

RESEARCH

Open Access



TTK is a potential therapeutic target for cisplatin-resistant ovarian cancer

Yixuan Liu^{1,2,3†}, Keyu Zhu^{1,2†}, Xiaolin Guan^{1,2}, Suhong Xie¹, Yanchun Wang¹, Ying Tong¹, Lin Guo^{1,2}, Hui Zheng^{1*} and Renquan Lu^{1,2*} 

Abstract

Background: Drug resistance and recurrence are main contributors to the poor prognosis of ovarian cancer. Cisplatin is a platinum compound which is widely used in the treatment of various solid tumors including ovarian cancer. Up to now, the mechanism of cisplatin resistance in ovarian cancer is unclear. Threonine and tyrosine kinase (TTK), an integral part of the spindle assembly checkpoint, may be a potential new target associated with chemotherapy sensitivity.

Results: TTK was up-regulated in the cisplatin-resistant ovarian cancer cell line. Down-regulation of TTK could recover the sensitivity of cisplatin-resistant ovarian cancer cells to cisplatin treatment. Mechanistically, the PI3K/AKT signaling pathway was activated in cisplatin-resistant cells, and this pathway would be affected by TTK expression. Furthermore, TTK was highly expressed in the tissues of ovarian cancer patients, especially those acquired resistance to cisplatin.

Conclusions: Our study revealed that TTK may be a promising therapeutic target for cisplatin-resistant ovarian cancer.

Keywords: Threonine and tyrosine kinase (TTK), Cisplatin resistance, Ovarian cancer, Signaling pathway

Introduction

Ovarian cancer is one of the most common lethal gynecologic malignancy with the third morbidity rate and the first mortality rate. According to the cancer statistics, there are estimated approximately 200,000 new cases of ovarian cancer every year, with about 150,000 deaths attributed to the disease [1] all over of the world. Although the 5years survival rate after early surgery is up to 80-90, 70% of the patients still have poor prognosis because it is usually diagnosed at advanced stages [2]. Surgery combined with cisplatin chemotherapy is the main treatment for malignant ovarian tumors. Most

of the women diagnosed with advanced ovarian cancer will benefit from this treatment [3]. The pharmacological work of cisplatin is mediated by DNA binding, which can cause DNA damage, hinder DNA replication and induce cell death [4]. Unfortunately, the patients will be resistant to cisplatin-based chemotherapy after several cycles of treatment. Patients with cisplatin resistance usually have no responses to other chemotherapy drugs, and their non-progression lifetime is approximately 3-4 months with a median survival for less than 1 year. Therefore, it is urgent to elucidate the mechanism of cisplatin resistance and discover new therapeutic targets in the treatment of ovarian cancer.

Threonine and tyrosine kinase (TTK), an integral part of the spindle assembly checkpoint, works as a monitor mechanism for ensuring chromosomal separation [5]. High expression levels of TTK could result in the subsequent development of aneuploid tumors

*Correspondence: zh19841207xx@163.com; renquanlu@fudan.edu.cn

†Yixuan Liu and Keyu Zhu contributed equally to this work.

¹ Department of Clinical Laboratory, Fudan University Shanghai Cancer Center, No.270, Dong'An Road, Xuhui District, Shanghai 200032, China
Full list of author information is available at the end of the article



© The Author(s) 2021. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

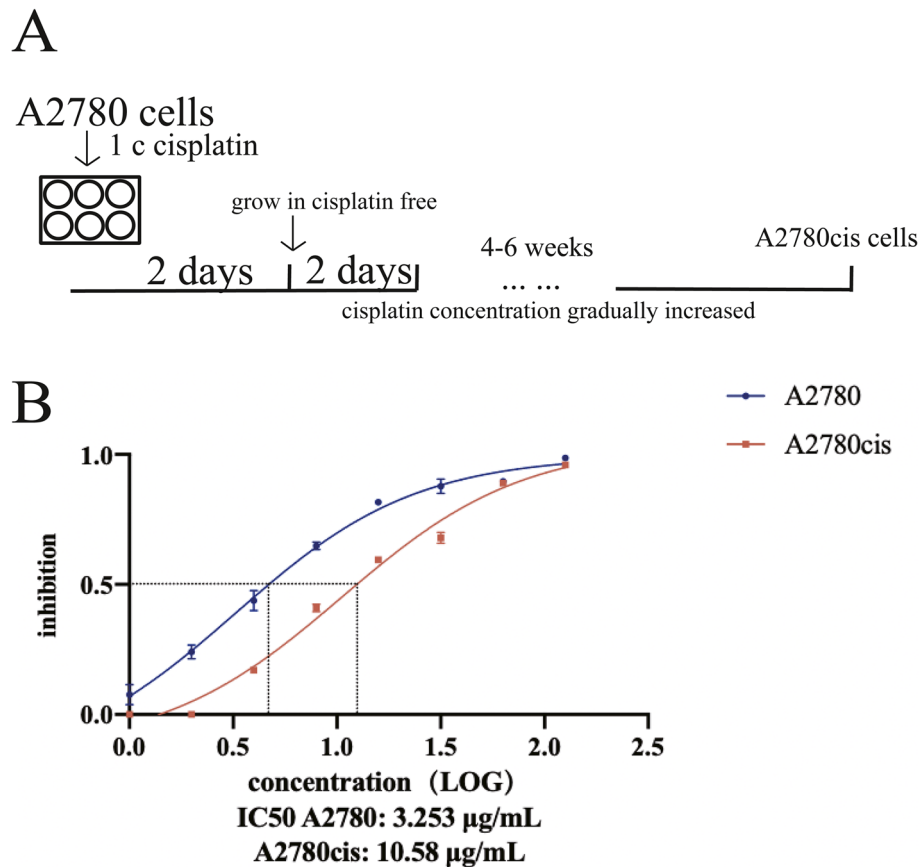


Fig. 1 **A** The induction process of cisplatin-resistant ovarian cancer cell line A2780cis. **B** IC50 values of cisplatin in A2780 and A2780cis cells were analyzed by CCK-8 assay. The cisplatin concentrations used were as follows: 1 μ g/mL, 2 μ g/mL, 4 μ g/mL, 8 μ g/mL, 16 μ g/mL, 32 μ g/mL, 64 μ g/mL, 128 μ g/mL

[6]. It has been reported that TTK is a predictor of poor prognosis in breast, lung, brain and colorectal cancer [7]. Meanwhile, recent studies have shown that TTK could mediate multiple drug resistance in lung cancer [1]. However, there was little information available regarding its role in ovarian cancer and cisplatin-resistance.

