

# TBOPP enhances the anticancer effect of cisplatin by inhibiting DOCK1 in renal cell carcinoma

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**Abstract.** The treatment of renal cell carcinoma (RCC) with chemotherapy remains a challenge; therefore, improving the knowledge of the molecular mechanisms underlying RCC chemoresistance and developing novel therapeutic strategies is important. Dedicator of cytokinesis 1 (DOCK1), the first member of the DOCK family to be discovered, displays various roles during tumorigenesis; however, its role during RCC progression is not completely understood. Therefore, the present study aimed to clarify the function of DOCK1 and 1-[2-(3'-(trifluoromethyl)-(1,1'-biphenyl)-4-yl)-2-oxoethyl]-5-pyrrolidinylsulfonyl-2(1H)-pyridone (TBOPP), a DOCK1-sensitive inhibitor, during RCC development and chemoresistance. The results of CCK-8 and EdU assay indicated that TBOPP decreased RCC cell viability and proliferation compared with the control group, and sensitized RCC cells to cisplatin. Moreover, RCC cells with high DOCK1 expression levels displayed increased resistance to cisplatin, whereas DOCK1 knockdown enhanced the lethal effects of cisplatin on RCC cells. Furthermore, the results determined by western blotting, CCK-8 and cell apoptosis assay indicated that TBOPP effectively reduced DOCK1 expression levels compared with the control group, and the

TBOPP-mediated cisplatin sensitizing effect was mediated by DOCK1 inhibition. The present study suggests that DOCK1 plays a vital role in RCC cell chemoresistance to cisplatin; therefore, TBOPP may serve as a novel therapeutic agent for RCC chemoresistance.

## Introduction

Renal cell carcinoma (RCC) is a common cancer that accounts for ~3% of all diagnosed human cases of cancer (1,2). Surgery is the primary treatment strategy for localized RCC, but a third of patients with localized RCC experience metastases after nephrectomy (3). Chemotherapy is often an ineffective treatment strategy for RCC (4,5). Although cisplatin is an effective therapeutic agent in a number of different types of cancer, RCC displays resistance to cisplatin (6), with only 4-6% of patients with RCC responding to chemotherapy alone (7). Therefore, improving the knowledge of the molecular mechanisms underlying RCC chemoresistance and identifying novel RCC therapeutic targets is required.

The dedicator of cytokinesis (DOCK) family is one of the two members of the RAC guanine nucleotide exchange factor (GEF) family, which contain the evolutionarily conserved lipid-binding DOCK homology region-1 (DHR-1) domain and the catalytic DHR-2 domain (8). As a RAC-specific GEF, DOCK1 regulates phagocytosis, myoblastic fusion, cell migration and circular dorsal fold formation (9,10). Abnormal expression and activity of DOCK1 is associated with the malignant characteristics of multiple tumors (11-14). Increasing evidence has indicated that DOCK1 regulates invasion and metastasis by acting on downstream receptor tyrosine kinases (15-17). Moreover, previous studies have revealed that DOCK1 expression levels correlate with chemoresistance in several types of cancer, such as bladder cancer and non-small-cell lung carcinomas (12,18). However, the function of DOCK1 during RCC is not completely understood.

Considering the important role of DOCK1 during tumor development (11), DOCK1-selective inhibitors have been investigated. TBOPP [1-[2-(3'-(trifluoromethyl)-(1,1'-biphenyl)-4-yl)-2-oxoethyl]-5-pyrrolidinylsulfonyl-2(1H)-pyridone] is a cellular activity inhibitor that binds to the DHR-2 domain of DOCK1 with high affinity, blocking its interaction with RAC family

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**Abbreviations:** RCC, renal cell carcinoma; DOCK1, dedicator of cytokinesis 1; TBOPP, 1-[2-(3'-(trifluoromethyl)-(1,1'-biphenyl)-4-yl)-2-oxoethyl]-5-pyrrolidinylsulfonyl-2(1H)-pyridone; GEF, guanine nucleotide exchange factor; DHR-1, DOCK homology region-1; RAC1, RAC family small GTPase 1

**Key words:** renal cell carcinoma, DOCK1, TBOPP, chemoresistance

small GTPase 1 (RAC1) to inhibit its GEF activity without influencing the GEF activity of the diffuse B-cell lymphoma family, including T cell lymphoma invasion and metastasis 1 and Trio Rho guanine nucleotide exchange factor (19). TBOPP also displays an anti-invasion effect (20). However, the role of TBOPP during RCC has not been previously reported; therefore, the present study aimed to investigate the role of DOCK1 and TBOPP during RCC cisplatin resistance.

