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Down-regulation of UTP23 promotes paclitaxel resistance and predicts poorer prognosis in ovarian cancer

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ABSTRACT

Objective: Frequent resistance to paclitaxel and carboplatin based chemotherapy remains a therapeutic challenge in ovarian cancer. UTP23, a small sub-unit processome component, is down-regulated in a paclitaxel-resistant cell line SKOV3-TR30 compared with its parental SKOV3 cells based on our previous study. However, the specific mechanism of UTP23 in regulating ovarian cancer chemotherapy resistance remains largely unknown.
Methods: Immunohistochemical (IHC) staining was used to measure UTP23 expression in 133 ovarian cancer tissues. Then we used short hairpin RNA (shRNA), over-expression plasmid and cell counting kit-8 (CCK-8) assay to evaluate the function of UTP23 on modulating paclitaxel resistance in ovarian cancer. RNA-sequencing (RNA-seq) was used to find targeted downstream molecular of UTP23. Quantitative real-time polymerase chain reaction (qRT-PCR) and western blotting were utilized to detect related genes expression.
Results: We confirmed that UTP23 was down-regulated in both SKOV3-TR30 and A2780-TR cells compared with their parental cells. Decreased UTP23 expression was observed in ovarian cancer tissues with paclitaxel resistance. Moreover, lower expression of UTP23 was tightly correlated with patients of worse prognosis. Further UTP23 silence by shRNA increased paclitaxel resistance in SKOV3 and A2780 cells. And UTP23 over-expression by plasmid decreased paclitaxel resistance in SKOV3-TR30 and A2780-TR cells. Additionally, RNA-seq and qRT-PCR validation revealed that growth differentiation factor 15 (GDF15) was probably a downstream target for UTP23. GDF15 was notably up-regulated upon the depletion of UTP23 in both SKOV3 and A2780 cells.
Conclusion: Our findings elucidated a previously unknown function for UTP23 in regulating paclitaxel sensitivity and UTP23 could serve as a potential prognostic predictor for ovarian cancer.

1. Introduction

Ovarian cancer remains the most fatal gynecological malignancy and the main cause of cancer-associated death, although managements improved both in surgical skills and chemotherapy over the past decades [1]. The overall 5-year survival of advanced ovarian cancer remains only 29% according to statistics from 2008 to 2014 in United States [2]. Current primary treatment strategy for ovarian cancer is cytoreductive surgical resection followed by paclitaxel and carboplatin based combination chemotherapy [3]. However, more than 70% of ovarian cancer patients relapse after primary therapy within 2–3 years, and almost all recurrent ovarian cancer patients are resistant to re-chemotherapy [4]. Recurrence and drug resistance have become the leading causes of management failure results in death among such patients. Although many hypotheses on paclitaxel resistance have been put forward, paclitaxel resistance is still an urgent issue to be solved.

According to our previous quantitative proteomic analysis between ovarian cancer cells SKOV3 and SKOV3-TR30, paclitaxel resistance of SKOV3-TR30 increased over 27-fold compared with its parental SKOV3 [5], and UTP23 was observed down-regulated remarkably in SKOV3-TR30 cells. UTP23 is a highly conserved constituent of 90S pre-ribosomes and is required for 18S rRNA early processing [6]. Ribosome synthesis and protein translation are closely bound up with cellular homeostasis. Dysregulation of any of these processes may induce cell death or unrestrained growth [7,8]. UTP23 was previously reported to be one of the most prominent regulated genes in the nuclear compartment to evaluate damage to the neurovascular unit in a mouse model of hyperglycemic memory [9]. In addition, another small subunit processome UTP18 was found to promote tumor aggressiveness and reduces patient survival by increasing stress resistance of cancer cells

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[10]. Nevertheless, the relationship between UTP23 and ovarian cancer paclitaxel resistance is largely unknown.

Here, we validated lower expression of UTP23 in ovarian cancer cells with paclitaxel resistance according to the previous proteomic analysis, and UTP23 down-regulation was correlated with a worse prognosis in patients with ovarian cancer. In addition, inhibition or over-expression of UTP23 significantly altered sensitivity to paclitaxel in ovarian cancer cells. All these results demonstrated UTP23 could serve as a novel marker in its prognosis.