In this study, cisplatin-resistant ovarian cancer cell line A2780 (A2780cis) was established to explore the relationship between TTK expression and cisplatin-resistance. We clarified the mechanism of cisplatin-resistance through knockdown or inhibition of TTK expression. Furthermore, the related signaling pathways activated by TTK in cisplatin-resistant cell line were analyzed by RNA-sequencing (RNA-seq). The conclusions from cell experiments were further verified in ovarian cancer tissues. Thus, TTK may be a potential therapeutic target in patients with platinum-resistant ovarian cancer.

Results

TTK was up-regulated in cisplatin-resistant ovarian cancer cell line

Cisplatin-resistant A2780 cell line was induced through continuous stimulation with cisplatin in vitro. A2780 cells were seeded in 6-well plate at 70-80% confluence and treated with 1 μ g/mL cisplatin for 2 days. After 2 days' culture, the cells were washed with PBS and recovered in medium without drug treatment for another 2 days. The above procedure was repeated for at least 4-6 weeks with gradually increased concentration of cisplatin (Fig. 1A). Then, we acquired a cisplatin-resistant A2780 cell line which could grow well in culture medium containing 10 μ g/mL cisplatin. This cell line was named A2780cis. The cell viability was assayed after the treatment with 2-fold increasing concentrations of cisplatin for 48 h. The IC50 values of A2780 and A2780cis cells were 3.253 μ g/mL and 10.58 μ g/mL respectively (Fig. 1B). Therefore, A2780cis cell line is cisplatin-resistant and can

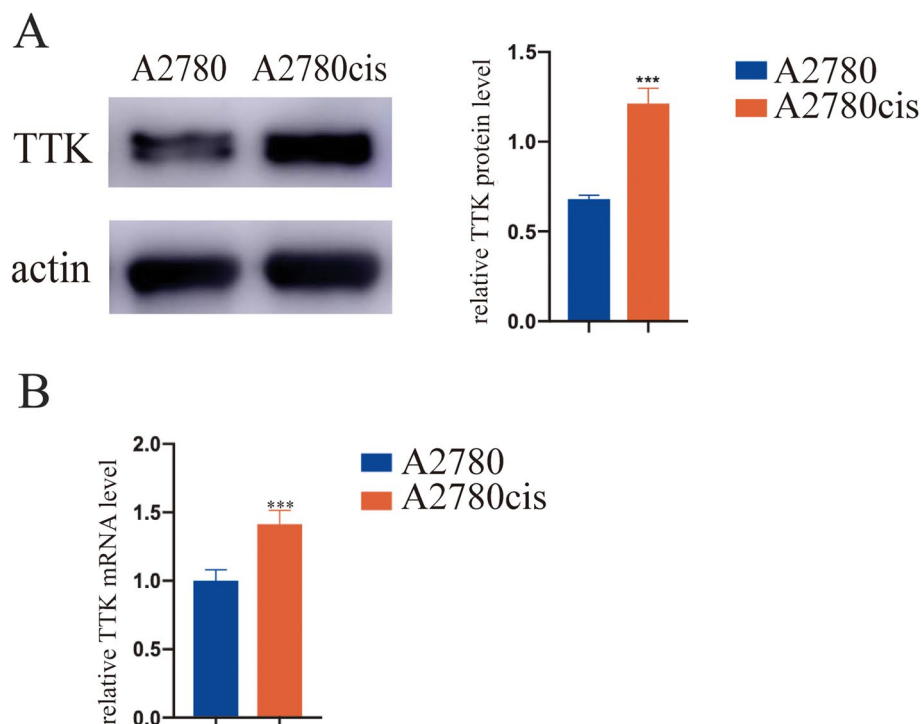


Fig. 2 The up-regulation of TTK in cisplatin-resistant cell line was verified by **A** western blot and **B** quantitative real-time PCR compared with parental cells. *** $P < 0.001$

tolerate more than three times higher concentration of cisplatin compared with parental A2780 cells. We found that the expression of TTK was increased in A2780cis cells at mRNA and protein levels (Fig. 2).

Down-regulation of TTK expression could recover the sensitivity of A2780cis cells to cisplatin

We found that the expression of TTK was increased in A2780cis cells at mRNA and protein levels (Fig. 2). To explore the relationship between TTK and cisplatin-resistance, TTK expression was down-regulated in A2780cis cells, and the knockdown efficiency was verified by Western blot and real-time PCR (Fig. 3A). As shown in Fig. 3B, knockdown of TTK protein inhibited the proliferation of A2780cis cells, and the influence was more obvious when the cells treated with cisplatin in culture medium. DNA synthesis detection by EdU (5-Ethynyl - 2'- deoxyuridine) staining also showed that the proliferation of A2780cis cells was suppressed after the down-regulation of TTK. Especially, knockdown of TTK could improve the cisplatin-sensitivity of A2780cis cells (Fig. 3C). Meanwhile, down-regulation of TTK in A2780cis cells reduced the quantities of cell colony and promoted cell apoptosis. Moreover, TTK inhibitor could function the same as TTK knockdown (Fig. 3D, E). Therefore, we indicated

that down-regulation or inhibition of TTK expression would suppress cell proliferation and increase cisplatin sensitivity of A2780cis cells.