## Materials and methods

**Cell culture.** The 786-O, ACHN, and Caki-1 cell lines were purchased from the American Type Culture Collection. 786-O cells were maintained in RPMI-1640 medium (Gibco; Thermo Fisher Scientific, Inc.) containing 10% fetal bovine serum (FBS; Gibco; Thermo Fisher Scientific, Inc.). Caki and ACHN cells were maintained in DMEM/F12 (Gibco; Thermo Fisher Scientific, Inc.) containing 10% FBS and 1% penicillin-streptomycin solution (Gibco; Thermo Fisher Scientific, Inc.). Cells were cultured at 37°C with 5% CO<sub>2</sub>. TBOPP was purchased from WuXi AppTec and dissolved in DMSO before use. Cisplatin was purchased from Sigma-Aldrich, Merck KGaA. For single agent treatment groups, renal carcinoma cells were treated with 0, 0.039, 0.078, 0.156, 0.312, 0.625, 1.25, 2.5, 5, 10, 20 or 40  $\mu$ M TBOPP for 48 h at 37°C, or 0, 0.625, 1.25, 2.5, 5 or 10  $\mu$ M cisplatin for 48 h at 37°C. For the combined treatment group, renal carcinoma cells were treated with 10  $\mu$ M TBOPP and 0, 0.625, 1.25, 2.5, 5 or 10  $\mu$ M cisplatin for 48 h at 37°C.

**Small interfering (si)RNA transfection.** The DOCK1-specific and negative control siRNAs were designed by Shanghai GenePharma Co., Ltd. The sequences of the DOCK1 siRNAs were as follows: sc-35207A sense, GAGACAGAUUGGCUUUGAATT and antisense, UUCAAGCCAAUCUGUCUCTT; sc-35207B sense, GAGAGAACCAUAUAACAATT and antisense, UUGUAUAUAUGGUUCUCUCTT; and sc-35207C sense, CAGCAAACAUAAGAGAUATT and antisense, UAUUCUCUUGAUGUUUGCUGTT. The sequences of the negative control siRNA were as follows: Sense, UUCUCCGAACGUGACGUTT and antisense, ACGUGACACGUUCGGAGAATT. Cells were transfected with 8  $\mu$ M DOCK1 siRNAs (the mix of three sequences) or negative control siRNAs using Lipofectamine® 2000 (Invitrogen; Thermo Fisher Scientific, Inc.), according to the manufacturer's protocol. After 24 h transfection, the cells were used for subsequent experimentation.

**Western blotting.** Western blotting was performed according to a previously described protocol (21). Following 24 h treated with TBOPP or transfected with siRNA, the cells were collected, and total protein was extracted using RIPA lysis buffer (Beyotime Institute of Biotechnology). Total protein was quantified using a bicinchoninic acid assay kit (Appligen Technologies, Inc.). Equal amounts of proteins (40  $\mu$ g per lane) were separated via 10% SDS-PAGE and transferred to a PVDF membrane. Subsequently, the membrane was blocked with 5% non-fat milk in TBS and 0.1% Tween-20 buffer for 1 h at room temperature. The membrane was incubated overnight at 4°C with primary antibodies targeted against: DOCK1 (dilution 1:1,000; cat. no. ab97325; Abcam) and GAPDH (1:1,000;

cat. no. ab9485; Abcam). Following primary incubation, the membrane was incubated with horseradish peroxidase-conjugated secondary antibodies (dilution 1:500; cat. no. 7074; Cell Signaling Technology) at room temperature for 2 h. Protein bands were visualized using a Pierce™ ECL kit according to the manufacturer's protocol (Thermo Fisher Scientific, Inc.). Protein expression was semi-quantified using ImageJ software (version 1.8.0; National Institutes of Health). GAPDH was used as the loading control.

**Cell Counting Kit-8 (CCK-8) assay.** Cell viability was assessed using the CCK-8 assay (Dojindo Molecular Technologies, Inc.), according to the manufacturer's protocol. Briefly, RCC cells treated with TBOPP or DOCK siRNA for 24 h were seeded (3x10<sup>4</sup> cells/well) into 96-well plates. Following treatment with cisplatin, 10  $\mu$ l CCK-8 solution was added to each well and incubated for 2 h at room temperature. The absorbance value of each well at a wavelength of 450 nm was measured using an MRX II microplate reader (Dynex Technologies).

**5-Ethynyl-2'-deoxyuridine (EdU) assay.** The Click-iTEdU Imaging kit (Invitrogen; Thermo Fisher Scientific, Inc.) was used for the EdU assay according to the manufacturer's protocol. Briefly, cells were seeded (1x10<sup>4</sup> cells/well) into a 96-well plate. Following treatment, cells were fixed with 4% formaldehyde for 30 min, permeated with 0.5% Triton-X-100 for 10 min at room temperature and washed with PBS. Subsequently, 100  $\mu$ l EdU reagent was added to each well for 30 min at room temperature and cells were incubated with 100  $\mu$ l Hoechst 33342 for 10 min to label the nuclei. Cells were observed using a fluorescence microscope at x200 magnification.