2. Materials and methods

2.1. Cell culture

We purchased human ovarian cancer cell line SKOV3 and A2780 from the American Type Culture Collection (ATCC). SKOV3-TR30 development was described before [11]. A2780-TR was kindly provided by Professor Ding Ma from Tongji Hospital, Huazhong University of Science and Technology, Wuhan, P.R. China. SKOV3 and A2780 were maintained in McCoy's 5A medium (BI, Israel) and RPMI-1640 medium (BI, Israel) supplemented with 10% fetal bovine serum (FBS) (Every Green, China) under 5% CO_2 and 37℃. The ovarian cancer sublines SKOV3-TR30 and A2780-TR were cultured in 30 nM and 100 nM paclitaxel (Aosaikang Pharm, China), respectively.

2.2. Patient specimens and immunohistochemical (IHC) staining

A total number of 133 paraffin embedded tissues collected from epithelial ovarian cancer patients from January 2008 to March 2014 were used for IHC analysis. The clinical characteristics are summarized in Table 1. The follow-up deadline was September 2018. All patients received initial cytoreductive surgery followed by 6–8 cycles standard paclitaxel-based chemotherapy regimen. The criteria for distinguishing paclitaxel sensitivity or resistance and the definition of progression-free survival (PFS) and overall survival (OS) were described previously [12]. Approvement by Zhejiang Cancer Hospital ethical committee was acquired (Reference number IRB-2019-8). Anti-UTP23 antibody (1:100, OmnimAbs, USA) was utilized for IHC analysis. The scoring and grading details of IHC analysis referred to our previous study [5].

Table 1
Association between UTP23 expression and clinicopathological parameters of female patients with ovarian cancer.

Clinicopathological features	Cases (n)	UTP23 expression		P value
		Low (n = 40)	High (n = 93)	
Age (years)				0.64
< 50	64	18	46	
≥ 50	69	22	47	
FIGO stage				0.37
I/II	15	3	12	
III/VI	118	37	81	
Tumor grade				0.43
High-grade	18	4	14	
Low-grade	115	36	79	
Ascitic fluid volume(ml)				0.33
< 500	47	11	36	
≥ 500	86	27	59	
Primary surgery(≤ 1 cm)				0.05*
Optimal	104	27	77	
Suboptimal	29	13	16	
Serum CA125(U/ml)				0.23
< 1000	67	17	50	
≥ 1000	66	23	43	
Chemosensitivity				0.0045**
Sensitive	109	27	82	
Resistant	24	13	11	

* P < 0.05.
** P < 0.01.

Table 2
Primer sequences used in this study.

Gene	Sequence
UTP23 forward	GCTTCTTCCGCAACAACTTCG
UTP23 reverse	CCTTTCCCAATGTTTCTAGCTCT
GDF15 forward	CGGATACTCACGCCAGAAG
GDF15 reverse	GAACAGAGCCCGGTGAAG
CHAC1 forward	GAACCCTGGTTACCTGGGC
CHAC1 reverse	CGCAGCAAGTATTCAAGGTTGT
STC2 forward	GGGTGTGGCGTGTTTGAATG
STC2 reverse	TTTCCAGCGTTGTGCAGAAAA
ADM2 forward	CTGAGCCCCATCTGAAGCC
ADM2 reverse	CAGCACTGCGTGTAGACCAG
FGFBP1 forward	CTTCACAGCAAAGTGGTCTCA
FGFBP1 reverse	GACACAGGAAAATTCATGGTCCA
BMP4 forward	GATGTGGGCTGGAATGAC
BMP4 reverse	GGTTGGTTGAGTTGAGGTG
ALDH3A1 forward	TGGAACGCCTACTATGAGGAG
ALDH3A1 reverse	GGGCTTGAGGACCACTGAG
DKK1 forward	CCTTGAACTCGGTTCTCAATTCC
DKK1 reverse	CAATGGTCTGGTACTTATTCCCG
GAPDH forward	TCACCACCATGGAGAAGGC
GAPDH reverse	GCTAAGCAGTTGGTGGTGCA

Abbreviations: GDF15: growth differentiation factor 15; CHAC1: glutathione-specific gamma-glutamylcyclotransferase 1; STC2: stanniocalcin 2; ADM2: adrenomedullin 2; FGFBP1: fibroblast growth factor binding protein 1; BMP4: bone morphogenetic protein 4; ALDH3A1: aldehyde dehydrogenase 3 family member A1; DKK1: dickkopf WNT signaling pathway inhibitor 1.

