YAP1-tead* promoter activity in C33A and CaSki cells. Each experiment was repeated three times. ***$p < 0.001$.

were divided into two groups (n = 6 per group) on day 5 after tumor implantation, and the mice received subcutaneous injection of verteporfin (100 mg/kg) or 8% DMSO every 2 days. The tumor growth was measured every week and the tumor volumes were calculated using the formula [length/2] $\times$ [width^2]. Mice were sacrificed 6 weeks after tumor implantation with CO_2 inhalation. Thereafter, the tumor was removed and weighed.

3.6 Immunohistochemistry (IHC)

Tumor tissues were collected, embedded with paraffin, cut into sections, de-waxed, hydrated, incubated with citrate buffer, and then blocked in TBST containing 5% BSA. After that, sections were incubated with anti-KI67 (dilution: 1:500; ab15580, Abcam, UK) or anti-YAP1 (dilution: 1:500; ab205270, Abcam, UK) antibodies at 4 °C overnight, washed in TBST for three times for 10 min and incubated with appropriate secondary antibody (dilution: 1:5000; Abcam, UK) for 2 h at room temperature, then washed again in TBST.

3.7 Quantitative real-time PCR (qRT-PCR)

Total RNA was extracted from the transfected cells using Trizol reagents (Invitrogen, USA). Then, the extracted RNA was served as template and reverse transcribed into cDNA using a PrimeScript™ RT reagent kit (Takara, Japan). Next, qRT-PCR assay was performed using a SYBR® Premix Ex Taq™ Kit (Takara, Japan). GAPDH was used as an internal control. Primer sequences used in this study are as follows: CTGF: forward 5′-CAAGGGCCTCTTCTGTGACT-3′, reverse 5′-ACGTGCACTGGTACTTGCAG-3′; GAPDH: forward 5′-GGAGCGAGATCCCTCCAAAAT-3′, reverse 5′-GGCTGTTGTCATACTTCTCATGG-3′.

3.8 Western blot

Equal amounts of proteins extracted from cells using RIPA buffer were separated by 10% SDS-PAGE, and electrophoretically transferred onto PVDF membranes. The membranes were successively incubated with primary antibodies, including ARID1A antibody (dilution: 1:700; ab242377, Abcam, UK), YAP1 antibody (dilution: 1:700; ab56701, Abcam, UK), CTGF antibody (dilution: 1:700; ab6992, Abcam, UK), CYR61(dilution: 1:700; ab230947, Abcam, UK) or GAPDH antibody (dilution: 1:700; ab8245, Abcam, UK)) overnight at 4 °C. Then, membranes were washed with TBST buffer and incubated with appropriate second antibody (dilution: 1:6000; Abcam, UK) for 2 hours at room temperature. Eventually, the protein expression was visualized by a BeyoECL kit (Beyotime, China).

3.9 Statistical analysis

All experiments were repeated at least three times and the data were recorded, calculated and presented as mean $\pm$ SD. Statistical analysis was conducted using GraphPad Prism software. Data were analyzed by using *t*-test or one-way ANOVA with Tukey's *post hoc* tests. A *p* value less than 0.05 was considered statistically significant.

4. Results

4.1 Mutation of ARID1A is associated with the activation of YAP1 signaling

Based on the cbioportal database (Fig. 1a), amplification of *YAP* was detected in 10% of cervical cancer cases. Besides, 6% of the cases had an alteration in the *ARID1A* gene, including deep depletion, truncating mutation and missense mutation. Interestingly, amplification of *YAP* displayed mutual exclusivity with *ARID1A* mutations. To explore the specific role of YAP1 in the context of *ARID1A*-mutated cervical cancers, two cell lines, C33A and CaSki, were regarded as *ARID1A*-mutated cell lines, in which *ARID1A* expression was severely reduced [14], whereas ME180 and HeLa cells served as wildtype cell lines. As shown in Fig. 1b, ARID1A protein was barely present in C33A and CaSki cells. This was in contrast with YAP1 protein, which was abundantly expressed in C33A and CaSki cells. The YAP1/TEAD complex activates the transcription of downstream oncogenes, such as *CTGF* [15]. Furthermore, *ARID1A* transcript level was significantly up-regulated in ME180 and HeLa cells, but barely detected in C33A and CaSki cells. Besides, the mRNA levels of *CTGF* and *CYR61* were also found to be reduced in ME180 and HeLa cells, while *YAP1* transcript level was markedly promoted in C33A and CaSki cells (Fig. 1c). Compared with ME180 and HeLa cells, *CTGF* expression was upregulated in C33A and CaSki cells, indicating that *ARID1A* mutation activates YAP1 signaling. Additionally, we observed a significant increase in *YAP1-tead* promoter activity in C33A and CaSki cells (Fig. 1d). These results illustrated that mutation of *ARID1A* promoted *YAP1-tead* promoter activity and activated YAP1 signaling.