**Cell apoptosis determination by flow cytometry.** Early and late apoptosis was detected using a FITC-conjugated Annexin-V and propidium iodide (PI) kit (BD Biosciences), according to the manufacturer's protocol. Cells (2-3x10<sup>5</sup>) were washed twice with pre-chilled PBS and resuspended in 100  $\mu$ l binding buffer with 5  $\mu$ l FITC-conjugated Annexin-V for 30 min at room temperature in the dark. Subsequently, cells were incubated with 100  $\mu$ l PI for 5 min at room temperature and then 400  $\mu$ l binding buffer was added. Apoptotic cells were analyzed using a BD Laser II flow cytometer (BD Biosciences) and FlowJo software 7.6 (FlowJo LLC).

**Statistical analysis.** Statistical analyses were performed using SPSS software (version 16.0; SPSS, Inc.) and GraphPad Prism (version 7; GraphPad Software, Inc.). Statistical differences between two groups were analyzed using a Student's t-test. Statistical differences among multiple groups were analyzed by one-way ANOVA followed by Tukey's post hoc test. Data are presented as the mean  $\pm$  standard deviation of three independent experiments. P<0.05 was considered to indicate a statistically significant difference.

## Results

**TBOPP decreases RCC cell proliferation and viability.** To investigate the function of TBOPP, RCC cells were treated with different concentrations (0-40  $\mu$ M) of TBOPP and cell