2.3. Western blotting

We extracted total cell protein lysates using RIPA lysis buffer (Beyotime, China) complemented with PMSF (Beyotime, China). Western blotting was conducted as previously described [13]. The antibodies used for western blotting were UTP23 (1:1000, OmnimAbs, USA), GDF15 (1:1000, Abclonal, China), GAPDH (1:2000, Diagbio, China).

2.4. Quantitative real-time polymerase chain reaction (qRT-PCR)

We extracted total RNA using TRIzol reagent (Invitrogen, USA). Reverse-transcription from RNA to cDNA was achieved using PrimeScript RT reagent kit together with gDNA eraser (Takara, Japan). Then PCR reactions were performed by TB Green Premix Ex Taq (Takara, Japan) and using bio-systems 7900 H T fast real-time PCR system (Life Technologies, USA). Primer sequences used are listed in Table 2. We used the 2-ΔΔCt method normalized to GAPDH to calculate the relative mRNA expression.

2.5. Plasmid and short hairpin RNA (shRNA) transfection

To construct the plasmid, we cloned the full-length human UTP23 with a FLAG tag into the pcDNA3.1 vector. Then we used X-treme GENE HP DNA Transfection reagent (Roche, Switzerland) to transfect the ovarian cancer cell according to the manufacturer's protocols.

Moreover, we constructed the UTP23-specific shRNA and cloned it into the PLKO.1 lentivirus expression vector. Then, we transfected the shRNA into adherent cancer cells according to instructions. After 72 h of transfection, the cells were selected by puromycin (SKOV3 4ug/ml, A2780 2ug/ml) for 4 days. The sequence of UTP23 shRNA was forward: CCGGAGGGAAATCCTCATCATTATTCTCGAGAATAATGATGAGGATTTCCCTTTTTTG, reverse: AATTCAAAAAAGGGAAATCCTCATCATTATTCTCGAGAATAATGATGAGGAT-TTCCCT.