TTK inhibition relieved the resistance of A2780cis cells to cisplatin by inhibiting PI3K/AKT pathway

The related signaling pathways activated by TTK were analyzed through RNA-seq. According to gene count and P value enriched by KEGG, we found the top 10 pathways differentially expressed in A2780cis cells with or without TTK knockdown (Fig. 4A). Among them, PI3K/AKT signaling pathway was reported to participate in cisplatin-resistance of ovarian cancer [8]. Actually, both p-PI3K and p-AKT were up-regulated in A2780cis cells, suggesting that PI3K/AKT signaling pathway was activated when the cells were resistant to cisplatin (Fig. 4B). Thus, we guessed that TTK mediated cisplatin-resistance through activating the PI3K/AKT signaling pathway. As shown in Fig. 4B, knockdown of TTK could inhibit the phosphorylation of PI3K and AKT in A2780cis cells. The inhibitor of TTK or PI3K could significantly suppress the activation of the PI3K/AKT pathway and enhanced the cisplatin sensitivity of A2780cis cells (Fig. 4C, D). These results proved that TTK facilitated proliferation of cisplatin-resistant cells by activating PI3K/AKT signaling pathway.

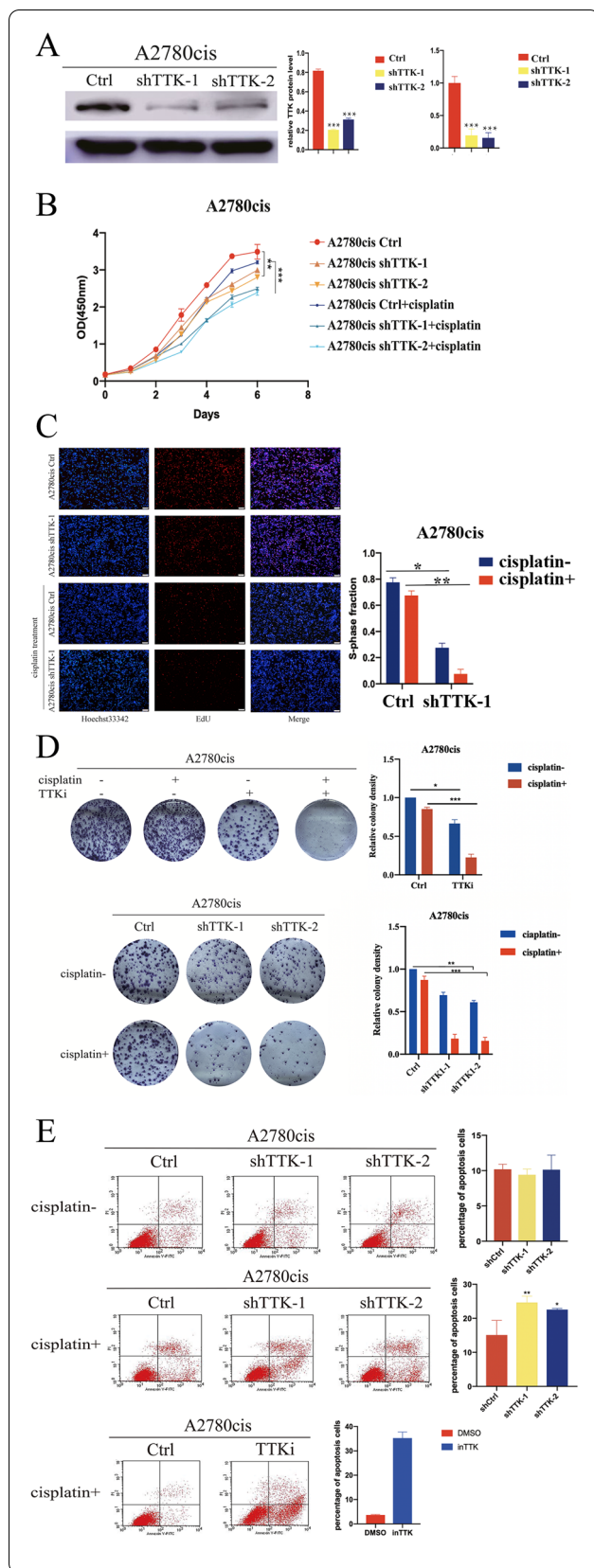


Fig. 3 Knockdown of TTK expression in cisplatin-resistant cells would suppress cell proliferation and increase the drug sensitivity to cisplatin. **A** The knockdown of TTK in A2780cis cell line was verified by western blot and quantitative real-time PCR. **B** The cell proliferation of A2780cis cells with or without TTK knockdown was assayed by CCK8 kit. The growth of A2780cis cells with TTK knockdown was suppressed, especially in combination with cisplatin treatment. **C** DNA synthesis detection by EdU staining. The red fluorescence represents the ability of cell proliferation. **D** Colony formation assay showed that TTK inhibitor performed the same function as TTK knockdown. The clones were reduced when TTK was inhibited or up-regulated, especially in combination with cisplatin treatment. **E** Down-regulation of TTK or TTK inhibitor could significantly increase cell apoptosis rates with cisplatin treatment. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