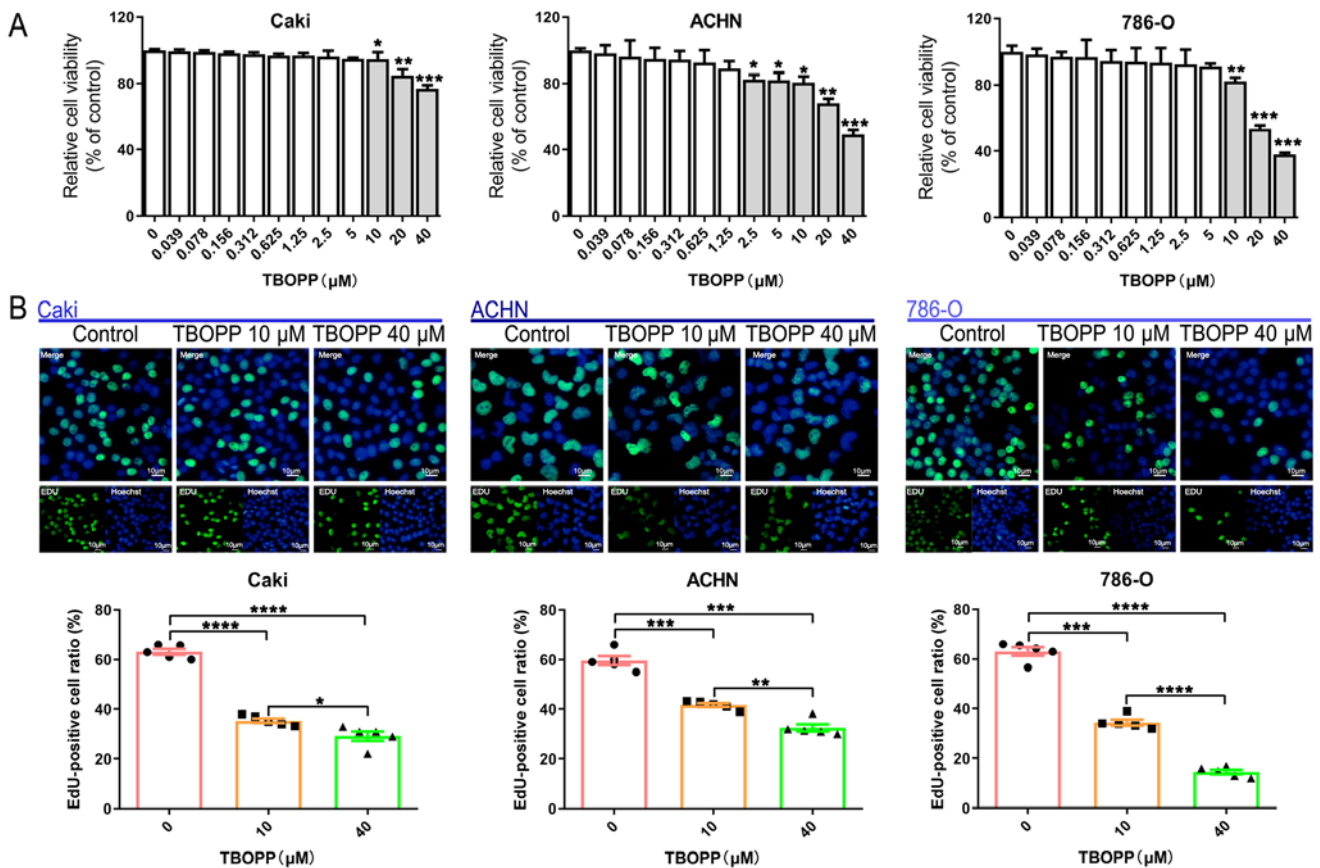


Figure 1. TBOPP reduces RCC cell viability and proliferation. (A) RCC cell viability was quantified using the Cell Counting Kit-8 assay. Grey columns indicate that there was a significant difference in cell viability compared with the control group. \* $P < 0.05$ , \*\* $P < 0.001$  and \*\*\* $P < 0.001$  vs. the control group. (B) RCC cell proliferation was assessed using the EdU assay. Scale bar, 10  $\mu\text{m}$ . The rate of EdU-positive cells in the S phase is presented. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  and \*\*\*\* $P < 0.0001$  as indicated. TBOPP, 1-[2-(3'-(trifluoromethyl)-(1,1'-biphenyl)-4-yl)-2-oxoethyl]-5-pyrrolidinylsulfonfyl-2(1H)-pyridone; RCC, renal cell carcinoma; EdU, 5-Ethynyl-2'-deoxyuridine.

viability was assessed using a CCK-8 assay. TBOPP decreased RCC cell viability from 10  $\mu\text{M}$  in a concentration-dependent manner (Fig. 1A). Subsequently, cells treated with two concentrations of TBOPP (10 and 40  $\mu\text{M}$ ) were assessed using the EdU assay. The results suggested that cell proliferation was also significantly decreased in the TBOPP treatment groups compared with the control group (Fig. 1B). The results demonstrated the anti-RCC function of TBOPP; 10  $\mu\text{M}$  TBOPP significantly reduced cell viability in all 3 cell lines and also significantly decreased cell proliferation in all 3 cell lines; thus, 10  $\mu\text{M}$  TBOPP was used for subsequent experiments.

**TBOPP inhibits RCC cell cisplatin resistance.** The effect of TBOPP on cisplatin resistance in RCC was investigated. TBOPP combined with cisplatin further reduced RCC cell viability compared with cisplatin alone (Fig. 2A). The EdU assay suggested that TBOPP significantly enhanced the antiproliferative activity of cisplatin in RCC cells (Fig. 2B). Moreover, TBOPP significantly increased cisplatin-induced RCC cell apoptosis (Fig. 2C). Collectively, the results demonstrated that TBOPP inhibited RCC cell cisplatin resistance.

**DOCK1 knockdown sensitizes RCC cells to cisplatin.** Subsequently, the role of DOCK1 during RCC was investigated. Firstly, the expression of DOCK1 in the three RCC cell lines was measured. DOCK1 expression levels were highest in the

Caki cell line, followed by the ACHN cell line and the 786-O cell line (Fig. 3A). The CCK-8 assay indicated that following treatment with cisplatin, the Caki cell line displayed the highest cell viability among the three RCC cell lines assessed ( $\text{IC}_{50}$  values: Caki, 7.804  $\mu\text{M}$ ; ACHN, 5.105  $\mu\text{M}$ ; 786-O: 3.770  $\mu\text{M}$ ) (Fig. 3B). To further verify the role of DOCK1 during RCC, a DOCK1 siRNA was used to significantly knockdown DOCK1 expression, which was confirmed by western blotting (Fig. 3C). The CCK-8 assay suggested that DOCK1 knockdown significantly enhanced cisplatin-mediated reductions in cell viability (Fig. 3D). Additionally, flow cytometry analysis of apoptosis demonstrated that DOCK1 knockdown promoted cisplatin-induced apoptosis (Fig. 3E). Furthermore, the EdU assay indicated that following treatment with cisplatin, the proliferation of DOCK1 siRNA-treated cells was significantly lower compared with the control cells (Fig. 3F). The results suggest that DOCK1 promotes RCC cell cisplatin resistance.

**TBOPP function during RCC is mediated by DOCK1.** TBOPP is an inhibitor of DOCK1; therefore, to explore the relationship between TBOPP and DOCK1 during RCC, the inhibitory role of TBOPP on DOCK1 expression in RCC cells was assessed by western blotting. TBOPP significantly decreased DOCK1 expression levels compared with the control group (Fig. 4). Subsequently, the cell viability of cells co-treated with cisplatin and DOCK1 siRNA alone or DOCK1 siRNA