4.2 Knockdown of YAP1 inhibits ARID1A-mutated cervical cancer cell growth

Verteporfin (VP) disrupts the interaction between YAP and TEAD and inhibits YAP activity [16]. To abolish the effect of YAP1, cells were treated with 1 μm verteporfin for 48 h. Our results demonstrated that treatment with verteporfin reduced cell viability of C33A, CaSki, ME180 and HeLa cells in a dose-dependent manner (Fig. 2a). In addition, colony formation assays showed that the number of cell colonies was significantly decreased upon treatment with verteporfin in C33A and CaSki (Fig. 2b). Western blotting results showed that verteporfin treatment reduced CTGF and CYR61 expression in C33A and CaSki cells, but had no effect in ME180 and HeLa cells (Fig. 2c). To investigate the role of YAP in cell growth, si-YAP#1 or si-YAP#2 was transfected into cells to knockdown *YAP1* expression (Fig. 2d). Results from the MTT assays indicated that cells transfected with si-YAP#1 or si-YAP#2 had decreased cell

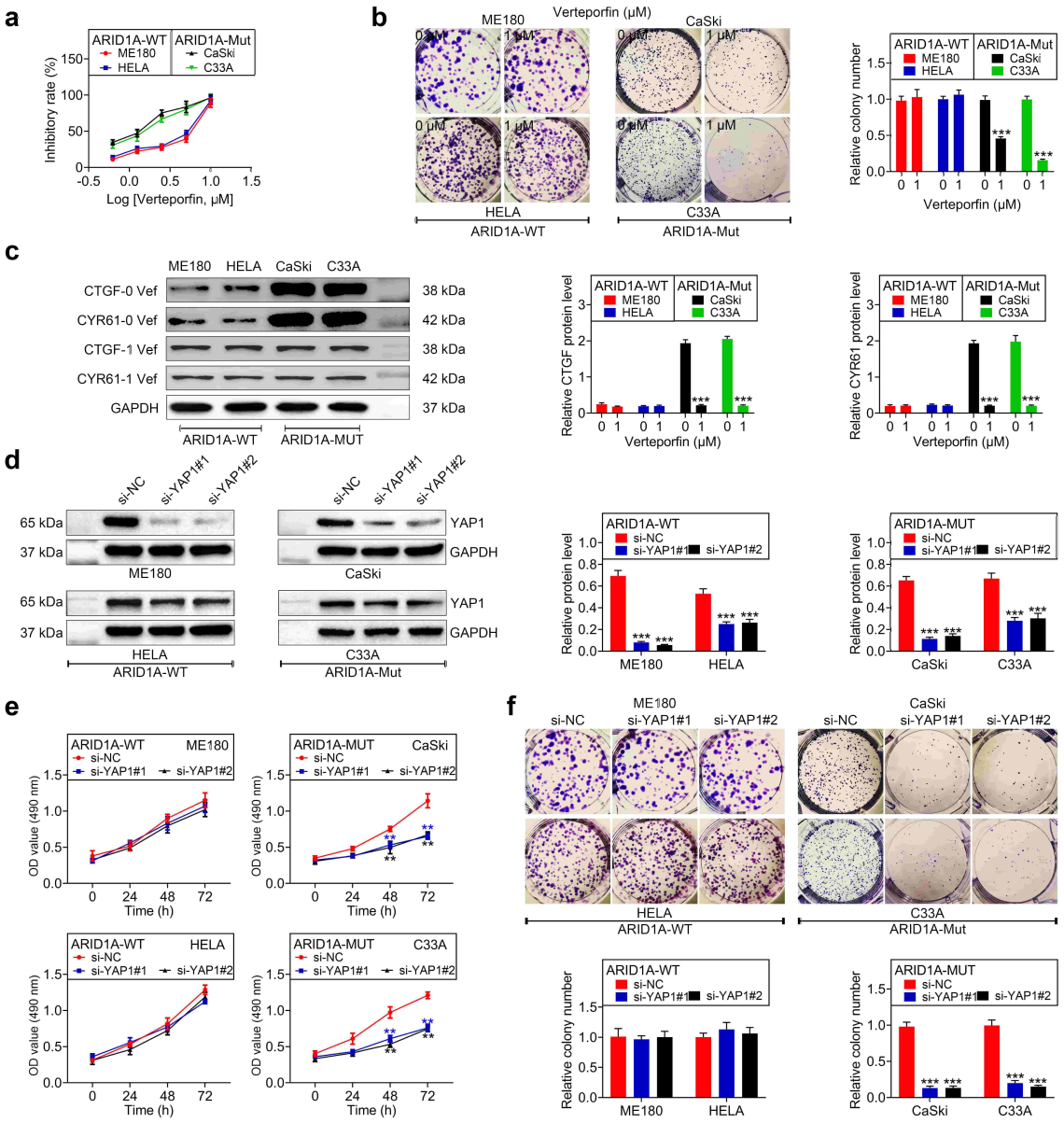

Fig. 2. Knockdown of YAP1 inhibits *ARID1A*-mutated cervical cancer cell growth. (a) ME180, HeLa, CaSki and C33A cells were treated with 0.625, 1.25, 2.5, 5 or 10 μM verteporfin for 48 h, and cell viability was measured by MTT assay. (b) Colony formation images show that 1 μM verteporfin treatment reduces cell growth in CaSki and C33A cells. (c) Verteporfin