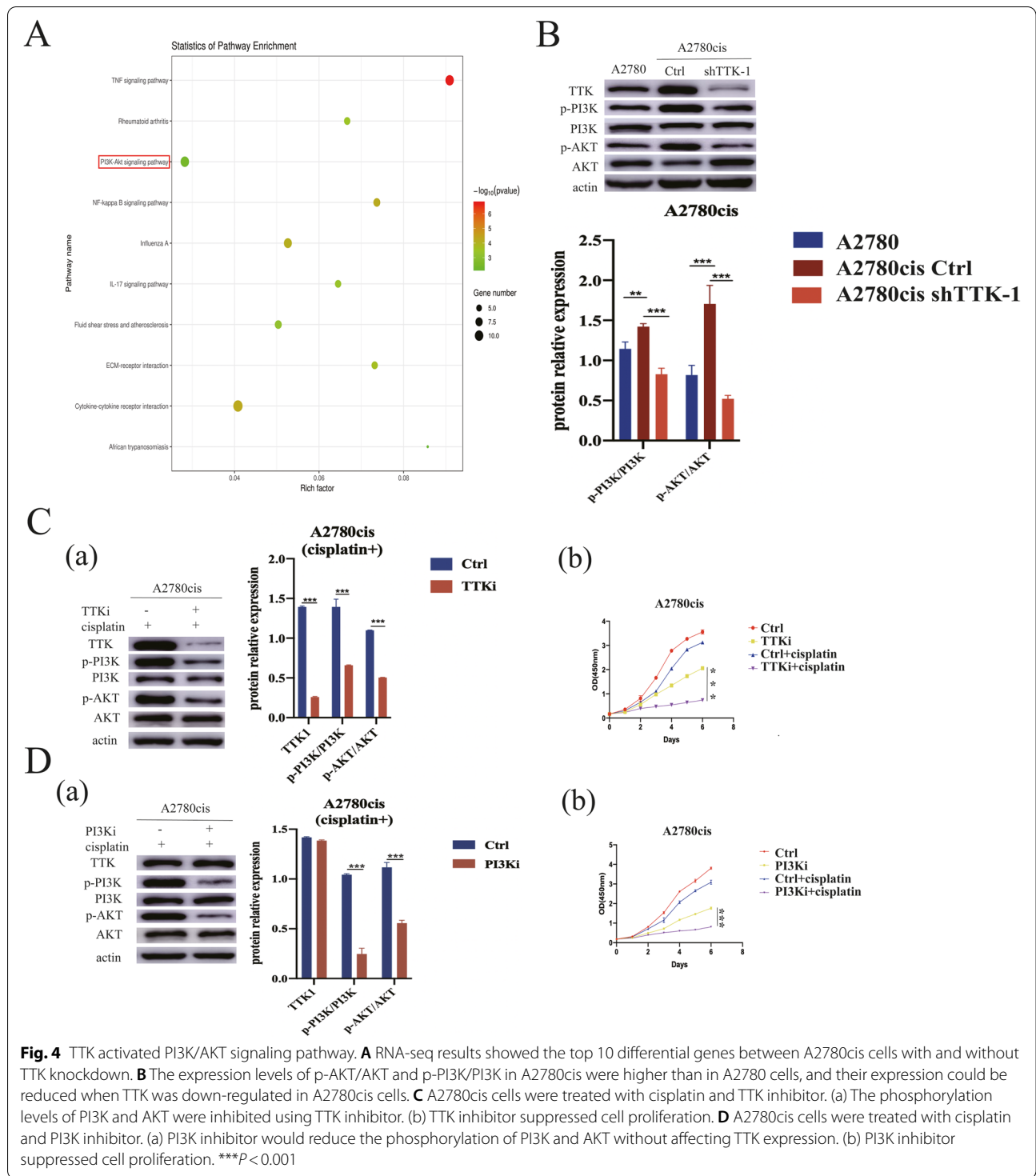
TTK was highly expressed in the tissues of ovarian cancer patients with cisplatin-resistance

Data from Oncomine (<http://www.oncomine.org/>) indicated that TTK was overexpressed in most types of cancer tissues than in normal tissues (Fig. 5A). We verified that the protein expression of TTK in ovarian tumor tissues was indeed higher than in normal controls by way of microarray chips- ($P < 0.01$) (Fig. 5B, Table 1). We further explored the expression of TTK in cisplatin-resistant ovarian cancer patients. Ovarian tumor tissues from 20 ovarian cancer patients were collected both before and after the cisplatin-resistance acquisition. We found that cisplatin-resistant tissues showed stronger TTK expression than the cisplatin-sensitive ones (Fig. 6, Table 2). Therefore, TTK may be a tumor promoter and cisplatin-resistance associated factor.

Discussion

Combination of surgery and cisplatin-based chemotherapy is the gold standard for the treatment of ovarian cancer. However, after short-term treatment, cisplatin resistance often occurs, which greatly weakened the therapeutic effect [9]. Cellular resistance to cisplatin occur through multiple mechanisms which can be divided into the following categories: a) reducing cross-linking in the DNA chain, such as preventing the drug intake and accelerating the drug efflux [10–12]. b) increasing the efficiency of DNA repair [13]. c) promoting cell survival through changing the signaling pathway that affects the tumor apoptosis [14, 15]. However, the key factors associated with chemotherapy resistance still need to be explored.