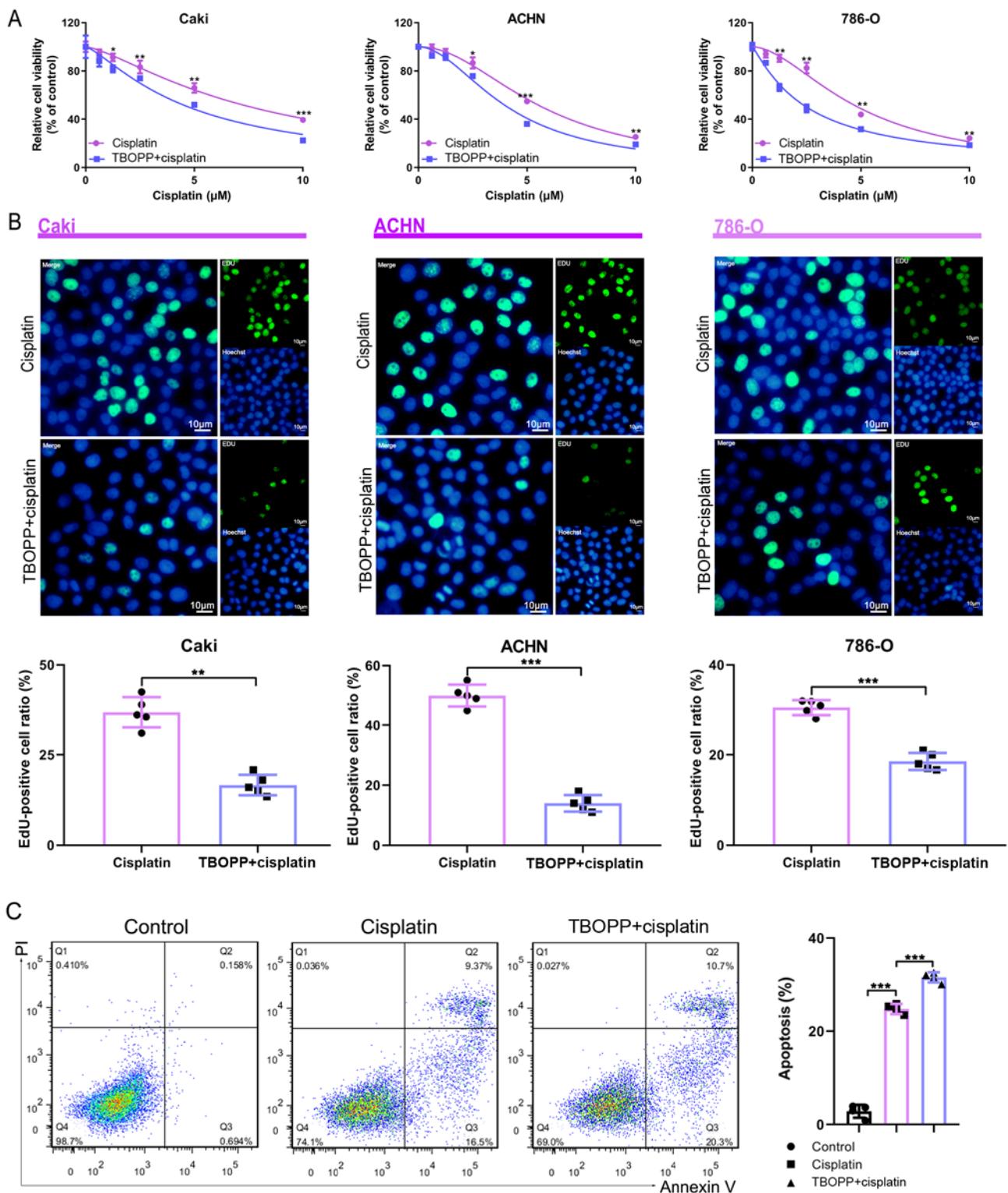


Figure 2. TBOPP sensitizes RCC cells to cisplatin. (A) RCC cell viability following treatment with cisplatin alone or cisplatin plus 10  $\mu\text{M}$  TBOPP, as determined by the Cell Counting Kit-8 assay. \* $P < 0.05$ , \*\* $P < 0.01$  and \*\*\* $P < 0.001$  vs. the TBOPP + cisplatin group. (B) RCC cell proliferation following treatment with cisplatin alone or cisplatin plus 10  $\mu\text{M}$  TBOPP, as determined by the EdU assay. Scale bar, 10  $\mu\text{m}$ . The rate of EdU-positive cells in the S phase is presented. \*\* $P < 0.01$  and \*\*\* $P < 0.001$ , as indicated. (C) Flow cytometric analysis of RCC cell apoptosis following treatment with cisplatin alone or cisplatin plus 10  $\mu\text{M}$  TBOPP. Cells in quadrants 2 and 3 were considered to be apoptotic. \*\*\* $P < 0.001$ , as indicated. TBOPP, 1-[2-(3'-(trifluoromethyl)-(1,1'-biphenyl)-4-yl)-2-oxoethyl]-5-pyrrolidinylsulfonfyl-2(1H)-pyridone; RCC, renal cell carcinoma; EdU, 5-Ethynyl-2'-deoxyuridine; PI, propidium iodide.

plus TBOPP was assessed by the CCK-8 assay. Cell viability in the DOCK1 siRNA group and the DOCK1 siRNA plus TBOPP group was not significantly different (Fig. 5A), which indicated that TBOPP-mediated cisplatin sensitivity did not

occur in the absence of DOCK1 expression. The relationship between TBOPP and DOCK1 during RCC was further indicated by the results of the flow cytometry analysis of cell apoptosis (Fig. 5B). Transfection efficiency of DOCK1 siRNA