treatment reduces CTGF and CYR61 expression in CaSki and C33A cells, but has no effect on ME180 and HeLa cells. (d) si-NC, si-YAP1#1 or si-YAP1#2 was transfected into ME180, HeLa, CaSki and C33A cells, and YAP1 expression was evaluated by western blot. (e) MTT assays show that knockdown of *YAP* reduces cell viability of CaSki and C33A cells. (f) Colony formation images show that knockdown of YAP inhibits CaSki and C33A cell growth. Each experiment was repeated three times. $^{**}p < 0.01$, $^{***}p < 0.001$.

viability at 48 and 72 h compared with cells transfected with si-NC in C33A and CaSki cells. However, no change was observed in ME180 and HeLa cells treated with si-YAP#1 or si-YAP#2 (Fig. 2e). Furthermore, as shown in Fig. 2f, si-YAP#1 or si-YAP#2 significantly reduced colony formation in C33A and CaSki cells compared with si-NC. These results suggested that the downregulation of YAP1 inhibits *ARID1A*-mutated cervical cancer cell growth.

4.3 Knockdown of ARID1A decreases ARID1A-wildtype cervical cancer cell resistance to verteporfin

In order to determine the role of *ARID1A* in cervical cancer, si-ARID1A#1, si-ARID1A#2 (for specific knockdown of *ARID1A*) or si-NC was transfected into *ARID1A*-wildtype cell lines, ME180 and HeLa. As shown in Fig. 3a, the protein level of ARID1A in ME180 and HeLa cells transfected with si-ARID1A#1 or si-ARID1A#2 was