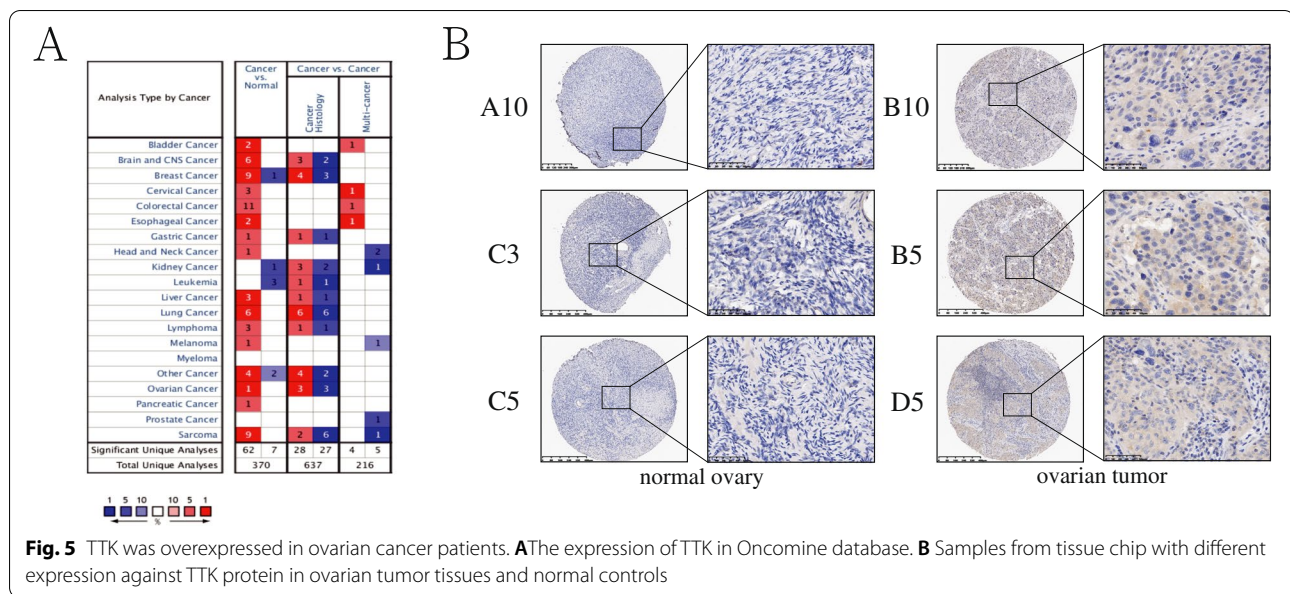
The protein kinase TTK (also known as Monopolar spindle 1, Mps1), a dual specificity kinase, is involved in the formation of mitotic checkpoint complex, regulation of cytokinesis, response to DNA damage, and facilitation of proper chromosome alignment [16]. TTK is hardly



detectable in normal organs except the testis and placenta. However, high levels of TTK are found in many types of human malignancies. Overexpression of TTK promotes tumor growth in prostate cancer [17], breast cancer [18] and colon cancer [19]. Thus, we guess that

TTK inhibitor in combination with antimetabolic cancer drugs will enhance their efficacy and potentially overcome resistance.

In this study, we explored the possibility of sensitivity-reacquisition to cisplatin in ovarian cancer cells through



targeting for TTK. Actually, TTK expression was reduced when ovarian cancer cells were treated with cisplatin, indicating that TTK may serve as a chemo-therapeutic target (Fig. S1). Cisplatin-resistant cell line A2780cis was established by continued stimulation with gradually increased concentration of cisplatin. In cisplatin-resistant ovarian cancer cells, TTK was up-regulated compared with the parent tumor cells. Meanwhile, the overexpression of TTK in cisplatin-resistant patients was verified by immunohistochemistry. In the present study, we focus not the reason to cause resistance, but on the way to overcome resistance. Therefore, it is unclear whether the overexpressed TTK leads to cisplatin resistance or the cisplatin-resistant cells cause TTK overexpression. In our study, tumor cells will become resistant to chemotherapy by several molecular mechanisms during the drug treatment. To tolerate genomic instability and aneuploidy, the cisplatin-resistant cells will develop adaptive mechanisms. The spindle assembly checkpoint (SAC) is the main mechanism that maintains chromosomal stability through the cell division. TTK is a critical SAC component, which can promote the formation of mitotic checkpoint complex. Overexpression of TTK may be one of the important mechanisms for resistant tumor cells to live with aneuploidy.

The results of the RNA-seq prove that TTK may have an impact through the change of p53 to affect the sensitivity of ovarian cancer to platinum drugs. p53 is an important tumor suppressor gene, involved in important biological processes such as cell differentiation, cell apoptosis, DNA repair, and cycle regulation [20]. The p53 signal pathway is an important way for platinum drugs to

cause tumor cell DNA damage. Studies have shown that p53 protein aggregation damages the normal transcription of p53 gene and its apoptotic functions in different types of tumor cells, and can promote platinum resistance in ovarian cancer [21].

JAK/STAT signal transduction pathway is the common pathway of many cytokines, and it is widely involved in the processes of cell proliferation, differentiation, apoptosis and inflammation [22]. JAK/STAT pathways [22, 23] play an important role in tumor occurrence, development and drug resistance, and may become a new target for tumor treatment.

PI3K/AKT/NF- κ B signal pathways [24, 25] are involved in tumor occurrence, development, invasion and metastasis. Some studies have shown that PI3K inhibitors are used for treatment of several human tumors, such as ovarian cancer [26], breast cancer [27], and leukemia [28]. In addition, it was also reported that activation of AKT was related to cisplatin-resistance in ovarian cancer [29]. We further clarified that the activated signaling pathway by TTK was PI3K/AKT pathway, which played an important role in proliferation, migration, invasion and chemotherapy resistance [25].

We verified that inhibition of TTK expression could prevent the activation of PI3K/AKT pathway in cisplatin-resistant cells. However, the specific mechanisms for TTK to activate PI3K/AKT pathway need to be explored.