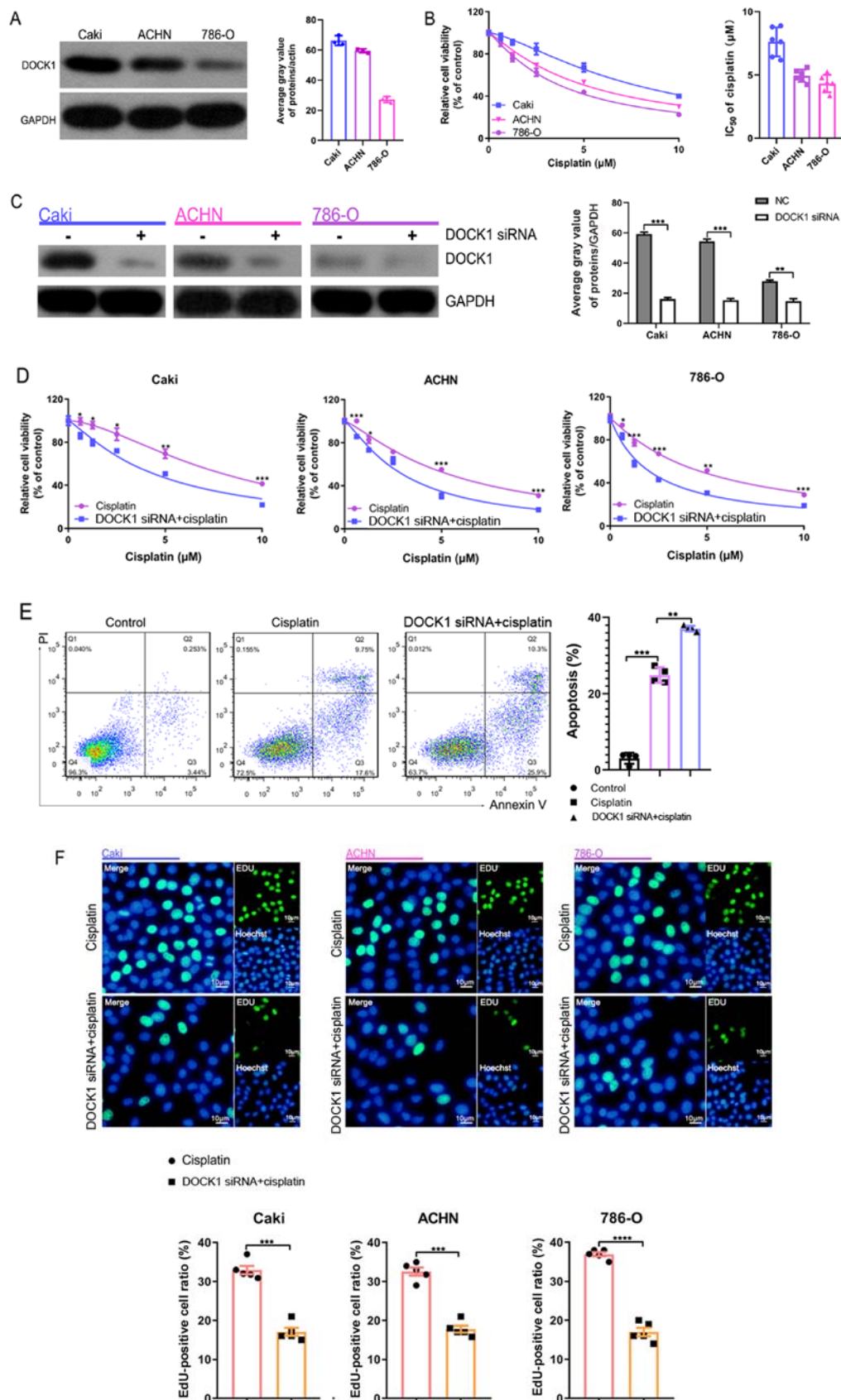


Figure 3. DOCK1 knockdown enhances cisplatin sensitivity during RCC. (A) DOCK1 expression levels in the three RCC cell lines were determined by western blotting. (B) The CCK-8 assay was performed to determine cell viability and the  $IC_{50}$  value of cisplatin in the three RCC cell lines. (C) The transfection efficiency of DOCK1 siRNA (the mix of three sequences) was assessed by western blotting.  $^{**}P<0.01$  and  $^{***}P<0.001$ , as indicated. (D) The CCK-8 assay was performed to determine cell viability in the three RCC cell lines following co-treatment with cisplatin and DOCK1 siRNA or negative control siRNA.  $^{*}P<0.05$ ,  $^{**}P<0.01$  and  $^{***}P<0.001$  vs. the cisplatin group. (E) Flow cytometry analysis of RCC cell apoptosis following co-treatment with cisplatin and DOCK1 siRNA or negative control siRNA.  $^{*}P<0.01$  and  $^{***}P<0.001$ , as indicated. (F) RCC cell proliferation was assessed by the EdU assay following co-treatment with cisplatin and DOCK1 siRNA or negative control siRNA. Scale bar, 10  $\mu m$ .  $^{***}P<0.001$  and  $^{****}P<0.0001$ , as indicated. DOCK1, dedicator of cytokinesis 1; RCC, renal cell carcinoma; CCK-8, Cell Counting Kit-8; siRNA, small interfering RNA; EdU, 5-Ethynyl-2'-deoxyuridine; NC, negative control; PI, propidium iodide.