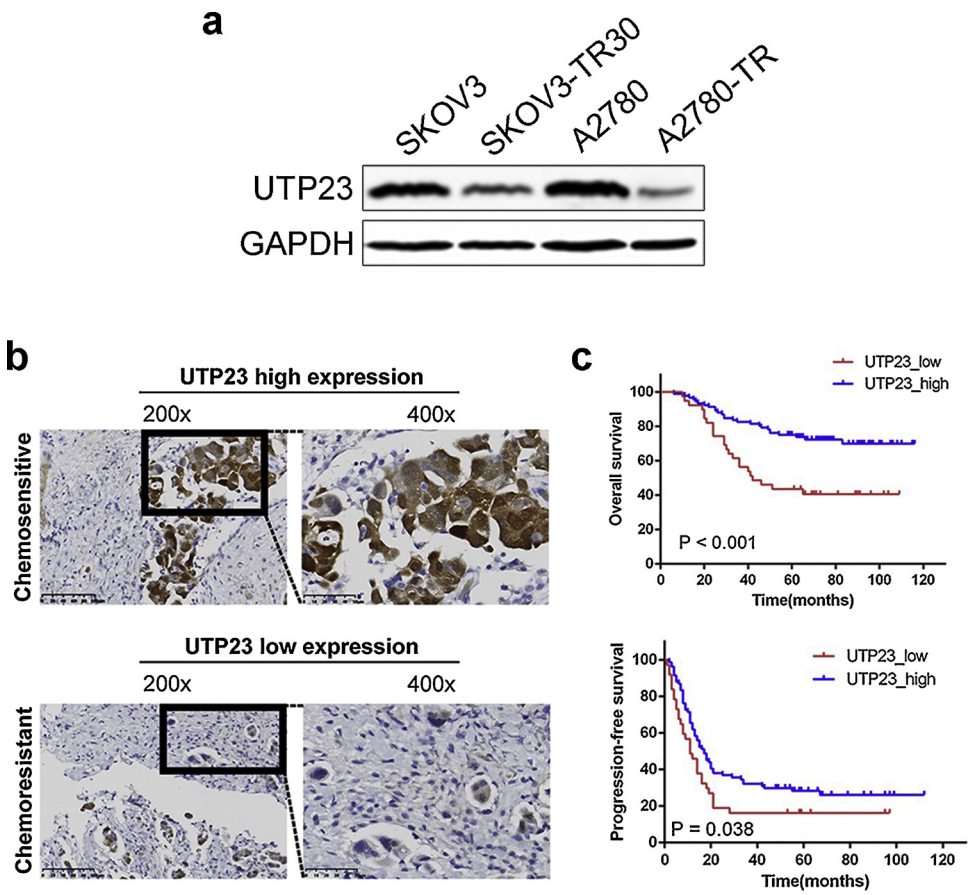

Fig. 1. The expression of UTP23 in ovarian cancer cells and tissues and survival analysis. (a) Protein level of UTP23 was determined by western blotting in paired SKOV3 vs. SKOV3-TR30 and A2780 vs. A2780-TR cell. GAPDH was loaded as control. (b) Representative UTP23 staining of ovarian cancer tissues is shown at 200x and 400x magnifications. (c) Kaplan-Meier survival curves for OS and PFS in ovarian cancer patients with different UTP23 protein levels. *P < 0.05, **P < 0.01, ***P < 0.001.

2.6. RNA-sequencing (RNA-seq) analysis and bioinformatics

Total RNA of SKOV3 cells transfected with UTP23 shRNA lentivirus or control shRNA was extracted using TRIzol reagent (three independent samples for each group). Then we sequenced the libraries using Illumina HiSeq platform. Following quality controls and bioinformatic analysis were described previously [13].

2.7. Cell viability detection

An appropriate quantity of cells (SKOV3 and A2780: 4000 cells per well, SKOV3-TR30 and A2780-TR: 5000 cells per well) was planted in the 96-well plates. After adhering to the plate, paclitaxel of graded concentrations (SKOV3 and A2780: 0, 1.25, 2.5, 5, 10, 20, 40, 80 nM; SKOV3-TR30: 0, 1.25, 2.5, 5, 10, 20, 40, 80, 160, 320, 640 nM; A2780-TR: 0, 1.25, 2.5, 5, 10, 20, 40, 80, 160, 320, 640, 1280 nM) was applied to cells for 48 h. Then we measured the cell viability by cell counting kit-8 (CCK-8) (Dojindo, Japan) following the protocols.

2.8. Statistical analysis

The correlation between UTP23 and clinicopathological features was measured as categorical data, using the Pearson's χ^2 test to evaluate the difference. Kaplan-Meier survival analyses were conducted to compare the survival parameters. Statistics were all analyzed two-sided, and $P \leq 0.05$ was considered to be statistically significant. Data were analyzed using SPSS software version 20.0 (SPSS, Inc) and pictures were conducted by GraphPad Prism software version 7.0 (GraphPad Software, Inc).

3. Results

3.1. UTP23 down-regulation is associated with worse prognosis in ovarian cancer

We firstly validated the different expression of UTP23 protein according to our previous proteomic analyses. Western blot analysis demonstrated UTP23 expression was notably down-regulated in SKOV3-TR30 and A2780-TR cells in contrast with SKOV3 and A2780 cells, respectively (Fig. 1a).