Conclusions

Our study demonstrated that TTK was overexpressed in ovarian cancer, and was further up-regulated in cisplatin-resistant cells. Knockdown or inhibition of TTK

Table 1 The scores of TTK expression in normal ovary and ovarian tumor

	Age	Stage	IHC Scoring				P-value
			Negative expression (0)	Weak expression (2–4)	Moderate expression (5–6)	Strong expression (7–8)	
Normal ovary (n = 20)	39–79	/	20	/	/	/	P < 0.0001
Ovarian tumor (n = 20)	34–66	III–IV	/	7	11	2	

expression could significantly suppress cell proliferation and overcome cisplatin resistance through inhibition of PI3K/AKT pathway. These findings revealed that TTK emerged as a potential therapeutic target in ovarian cancer, especially in combination with chemotherapy.

Materials and methods

Cell culture

A2780cis and A2780 cells were cultured in RPMI-1640 medium (Gibco, USA) containing 10% fetal bovine serum (Gibco) and 1% penicillin-streptomycin (Gibco). HEK 293 T cells were cultured in DMEM (Gibco) containing 10% fetal bovine serum (Gibco) and 1% penicillin-streptomycin (Gibco). All cells were cultured at 5% CO₂ in a 37 °C incubator.

Tissue samples

Twenty ovarian cancer tissues and 20 normal ovarian tissues were obtained from patients undergoing resection

of ovarian cancer or other diseases at the Department of Ovarian Surgery, Fudan University Shanghai Cancer Center. After the histopathologic diagnosis was defined by professional pathologists, the corresponding tissue samples were collected for TTK detection. Written informed consent was available from all patients.

Inhibitors and antibodies

The inhibitors used in this study were TTKi (5 μM, MPI-0479605, Selleck) and PI3Ki (1 μM, BYL719, Selleck). All compounds were dissolved in DMSO at a concentration of 10 mM and stored at –80 °C before use. The cells were treated with inhibitors for 3 days while the control cells were treated with DMSO only. The antibodies used in western blot were as follows: TTK (sc-376,842, 1:500 dilution, SANTA CRUZ, USA), β-actin (60008-1-Ig, 1:3000 dilution, Proteintech Group, China), AKT (4685 T, 1:1000 dilution, CST, MA, USA), p-AKT (4056, 1:1000 dilution, CST, MA, USA), PI3K (4257, 1:1000 dilution,

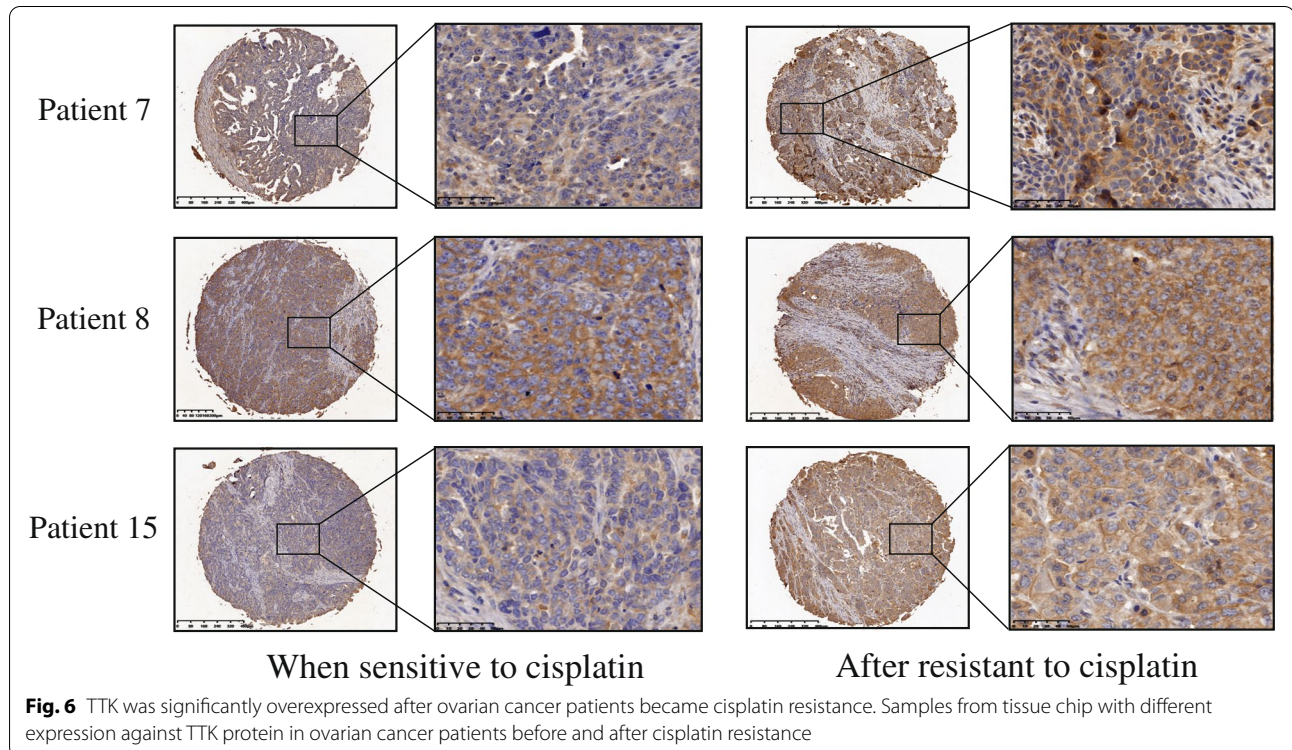


Table 2 The scores of TTK expression in ovarian cancer patients before and after resistant to cisplatin

	IHC Scoring				P-value
	Negative expression (0)	Weak expression (2-4)	Moderate expression (5-6)	Strong expression (7-8)	
When sensitive to cisplatin (n = 20)	0	9	7	4	P < 0.001
After resistant to cisplatin (n = 20)	0	0	3	17	

CST, MA, USA), p-PI3K (4228, 1:1000 dilution, CST, MA, USA). Western blot was performed according to a previous publication [25]. The protein bands were analyzed by Image J software (NIH, USA).