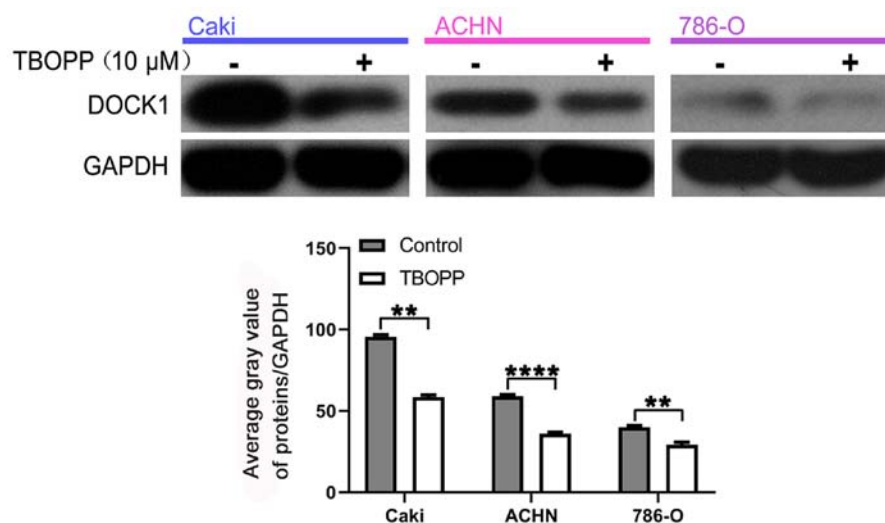


Figure 4. TBOPP inhibits DOCK1 expression. The inhibitory effect of TBOPP on DOCK1 expression levels was assessed by western blotting. \*\* $P < 0.01$  and \*\*\*\* $P < 0.0001$ , as indicated. TBOPP, 1-[2-(3'-(trifluoromethyl)-(1,1'-biphenyl)-4-yl)-2-oxoethyl]-5-pyrrolidinylsulfonyl-2(1H)-pyridone; DOCK1, dedicator of cytokinesis 1.