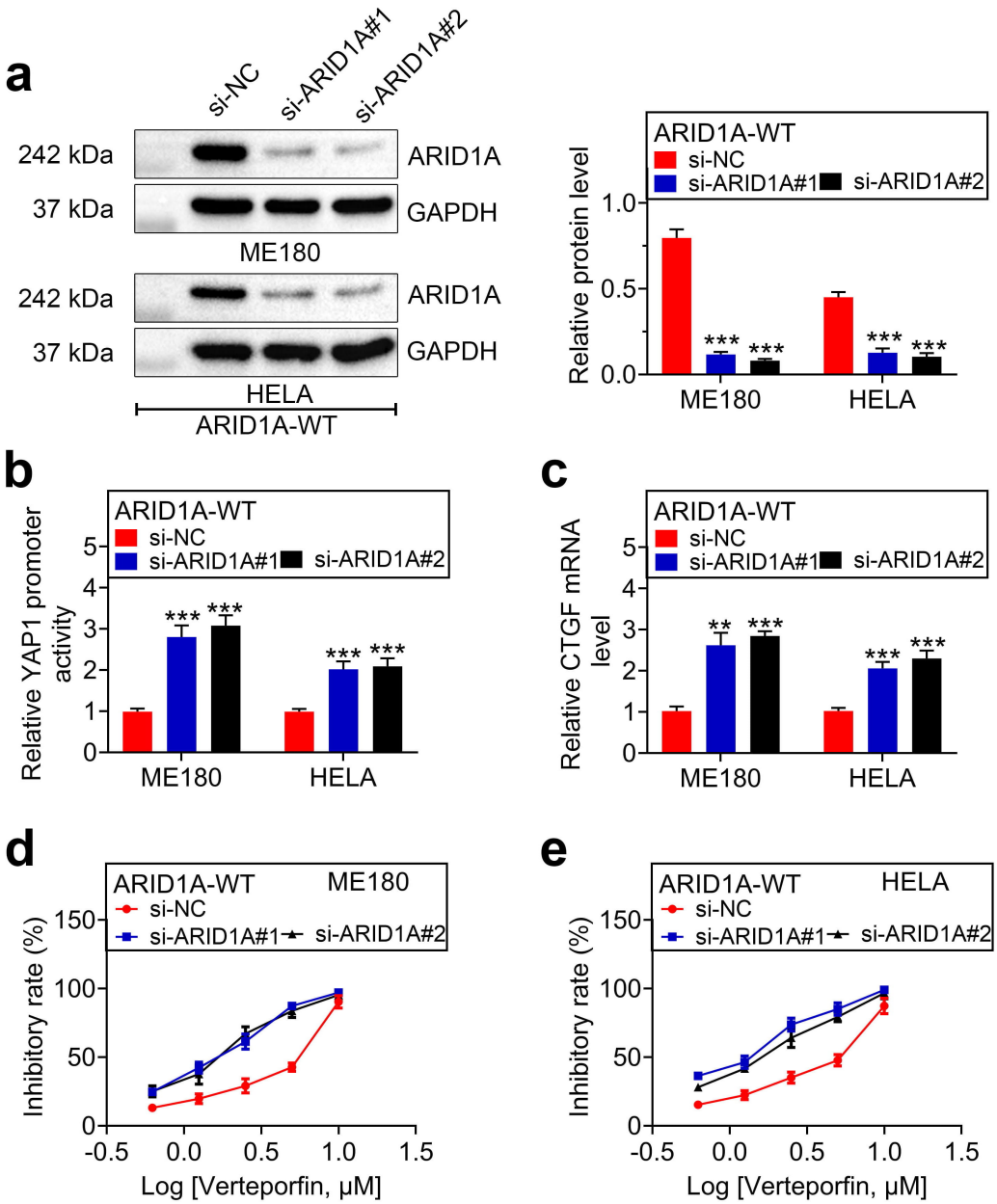

Fig. 3. Knockdown of *ARID1A* decreases *ARID1A*-wildtype cervical cancer cell resistance to verteporfin. (a) si-NC, si-ARID1A#1 or si-ARID1A#2 was transfected into *ARID1A*-wildtype cervical cancer cell lines, ME180 and HeLa. (b) *YAP1-tead* promoter activity was determined by luciferase activity assay. (c) Histograms show that *ARID1A* knockdown promotes the transcript level of *CTGF* in ME180 and HeLa cells, as determined by qRT-PCR. (d,e) MTT assays show that knockdown of *ARID1A* decreases *ARID1A*-wildtype cervical cancer cell resistance to verteporfin. Each experiment was repeated three times. $^{**}p < 0.01$, $^{***}p < 0.001$.

evidently decreased compared with that of si-NC. Furthermore, luciferase activity assay indicated that knockdown of *ARID1A* induced *YAP1-tead* promoter activity (Fig. 3b). In addition, the expression of YAP1 downstream target, *CTGF*, was significantly enhanced in ME180 and HeLa cells (Fig. 3c). More importantly, knockdown of *ARID1A* decreased ME180 and HeLa cell resistance to verteporfin (Fig. 3d,e). Altogether, these findings indicated that knockdown of *ARID1A* promotes YAP1 signaling and decreases ME180 and HeLa cell resistance to verteporfin.