Immunohistochemistry and evaluation

TTK was detected with a mouse monoclonal antibody at a dilution of 1:50 (sc-376,842, Santa Cruz Biotechnology, CA, USA). IHC stain and scoring criteria for TTK was described as our previous publications [30].

TTK knockdown in tumor cells

The short hairpin RNA (shRNA) was designed with the manufacturer's RNAi Designer program, and the sequences are shown in Table 3. The recombinant pLKO.1 plasmids along with packing plasmids psPAX2 and pMD2.G (Addgene) were transfected into HEK293T cells using Lipofectamine 3000 transfection reagent (Invitrogen, CA, USA). After 48 h, virus supernatant was collected and ovarian cancer cells were infected with the virus in the presence of 8 µg/mL polybrene (Sigma, USA). The stable transfected cells (shCtrl, shTTK-1, shTTK-2) were selected for 3-5 days using 2-10 mg/mL puromycin (Sigma-Aldrich, MO, USA).

Colony formation assay

Cells were seeded into 6 well-plates at a density of 1000 cells/well and incubated for 10-14 days until visible clones

Table 3 Sequences of shRNA against TTK for transfection

Name	Sequence
shCtrl (scrambled sequence)	5'-CCTAAGGTTAAGTCGCCCTCG-3'
shTTK-1	5'-GATAAGATCATCCGACTTTAT-3'
shTTK-2	5'-GCACAATTTGAAGTGCACAA-3'

Table 4 Primer sequences for real-time qPCR

Gene	Sequence (5'-3')
TTK	F: TCCCCAGCGCAGCTTTCTGTAGA
	R: CCAGTCCTCTGGGTTGTTTGCCAT
GAPDH	F: GGAGCGAGATCCCTCCAAAAT
	R: GGCTGTTGTCATACTTCTCATGG

were appeared. Colonies were stained with 0.5% crystal violet and a microscope was used to determine the quantity of colonies.

Quantitative real-time PCR (qRT-PCR)

Total RNA was isolated from cultured cells using Trizol reagent (Invitrogen, USA) according to manufacturer's instructions. Total RNA was reversely transcribed into complementary first strand DNA using RT kit (TaKaRa, Japan). PCR was performed with SYBR Green PCR Kit (Thermo Fisher Scientific, Rockford, USA) using an ABI PRISM Detection System (Applied Biosystems, Life Technologies). All samples were performed in triplicate and normalized to GAPDH levels. The specific primers used are listed in Table 4.

DNA synthesis measuring

EdU (5-Ethynyl-2'-deoxyuridine) is a thymidine analogue, which can replace thymine (T) to be incorporated into the replicating DNA molecule during cell proliferation. EdU kit (Cell-Light EdU Apollo 488 In Vitro Imaging Kit, RiboBio, Guangzhou, China) was used to measure DNA synthesis according to the manufacturer's instructions. After incubation with 50 µM EdU for 2 h at 37 °C, cells were washed with PBS and then fixed with 4% paraformaldehyde for 30 min, followed by incubation with 2 mg/mL glycine for 5 min. Nucleus was stained with DAPI.

Cell proliferation detection

Cells were seeded into 96-well plates and treated with different concentrations of cisplatin (0-128 µg/mL). Cell proliferation was detected using cell counting kit-8 (Dojindo, Japan) according to the manufacturer's instructions. Optical density (OD) value was detected at 450 nm on a microplate reader. Viability was measured using the following formula: relative viability (experimental absorbance - background absorbance) / (untreated controls absorbance - background absorbance) * 100%. The IC50 values of cisplatin were calculated using nonlinear regression (GraphPad Prism v3.0, GraphPad software).

Cell apoptosis detection

The cells were harvested and re-suspended in 0.5 ml binding buffer, then incubated with Annexin-V fluorescein

isothiocyanate/PI dual stain (BD Biosciences) for 15 min and finally determined by flow cytometry.

RNA sequencing analysis

The total RNA in A2780cis cells and A2780cis cells with TTK knockdown cells were extracted using the Trizol (Invitrogen, USA) and then were sent to Minigma Biotechnology Company (Shanghai) for sequencing. Sequencing results were further analyzed using R language.

Statistical analysis

Statistical analysis was performed using SPSS 24.0 software. The data were compared between two groups by an independent Students' *t*-test. The positive proportion of TTK expression was analyzed using chi-square test. Differences were considered statistically significant when $P < 0.05$.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13048-021-00884-z>.

Additional file 1: Fig. S1. (A) Tissue chip of TTK expression in ovarian tumor tissues and normal controls. (B) Tissue chip of TTK protein in cisplatin-sensitive and cisplatin-resistant ovarian tumor tissues. (C) TTK expression was reduced after cisplatin treatment in A2780 cells.

Acknowledgements

We are grateful for the contribution of all databases including TCGA, GEO and Oncomine because they provide free online tools and resources.

Authors' contributions

YXL and RQL designed the experiments. YXL and KYZ performed the main experiments and wrote the manuscript, and HZ revised the manuscript. XLG and SHX conducted some supplemental experiments. YCW and YT analyzed the data. LG, HZ and RQL provide financial supports. All authors read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China [grant number NSF-81772774, NSF-81772808, NSF-82072876] and Science and Technology Commission of Shanghai Municipality [grant number 19ZR1410300].

Availability of data and materials

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures were approved by the Ethics Committee of Fudan University Shanghai Cancer Center.

Consent for publication

Not applicable.

Competing interests

The authors declare that there are no conflicts of interest regarding the publication of this article.

Author details

¹Department of Clinical Laboratory, Fudan University Shanghai Cancer Center, No.270, Dong'An Road, Xuhui District, Shanghai 200032, China. ²Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China. ³Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, China.