Furthermore, to investigate the role of UTP23 in ovarian cancer, we stained UTP23 in 133 ovarian cancer tissues using IHC. UTP23 was observed stained as brown both in the cytoplasm and nucleus (Fig. 1b). Next we analyzed the association between UTP23 expression and clinicpathological data of patients with ovarian cancer (Table 1). UTP23 low-expression occupied 54.2% (13/24) in 24 cases of chemo-resistant tissues, however, it accounted for only 32.9% (27/82) in 82 chemo-sensitive cases, significantly differed than the former ($P = 0.0045$). Moreover, UTP23 low-expression was significantly correlated with suboptimal primary cytoreductive surgery ($P = 0.050$) and chemo-resistance ($P = 0.0045$), however, no significant differences were identified with age, FIGO stage, tumor grade, ascitic fluid volume and serum CA125. Further survival analysis revealed that UTP23 low-expression ovarian cancer patients had significantly worse OS and PFS than that of high-expression ($P < 0.001$, $P = 0.038$, respectively) (Fig. 1c). Taken together, our data indicate that UTP23 down-regulation implies a worse prognosis in ovarian cancer and lower-expression of UTP23 may induce resistance to paclitaxel in ovarian cancer cells.

3.2. UTP23 modulates paclitaxel sensitivity in ovarian cancer cells

As demonstrated above, UTP23 expression implied the prognosis of

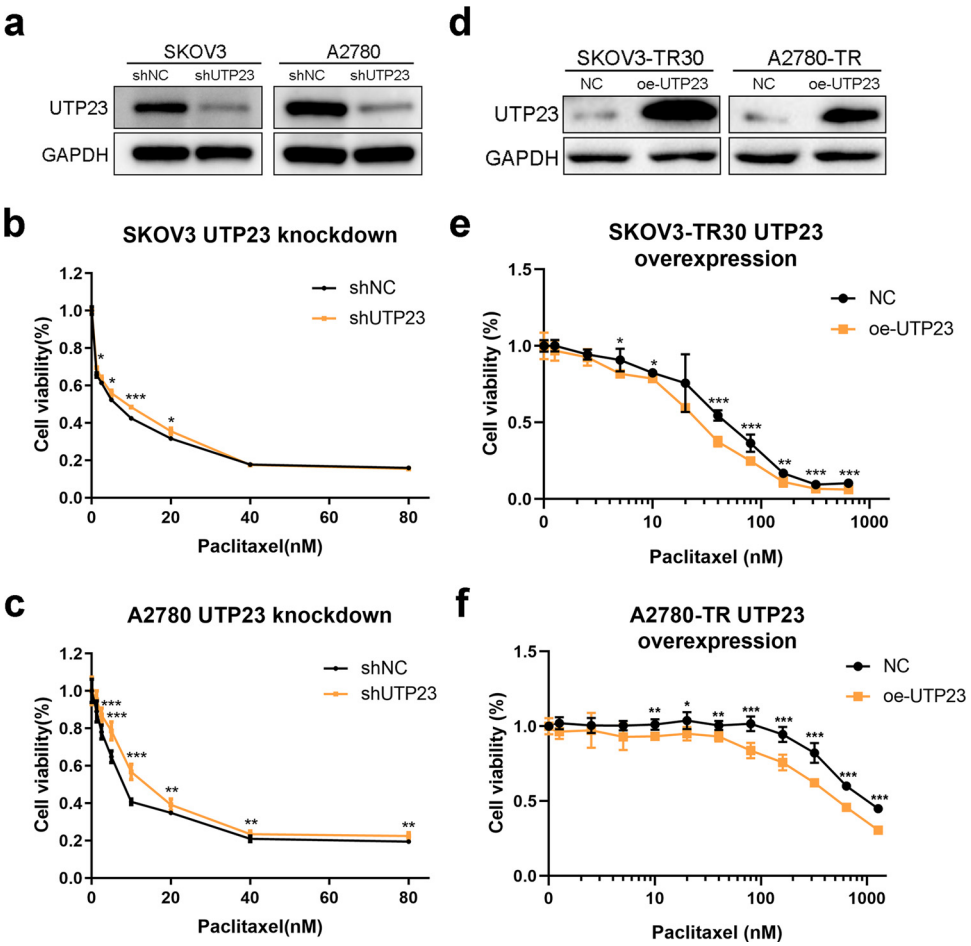

Fig. 2. UTP23 modulates paclitaxel sensitivity. (a) SKOV3 and A2780 cells were transfected with shUTP23 or negative control shRNA; (d) SKOV3-TR30 and A2780-TR cells were transfected with a pcDNA3.1-UTP23 plasmid or empty vector, then western blotting analysis was conducted to vindicate the transfection efficiency. (b, c, e and f) SKOV3, A2780, SKOV3-TR30 and A2780-TR cells were seeded in 96-well plates and exposed to various concentrations of paclitaxel and cell viability was measured by CCK-8 kit after 48 h. Data represents the mean ± SD of three independent experiments, *P < 0.05, **P < 0.01, ***P < 0.001.