4.4 Overexpression of ARID1A increases ARID1A-mutated cervical cancer cell resistance to verteporfin

To further validate the role of *ARID1A* in cell resistance of cervical cancer cells to verteprofin, pcDNA3-ARID1A (for overexpression of *ARID1A*) or pcDNA3 vector was transfected into *ARID1A*-mutated cell lines, C33A and CaSki. As shown in Fig. 4a, the protein level of ARID1A was significantly induced in C33A and CaSki cells transfected with pcDNA3-ARID1A compared to that

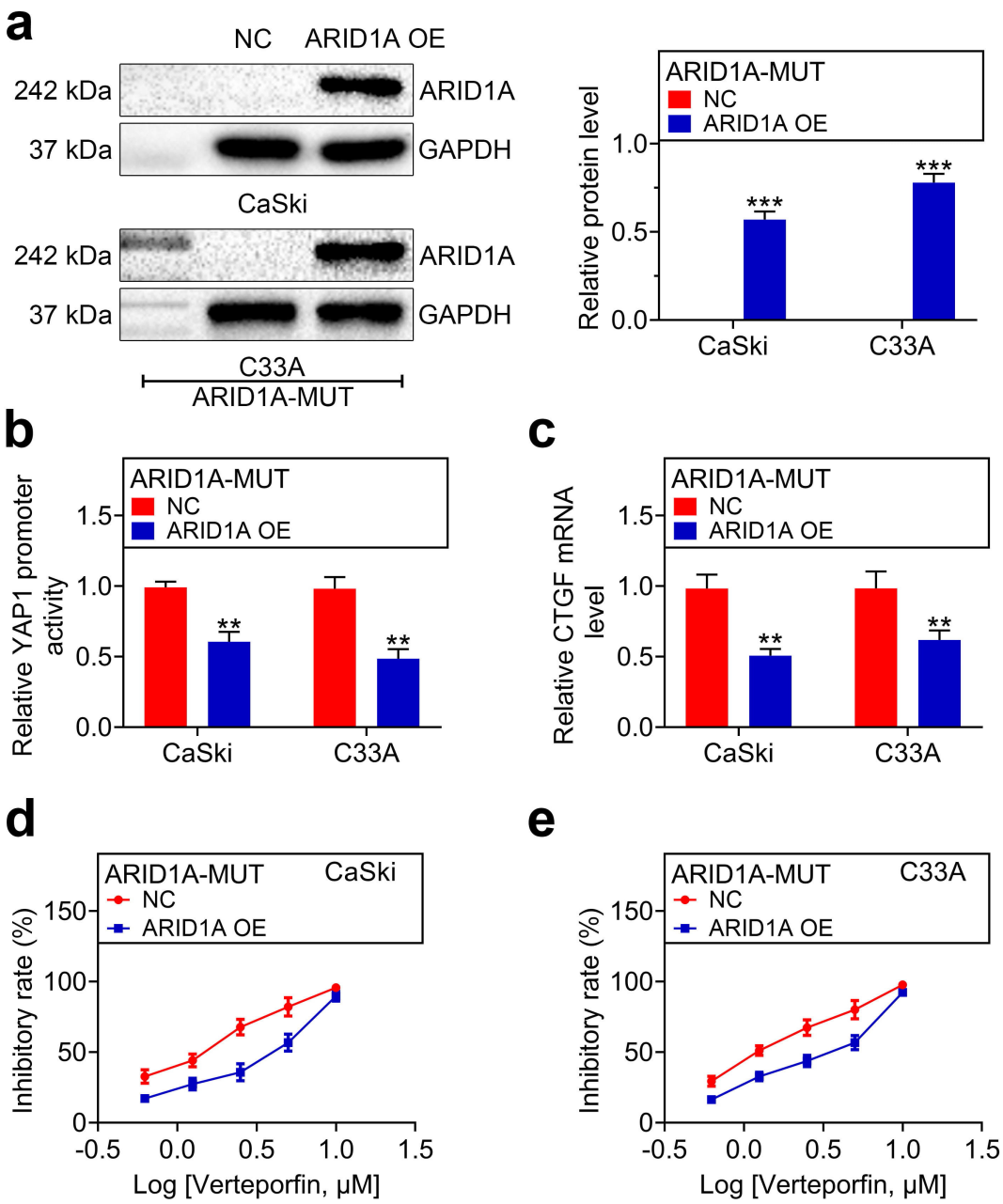

Fig. 4. Overexpression of ARID1A increases *ARID1A*-mutated cervical cancer cell resistance to verteporfin. (a) pcDNA3-ARID1A or pcDNA3 was transfected into *ARID1A*-mutated cervical cancer cell lines, CaSki and C33A. (b) *YAP1-tead* promoter activity was evaluated by luciferase activity assay. (c) Histograms show that overexpression of *ARID1A* reduces the transcript level of *CTGF* in CaSki and C33A cells. (d,e) MTT assays show that *ARID1A* overexpression promotes *ARID1A*-mutated cervical cancer cell resistance to verteporfin. Each experiment was repeated three times. $^{**}p < 0.01$, $^{***}p < 0.001$.