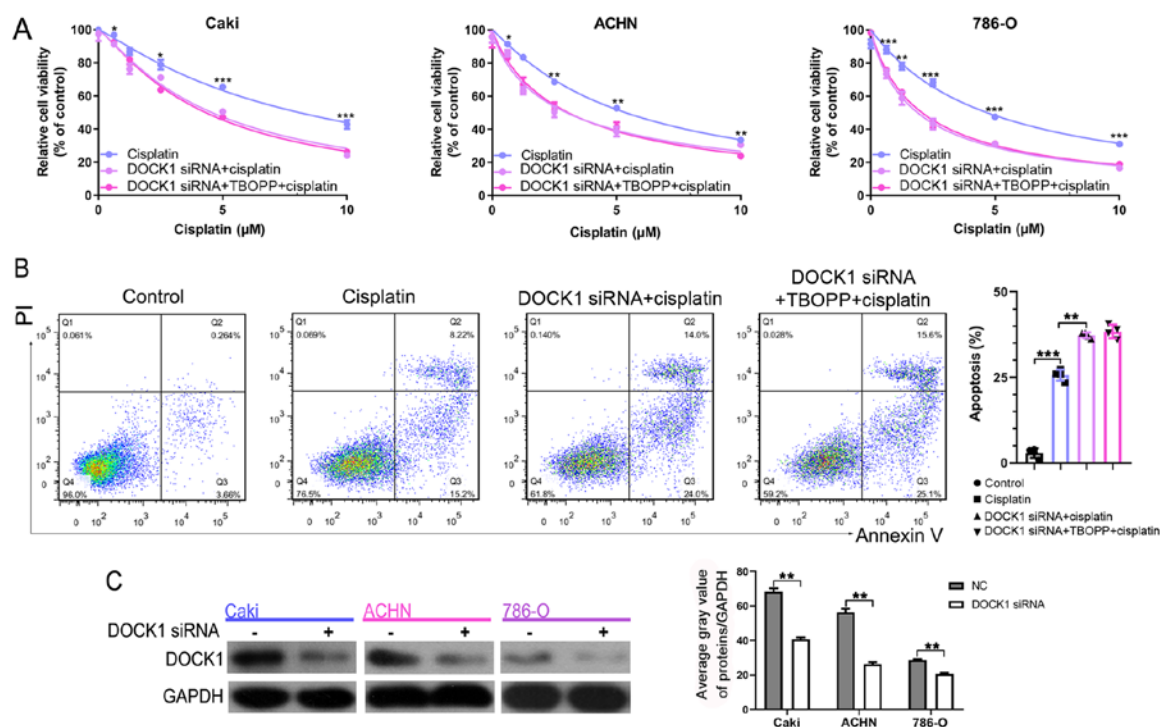


Figure 5. TBOPP enhances cisplatin sensitivity by inhibiting DOCK1. (A) RCC cell viability following co-treatment with cisplatin and DOCK1 siRNA or DOCK1 siRNA plus 10 μM TBOPP. \* $P < 0.05$ , \*\* $P < 0.01$  and \*\*\* $P < 0.001$  vs. TBOPP + cisplatin. (B) Flow cytometry analysis of RCC cell apoptosis following co-treatment with cisplatin and DOCK1 siRNA or DOCK1 siRNA plus 10 μM TBOPP. \*\* $P < 0.01$  and \*\*\* $P < 0.001$ , as indicated. (C) The transfection efficiency of DOCK1 siRNA (the mix of three sequences) was assessed by western blotting. \*\* $P < 0.01$ , as indicated. TBOPP, 1-[2-(3'-(trifluoromethyl)-(1,1'-biphenyl)-4-yl)-2-oxoethyl]-5-pyrrolidinylsulfonyl-2(1H)-pyridone; DOCK1, dedicator of cytokinesis 1; RCC, renal cell carcinoma; siRNA, small interfering RNA; NC, negative control; PI, propidium iodide.

was confirmed by western blotting (Fig. 5C). The results demonstrated that DOCK1 was involved in TBOPP-mediated cisplatin sensitivity.

## Discussion

In patients with RCC, infrequent responses due to intrinsic and acquired chemoresistance significantly limit the clinical

use of chemotherapeutic agents (22). Therefore, identifying the mechanisms underlying RCC chemoresistance and developing novel therapeutic strategies to resensitize RCC to anticancer drugs is important. The present study aimed to investigate the role of DOCK1 and its inhibitor TBOPP during RCC chemoresistance. The results suggested that TBOPP and DOCK1 may serve as therapeutic targets to alleviate chemoresistance in patients with RCC.

A previous study demonstrated the inhibitory role of TBOPP against DOCK1, and TBOPP has been reported to display an antitumor role in other types of cancer, such as colon cancer and skin malignant melanoma (19,20). The present study further demonstrated the inhibitory effect of TBOPP on DOCK1, and displayed the role of TBOPP during RCC, suggesting that TBOPP may serve as a chemotherapeutic sensitizer for RCC.

The DOCK family comprises 11 members, which are atypical Rho guanine nucleotide exchange factors (23). Previous studies have revealed the essential roles of DOCK in several cellular processes, including tumorigenesis (15,24). By activating RAC1, DOCK1 displays key functions in cytoskeletal organization, myoblast fusion and phagocytosis (25-27). A number of studies have suggested that DOCK1 is related to tumorigenesis, tumor growth and invasion in several types of cancer, such as glioblastoma and ovarian cancer, implying that DOCK1 plays a vital role in human cancer progression (28-30). Moreover, the biological role of DOCK1 during bladder cancer suggested that downregulation of DOCK1 could sensitize bladder cancer cells to cisplatin by inhibiting the epithelial-mesenchymal transition (12). In addition, DOCK1 inhibition by enoxaparin could improve the antitumor and antimigration activity of gefitinib during lung cancer (18). However, the role of DOCK1 during RCC has not been previously reported. The results of the present study suggested that DOCK1 expression levels were associated with cisplatin resistance, which was alleviated by DOCK1 inhibition, suggesting that DOCK1 was related to RCC cisplatin resistance.

Although the results indicated that TBOPP sensitized RCC to cisplatin by inhibiting DOCK1, the present study had a number of limitations. Firstly, the present study did investigate the role of DOCK1 and TBOPP in normal kidney cells. Secondly, the effect of TBOPP on the sensitivity of newer, more RCC specific agents, including sorafenib or pazopanib, was not investigated. Thirdly, Tajiri *et al* (19) reported that DOCK1 expression is driven by oncogenic mutations of RAS; however, the relationship between DOCK1 and RAS was not explored in the present study.

In conclusion, the present study demonstrated that DOCK1 was associated with RCC cisplatin resistance, which was ameliorated by TBOPP. The results suggested that DOCK1 inhibition may serve as a potential therapeutic strategy to alleviate RCC chemoresistance, and TBOPP might serve as a chemotherapeutic sensitizer.

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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

LX and WC conceived the study. XZ, SX and SZ performed the experiments. JM, YC and XL analyzed the data. WZ participated in the design of the study and drafted the manuscript. HN conceived the study and revised the manuscript. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

#### 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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