Table 3
IC50 of each group in different ovarian cancer cells.

Cells	Treatment	IC50 (nM)
SKOV3	shNC	5.1
	shUTP23	8.1
A2780	shNC	10.3
	shUTP23	15.9
SKOV3-TR30	NC	48.1
	oe-UTP23	28.3
A2780-TR	NC	993.5
	oe-UTP23	853.7

ovarian cancer, so we supposed that UTP23 might participate in modulating paclitaxel resistance in ovarian cancer cells. Stable UTP23 down-regulated ovarian cancer cells were obtained by infecting SKOV3 and A2780 cells with shRNA lentivirus and being selected by puromycin. We used western blotting analysis to verify the transfection efficiency (Fig. 2a). And the CCK-8 assay showed that UTP23 silencing significantly decreased cell viability in both SKOV3 and A2780 cells when exposed to various concentrations of paclitaxel at 48 h (Fig. 2b, c). Next, SKOV3-TR30 and A2780-TR cells were transfected with a pcDNA3.1-UTP23 plasmid. Western blotting analysis showed evident increases of UTP23 expression in both paclitaxel resistant cells (Fig. 2d). And reversely, UTP23 overexpression significantly increased the paclitaxel sensitivity in SKOV3-TR30 and A2780-TR cells (Fig. 2e, f). And the inhibitory concentration 50 (IC50) of each group in different ovarian cancer cells was calculated and analysed (Table 3). Thus, our results suggest that UTP23 down-regulation may facilitate ovarian cancer cells resistance to paclitaxel.

3.3. Candidate downstream target for UTP23

As UTP23 modulates paclitaxel sensitivity in ovarian cancer cells, we intended to find the potential downstream targets of UTP23. RNA-seq was conducted between UTP23 stably downregulated SKOV3 and negative control SKOV3 cells, each group has three independent repeats. A hierarchical-clustering heat map showed a series of differentially expressed genes based on the screening criteria as | log (fold change) | > 1, and p < 0.05 (Fig. 3a). Further KEGG analysis showed that genes were significantly enriched in transcriptional misregulation in cancer, protein processing, p53 signaling pathway, etc (Fig. 3b). We validated top eight differentially expressed genes by qRT-PCR analysis in both SKOV3 and A2780 cells (Fig. 3c, d). We focused on growth differentiation factor 15 (GDF15), which was shown to be particularly up-regulated when UTP23 was silenced. Moreover, researches indicated that GDF15 might be associated with first-line chemo-resistance in epithelial ovarian cancer [14]. Then We observed GDF15 expression in protein level in SKOV3 and A2780 cells. Western blotting analysis showed that GDF15 protein was obviously up-regulated after UTP23 knock-down in both SKOV3 and A2780 cells (Fig. 3e). Our results indicate that GDF15 may act as a downstream of UTP23 in ovarian cancer cells.