of negative control (NC). Luciferase activity assay indicated that overexpression of *ARID1A* reduced *YAP1-tead* promoter activity (Fig. 4b). Additionally, the transcription of YAP1 downstream target, *CTGF*, was found to be significantly suppressed in C33A and CaSki cells (Fig. 4c). Interestingly, overexpression of *ARID1A* increased C33A and CaSki cell resistance to verteporfin (Fig. 4d and 4e). Together, these data demonstrated that *ARID1A* overexpression increases *ARID1A*-mutated cervical cancer cell resistance to verteporfin.

4.5 Blocking YAP1 signaling inhibits the tumor formation caused by ARID1A-mutated cervical cancer cells

Given the tumor-suppressive function of verteporfin in *ARID1A*-mutated cervical cancer cells *in vitro* (Fig. 2b), next we sought to determine whether inhibition of YAP1 signaling could inhibit tumor formation caused by *ARID1A*-mutated cervical cancer cells *in vivo*. As shown in Fig. 5b, there was no significant difference

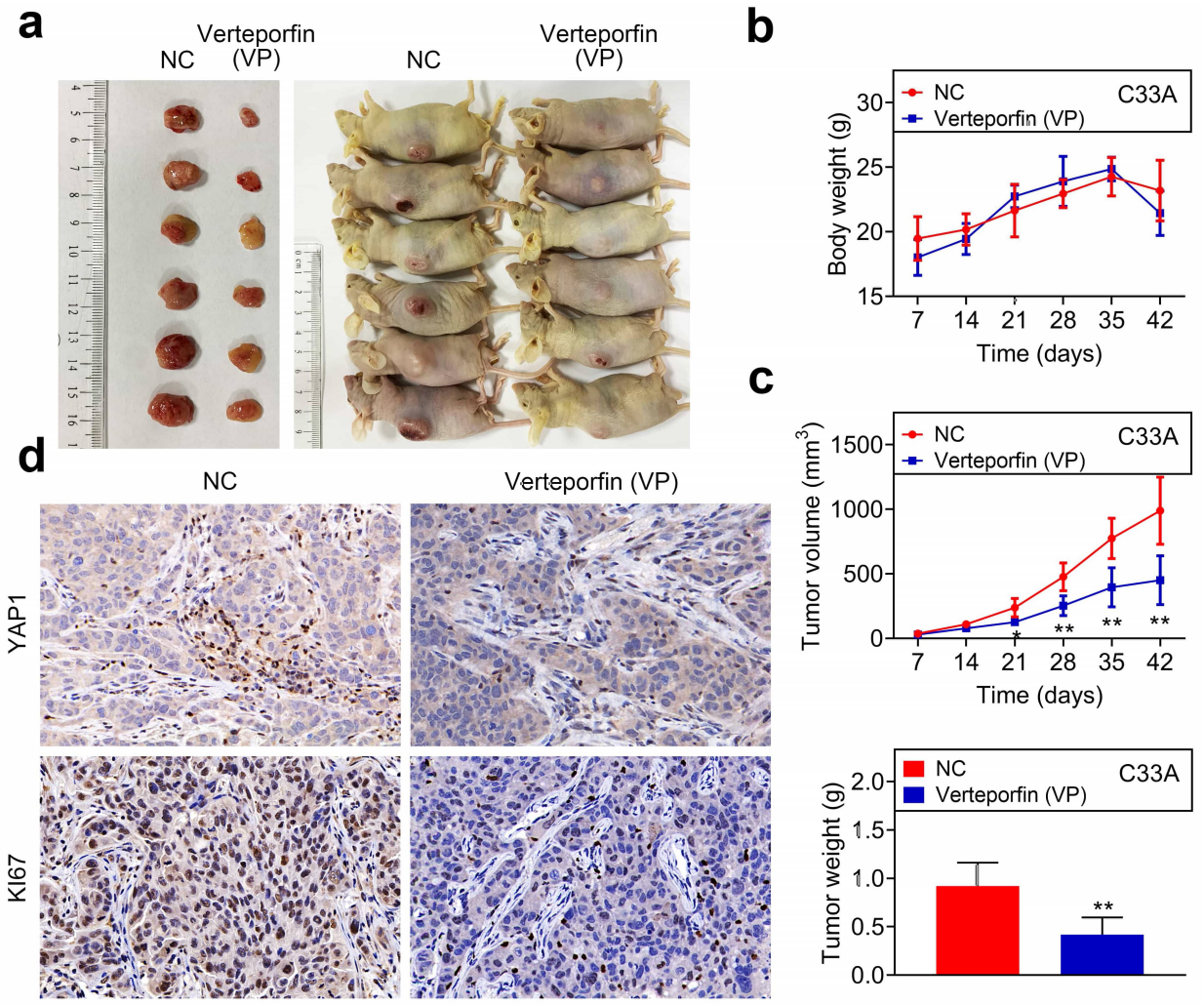

Fig. 5. Blocking YAP1 signaling inhibits tumor formation caused by *ARID1A*-mutated cervical cancer cells. ARID1A-mutated cervical cancer cells (C33A cells) were subcutaneously injected into nude mice, followed by verteporfin or DMSO treatment. (a,c) The tumor volume and weight were measured. (b) Line chart shows that verteporfin treatment does not affect the body weight of mice. (d) Representative IHC images of YAP1 and Ki67 staining show that verteporfin treatment inhibits tumor formation and reduces YAP1 and Ki67 expression. Each experiment was repeated six times. $*p < 0.05$, $**p < 0.01$.

between the body weight of NC or verteporfin-treated mice, indicating that verteporfin was not detrimental to their health. Subsequently, C33A cells were implanted subcutaneously into nude mice to investigate the role of YAP1 inhibition in tumor formation caused by *ARID1A*-mutated cervical cancer cells. Consistent with the results obtained from the *in vitro* experiments as described in Fig. 2, verteporfin impaired tumor growth in mouse model. The volumes and body weight of implanted tumors were significantly decreased in verteporfin-treated mice compared with NC mice (Fig. 5a and 5c). Furthermore, IHC of implanted tumors showed that the number of YAP1- and Ki67-positive cells was also reduced in verteporfin-treated mice compared with NC mice (Fig. 5d). These results demonstrated that blocking YAP1 signaling inhibits tumor formation caused by *ARID1A*-mutated cervical cancer cells.