Received: 17 March 2021 Accepted: 19 September 2021

Published online: 02 October 2021

References

1. Ceccarelli S, et al. Notch3 targeting: a novel weapon against ovarian cancer stem cells. *Stem Cells Int*. 2019;2019:6264931.
2. Jiang X, et al. PARP inhibitors in ovarian cancer: sensitivity prediction and resistance mechanisms. *J Cell Mol Med*. 2019;23(4):2303–13.
3. Fields EC, et al. Radiation treatment in women with ovarian cancer: past, present, and future. *Front Oncol*. 2017;7:177.
4. Marques MP, et al. A molecular view of cisplatin's mode of action: interplay with DNA bases and acquired resistance. *Phys Chem Chem Phys*. 2015;17(7):5155–71.
5. Siddik ZH. Cisplatin: mode of cytotoxic action and molecular basis of resistance. *Oncogene*. 2003;22(47):7265–79.
6. Zaman GJR, et al. TTK inhibitors as a targeted therapy for CTNNB1 (β -catenin) mutant cancers. *Mol Cancer Ther*. 2017;16(11):2609–17.
7. Maia AR, et al. Inhibition of the spindle assembly checkpoint kinase TTK enhances the efficacy of docetaxel in a triple-negative breast cancer model. *Ann Oncol*. 2015;26(10):2180–92.
8. Tannous BA, et al. Effects of the selective MPS1 inhibitor MPS1-IN-3 on glioblastoma sensitivity to antimetabolic drugs. *J Natl Cancer Inst*. 2013;105(17):1322–31.
9. Housman G, et al. Drug resistance in cancer: an overview. *Cancers (Basel)*. 2014;6(3):1769–92.
10. Komatsu M, et al. Copper-transporting P-type adenosine triphosphatase (ATP7B) is associated with cisplatin resistance. *Cancer Res*. 2000;60(5):1312–6.
11. Nakayama K, et al. Prognostic value of the Cu-transporting ATPase in ovarian carcinoma patients receiving cisplatin-based chemotherapy. *Clin Cancer Res*. 2004;10(8):2804–11.
12. Borst P, et al. A family of drug transporters: the multidrug resistance-associated proteins. *J Natl Cancer Inst*. 2000;92(16):1295–302.
13. Papouli E, Cejka P, Jiricny J. Dependence of the cytotoxicity of DNA-damaging agents on the mismatch repair status of human cells. *Cancer Res*. 2004;64(10):3391–4.
14. Bieg D, et al. Morin decreases galectin-3 expression and sensitizes ovarian cancer cells to cisplatin. *Arch Gynecol Obstet*. 2018;298(6):1181–94.
15. Mansouri A, et al. Cisplatin resistance in an ovarian carcinoma is associated with a defect in programmed cell death control through XIAP regulation. *Oncol Res*. 2003;13(6-10):399–404.
16. Lara-Gonzalez P, Westhorpe FG, Taylor SS. The spindle assembly checkpoint. *Curr Biol*. 2012;22(22):R966–80.
17. Chen S, et al. Silencing TTK expression inhibits the proliferation and progression of prostate cancer. *Exp Cell Res*. 2019;385(1):11669.
18. King JL, et al. TTK promotes mesenchymal signaling via multiple mechanisms in triple negative breast cancer. *Oncogenesis*. 2018;7(9):69.
19. Zhang L, et al. Mitotic checkpoint kinase Mps1/TTK predicts prognosis of colon cancer patients and regulates tumor proliferation and differentiation via PKCa/ERK1/2 and PI3K/Akt pathway. *Med Oncol*. 2019;37(1):5.
20. Song H, et al. Cisplatin induced apoptosis of ovarian cancer A2780s cells by activation of ERK/p53/PUMA signals. *Histol Histopathol*. 2018;33(1):73–9.
21. Yang-Hartwich Y, et al. p53 protein aggregation promotes platinum resistance in ovarian cancer. *Oncogene*. 2015;34(27):3605–16.
22. Mullen M, Gonzalez-Perez RR. Leptin-induced JAK/STAT signaling and cancer growth. *Vaccines (Basel)*. 2016;4(3):26.
23. Cai Y, et al. Effect of Withaferin A on A549 cellular proliferation and apoptosis in non-small cell lung cancer. *Asian Pac J Cancer Prev*. 2014;15(4):1711–4.

24. Shao N, et al. Interleukin-8 upregulates integrin $\beta 3$ expression and promotes estrogen receptor-negative breast cancer cell invasion by activating the PI3K/Akt/NF- κ B pathway. *Cancer Lett.* 2015;364(2):165–72.
25. Xiao Y, et al. The PI3K/mTOR dual inhibitor GSK458 potently impedes ovarian cancer tumorigenesis and metastasis. *Cell Oncol (Dordr).* 2020;43(4):669–80.
26. Mabuchi S, et al. The PI3K/AKT/mTOR pathway as a therapeutic target in ovarian cancer. *Gynecol Oncol.* 2015;137(1):173–9.
27. Ellis H, Ma CX. PI3K inhibitors in breast cancer therapy. *Curr Oncol Rep.* 2019;21(12):110.
28. Bertacchini J, et al. Targeting PI3K/AKT/mTOR network for treatment of leukemia. *Cell Mol Life Sci.* 2015;72(12):2337–47.
29. Stronach EA, et al. DNA-PK mediates AKT activation and apoptosis inhibition in clinically acquired platinum resistance. *Neoplasia.* 2011;13(11):1069–80.
30. Zheng H, et al. Elevated serum HER-2 predicts poor prognosis in breast cancer and is correlated to ADAM10 expression. *Cancer Med.* 2019;8(2):679–85.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