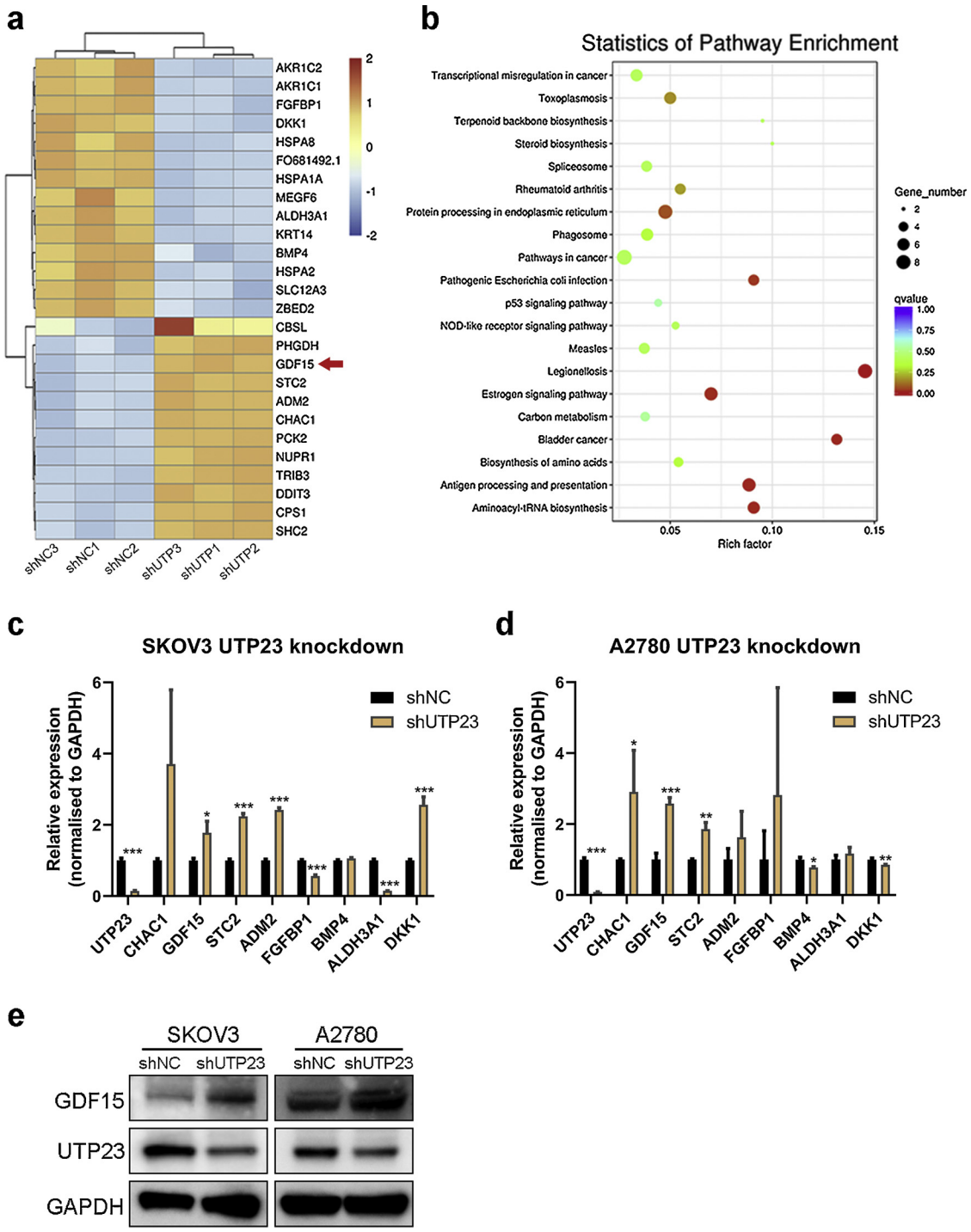

Fig. 3. Candidate downstream target for UTP23. (a) Heat-map hierarchical clustering showed representative differentially expressed genes between UTP23 stably downregulated SKOV3 and negative control SKOV3 cells. Up-regulated genes were shown in yellow, and down-regulated ones in blue. The red arrow indicated GDF15. (b) Top twenty significantly enriched pathways were ranked by q value in a KEGG scatterplot. (c and d) QRT-PCR analysis of top eight differentially expressed mRNA expression regulated by UTP23 in SKOV3 and A2780 cells. Data represents the mean ± SD of three independent experiments, *P < 0.05, **P < 0.01, ***P < 0.001. (e) Protein level of GDF15 and UTP23 was determined by western blotting.