5. Discussion

Cervical cancer is a leading cause of morbidity and cancer deaths in women worldwide [17]. In this study, we have demonstrated that *ARID1A* mutation was associated with the activation of YAP1 signaling. Moreover, knockdown of YAP1 inhibited *ARID1A*-mutated cervical cancer cell growth. Verteporfin is an inhibitor of YAP1 signaling. In addition, knockdown of *ARID1A* decreased *ARID1A*-wildtype cervical cancer cell resistance to verteporfin, whereas *ARID1A* overexpression led to the opposite effect. Interestingly, blocking YAP1 signaling inhibited tumor formation of *ARID1A*-mutated cervical cancer cells *in vivo*. Altogether, these findings indicated that blocking YAP1 signaling suppresses *ARID1A*-mutated-induced tumorigenesis in cervical cancer, providing a novel therapeutic strategy for cervical cancer.

ARID1A mutations have been frequently found in various types of cancers [18]. It has been reported that ARID1A maintains differentiation of pancreatic ductal cells and inhibits development of pancreatic ductal adenocarcinoma [19]. In addition, loss of ARID1A is commonly observed in ovarian clear cell carcinoma patients with tumor recurrence, and it is accompanied by worse survival outcome [20]. Similarly, ARID1A inactivation is associated with lymphatic invasion, lymph node metastasis and poor prognosis in gastric adenocarcinomas [21]. Thus, loss of ARID1A is closely related to the malignant phenotype and poor prognosis of cancers. Currently, accumulating evidence has pointed out that loss of ARID1A induces cell proliferation in cancers and organs via the AKT signaling and p53-dependent apoptotic pathway [22–24]. Interestingly, in cervical cancer, 6% of the patients had different mutations in ARID1A expression [25]. Besides, we demonstrated that the amplification of YAP displayed mutual exclusivity with *ARID1A* mutations. When the YAP1 signaling was blocked, the proliferation of *ARID1A*-mutated cells was suppressed, indicating the potential mechanism of ARID1A in cancers might be associated with YAP1 signaling.