4. Discussion

Chemo-resistance remains one of the leading causes of systemic management failure which results in death among patients with ovarian cancer. Paclitaxel inhibits mitosis by microtubule toxicity. Due to its anti-neoplastic effect, the US Food and Drug Administration (FDA) approved paclitaxel to be used in systemic treatment of ovarian cancer since 1994 [15]. Although ovarian cancer has a high response rate to paclitaxel-based combination chemotherapy, the risk of recurrence remains high, the benefits of paclitaxel have encountered a bottleneck. Therefore, it is vital to solve chemo-therapeutic resistance issues before the advent of new effective chemotherapeutic regimens. Proteomics analysis provides an approach to determine the proteins involved in chemoresistance and to reveal underlying mechanisms in ovarian cancer. In our previous research, we identified 356 proteins with differential expression at no less than 1.5-fold between SKOV3 cells and a

paclitaxel-resistant cell line SKOV3-TR30 using quantitative proteomic analysis. In this study, we focused on UTP23 protein, which was down-regulated a 5.39-fold intensity in SKOV3-TR30 cells. Similar results were further confirmed by western blot analysis between SKOV3, A2780 and their paclitaxel-resistant cell lines, SKOV3-TR30, A2780-TR, respectively.

Synthesis of ribosome in eukaryote has been proved to be an extremely sophisticated process, which consumes a lot of energy involving transcription, protein modification, pre-rRNA folding and processing, and nuclear export [16,17]. It requires over 200 conserved assembly factors. UTP23 is identified to work as a trans-acting factor of early assembling the 18S of rRNA. The functionally significant regions, such as the C-terminal tail, zinc finger, and helix α1, were found to be located outside the key structure of the highly-conserved PIN domain of UTP23 [18]. Although some studies have analyzed the structure of UTP23, few studies mention the role of UTP23 in tumorigenesis and progression. Thus, on the basis of our previous proteomic analyses, we detected UTP23 expression in 133 epithelial ovarian carcinoma tissues by IHC and found UTP23 was significantly down-regulated in ovarian cancer chemo-resistant tissues than chemo-sensitive ones. The clinical analysis showed that down-regulation of UTP23 was notably correlated with suboptimal primary cytoreductive surgery and chemo-resistance. Patients of ovarian cancer with lower expression of UTP23 had worse OS and PFS, compared with those of higher expression of UTP23. Our findings demonstrated that UTP23 down-regulation may predict a poorer prognosis for such patients. To understand further the molecular mechanism of its function, UTP23 expression was down-regulated and up-regulated by using shRNA and a pcDNA3.1-UTP23 plasmid, respectively. The CCK-8 assays showed paclitaxel resistance was increased when UTP23 was silenced and on the contrary, attenuated when UTP23 was overexpressed. Our findings suggest that down-regulation of UTP23 expression may induce ovarian cancer cells to be resistant to paclitaxel, and thus resulted in poorer prognosis of ovarian cancer.

Moreover, to explore the potential mechanism how UTP23 expression alters the cellular sensitivity to paclitaxel, we performed RNA-seq to find possible downstream target genes for UTP23. RNA-seq and further qRT-PCR validation revealed that GDF15 was probably a downstream target for UTP23. UTP23 knockdown increased mRNA and protein levels of GDF15 in both SKOV3 and A2780 cells. GDF15 origins from the transforming growth factor beta (TGF-β) superfamily, previous studies showed that GDF15 played an crucial part in cancer proliferation, metastasis, and angio-genesis as well in multiple cancer types [19–22]. However, the underlying mechanism of how UTP23 regulating GDF15 was not revealed in our current study and was to be resolved.

In conclusion, UTP23 is down-regulated in ovarian cancer cells with paclitaxel resistance. Lower expression of UTP23 is associated with worse prognosis of patients with ovarian cancer. Loss of UTP23 may promote ovarian cancer cells resistance to paclitaxel through upregulating GDF15. UTP23 may serve as a novel prognostic predictor for patients with ovarian cancer.

Ethical approval

All the procedures performed in this study involving human participants were consistent with the ethical standards of Helsinki declaration and its later amendments or comparable ethical Standards. The ethical committee of Zhejiang Cancer Hospital approved this study (reference number IRB-2019-8).

Informed consent

All the patients signed a written Informed consent before surgery, and all the tissues were collected from the bio-bank of Zhejiang Cancer Hospital.

Declaration of Competing Interest

None.

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