YAP signaling has various biological functions. Dysregulation of YAP signaling modulates resistance to chemotherapies [26]. Moreover, YAP can induce cancer cells to program into cancer stem cells, promote cell proliferation, and trigger tumor initiation, progression and metastasis [11]. In cervical cancer, activated YAP facilitates upregulation of TGF-α, AREG, and EGFR, forming a positive feedback loop that drives cell proliferation [27]. Mechanically, increased YAP expression has been observed in cervical cancer and is related to epithelial homeostasis [28]. Endogenous YAP1 activation drives immediate onset of cervical carcinoma *in situ* in mice [29]. A recent study has demonstrated that hyperactivation of YAP1 is sufficient to induce cervical carcinogenesis [30]. Fortunately, in *ARID1A*-mutated cells, knockdown of YAP1 only inhibited *ARID1A*-mutated cell growth and had no effect on *ARID1A*-wildtype cells, which was consistent with the results of YAP1 signaling inhibition. These findings have provided strong evidence that loss of *ARID1A* is closely related to the activation of YAP1 signaling.

Furthermore, we have demonstrated that knockdown of *ARID1A* promoted *YAP1-tead* promoter activity and activated YAP signaling. Thus, it decreased *ARID1A*-wildtype cervical cancer cell resistance to verteporfin. Consistently, we have shown that *ARID1A* overexpression in *ARID1A*-mutated cervical cancer cells led to the opposite effect. These results strongly suggested that loss of *ARID1A* in cervical cancer cells was mediated by the activation of YAP1 signaling. For *in vivo* study, activation of YAP initiates pancreatic cancer development from ductal cells in mice [31]. In contrast, YAP deficiency causes dysfunctional regulatory T cells fail to promote tumor growth in mice [32]. In accordance with these previous findings, in the current study, we have shown that blocking YAP1 signaling suppressed tumor growth caused by *ARID1A*-mutated cervical cancer cells in mice, suggesting that cervical cancer cell proliferation caused by loss of *ARID1A* was caused by the activation of YAP1 signaling *in vivo*. Other targets have also been proposed to be able to regulate YAP signaling in cervical cancer. Zhao *et al*. [33] reported that miR-216a-3p suppresses the proliferation and invasion of cervical cancer cells through downregulation of ACTL6A-mediated YAP signaling. Thyroid hormone receptor interacting protein 6 (TRIP6), a novel tumor-related regulator, can up-regulate oncogenic YAP signaling and accelerate cervical cancer cell proliferation and invasion [34]. Besides, hsa_circ_0023404 promotes development cervical cancer and progression through regulating miR-136/TFCP2/YAP pathway [35]. Collectively, these molecules are the regulators of YAP signaling, which may also be correlated with the expression of *ARID1A* in cancers. However, their relationship and the underlying regulatory mechanism remain unknown. Thus, future study should focus on these potential targets, which might be related to the loss of *ARID1A* in cervical cancer.

6. Conclusions

In summary, our study has demonstrated that targeting YAP signaling using YAP signaling inhibitor in *ARID1A*-mutated cells represents a therapeutic strategy. This approach provides a promising future in precision medicine since it is based on *ARID1A* mutational status and the mutual exclusivity of *ARID1A* mutations and YAP amplification. The YAP signaling inhibitor, verteporfin, is an ideal agent for various cancer types [36]. Notably, more effort is warranted to interrogate the potential of verteporfin in the clinical trials of cervical cancer. Thus, our study provides a scientific rationale for the potential translation of these findings by repurposing clinically applicable verteporfin for *ARID1A*-mutated cervical cancer.

7. Author contributions

FG and PL designed the study, supervised the data collection. XK analyzed the data, interpreted the data. TS, QH and SZ prepare the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

8. Ethics approval and consent to participate

Ethical approval was obtained from the Ethics Committee of the 2nd Affiliated Hospital of Harbin Medical University (Approval No. SYDW2019-64).

9. Acknowledgment

Not applicable.

10. Funding

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11. Conflict of interest

The authors declare no conflict of interest.

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Send correspondence to: Peiling Li, Department of Obstetrics and Gynecology, The 2nd Affiliated Hospital of Harbin Medical University, 150081 Harbin, Heilongjiang, China, E-mail: pl0902hz@163.com