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Overexpression of long non-coding RNA PVT1 in gastric cancer cells promotes the development of multidrug resistance

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ABSTRACT

Background: The development of multidrug resistance (MDR) is a crucial problem of therapy failure in gastric cancer, which results in disease recurrence and metastasis. Plasmacytoma variant translocation 1 (PVT-1), a long non-coding RNA (lncRNA), was previously found to be increased in gastric cancer patients and regulated the chemotherapy sensitivity in pancreatic cancer cells. However, the role of PVT1 in multidrug resistant Gastric cancer remains largely unexplored.
Methods: In this study, the mRNA levels of PVT1 in gastric cancer tissues of cisplatin-resistant patients and two kinds of cisplatin-resistant cells BGC823/DDP and SGC7901/DDP were detected by qRT-PCR. The influence of PVT1 knockdown or overexpression on anticancer drug resistance was assessed by measuring the cytotoxicity of cisplatin and the rate of apoptosis detected by CCK-8 assay and flow cytometry, respectively. Further, we investigated the expression levels of MDR1, MRP, mTOR and HIF-1α by qRT-PCR and western blotting.
Results: PVT-1 was highly expressed in gastric cancer tissues of cisplatin-resistant patients and cisplatin-resistant cells. In addition, BGC823/DDP and SGC7901/DDP cells transfected with PVT-1 siRNA and treated with cisplatin exhibited significant lower survival rate and high percentage of apoptotic tumor cells. While, PVT1 overexpression exhibit the anti-apoptotic property in BGC823 and SGC7901 cells transfected with LV-PVT1-GFP and treated with cisplatin. Moreover, qRT-PCR and western blotting revealed that PVT1 up-regulation increased the expression of MDR1, MRP, mTOR and HIF-1α.
Conclusions: Overexpression of LncRNA PVT1 in gastric carcinoma promotes the development of MDR, suggesting an efficacious target for reversing MDR in gastric cancer therapy.

1. Introduction

Gastric cancer (GC) remains one of the common causes of cancer-related deaths worldwide and presents a high incidence in China [1]. Despite the substantial improvements made in chemotherapy, radiotherapy and surgical techniques for gastric cancer over the past few decades, the prospect for patients with gastric cancer was not optimistic. One of the main reasons for deaths of gastric cancer is the multidrug resistance (MDR) to chemotherapies [2]. Several drug resistance common mechanisms were reported by Magali Rebucci et al., including change in drug export, failure of apoptosis, change in drug metabolism, and failure of DNA repair [3]. Although some factors have been identified to promote the development of multidrug resistant in gastric cancer, such as CDX2 [4], it is not fully understood about the regulators that influence the chemo-resistance of gastric cancer.

PVT1 is a long non-coding RNA (lncRNA) and locates near MYC at human chromosome 8q24 [5]. Several researchers have observed that PVT1 plays a role in tumorigenesis through DNA rearrangements or amplifications in non-small cell lung cancer and hepatocellular carcinoma [6,7]. PVT1 also has been reported to be in high level and inhibit apoptosis in breast, colorectal and ovarian cancer [8]. Wang et al. found that PVT1 promoted cell proliferation, the acquisition of stem cell like properties and cell cycling in hepatocellular carcinoma cells by stabilizing NOP2 protein [9]. Furthermore, PVT1 was significantly higher in gastric cancer patients and might be novel biomarkers for predicting gastric cancer [10]. Lei You et al. identified that PVT1 regulated the chemotherapy sensitivity in pancreatic cancer cells using a

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piggyBac transposon-based genome-wide mutagenesis strategy [11]. While the role of PVT1 in multidrug resistant gastric cancer remains largely unexplored.

In the present study, we aim to explore the role of lncRNA PVT1 in cisplatin resistance gastric cancer and further investigate the effects of up-regulation PVT1 on the expression of genes associated with multidrug resistant, including MDR1, MRP, mammalian target of rapamycin (mTOR), and hypoxiainducible factor-1(HIF-1α).

2. Materials and methods

2.1. Patient characteristics and clinicopathological features

A total of 70 patients with primary gastric cancer were enrolled in this study. The GC patients received Cisplatin-based (EP plan) palliative chemotherapy (75 mg/m^2 of Cisplatin (Cisplatin for injection, QILU Pharmaceutical, China) on day 1 through day 3, in a 3-week cycle without surgery. Obvious primary tumor shrinkage and reduce of malignant pleural effusions were considered effective treatment, which displayed in all 70 patients. Cisplatin-resistant cases were distinguished when primary tumor enlarged, pleural effusions increased or new metastasis occurred within 6–15 months (n = 10), otherwise Cisplatin-sensitive case was defined (n = 10). The median age of the patients was 65 years (range 33–75 years) and the ratio of males to females was 37:33. The detailed information of the patient characteristics was showed in Supplemental Table. The tumor tissue samples were collected from these patients. This study received approval from the ethics committee of Northern Jiangsu People's Hospital, and all patients provided written informed consent.

2.2. Cell lines and culture

Human gastric cancer cell lines BGC823 and SGC7901 were purchased from the Type Culture Collection of the Chinese Academy of Sciences (Shanghai, China). All the cells were cultured in RPMI 1640 medium supplemented with 10% of fetal bovine serum, 100 U/ml of penicillin and 100 μg/ml of streptomycin. The cells were grown at 37 °C in a humidified incubator with 5% CO_2. Cisplatin was obtained from Sigma–Aldrich. The cisplatin-resistant BGC823/DDP cells were developed from the parental BGC823 cells that were subjected to persistent gradient exposure to cisplatin for about 12 months, through increasing cisplatin concentration from 0.05 μg/ml until the cells acquired resistance to 1 μg/ml. The cisplatin-resistant SGC7901/DDP cells were obtained by the same way. Prior to each experiment, BGC823/DDP and SGC7901/DDP cells were cultured in drug-free RPMI 1640 medium for 2 weeks.

2.3. Plasmids and transfection

PVT1-overexpression lentiviral vector (LV-PVT1-GFP) and control PLNCX lentiviral vector (LV-GFP) purchased from Shanghai Cancer Institute, China. siRNA specific for PVT1 (sense 5′-GCUUGGA GGCUGAGGAGUUTT-3′ and antisense 5′-AACUCCUCAGCCUCCA AGCTT-3′) were synthesized (Ribobio, Guangzhou, China). BGC823 and SGC7901 cells (or BGC823/DDP and SGC7901/DDP cells) were seeded in six-well plates with antibiotic-free medium. After 24 h incubation, cells were infected with viral supernatant or siRNA oligonucleotide (30 nmol l^{-1}) in Opti-MEM (Invitrogen) at a multiplicity of infection of 200 PFU per cell (MOI = 200), and the stable-transfected cell lines were obtained by culturing transfected cells in the presence of 700 mg/mL G418 (Invitrogen, Carlsbad, CA, United States) for 3–4 wk.

2.4. Cytotoxicity assay

Cell Counting Kit-8 (CCK-8) assay was performed to detect the cytotoxicity of gene transfection according to the manufacturer's instructions [13]. After transfected siPVT1 into BGC823/DPP and SGC7901/DDP, cells were seeded in 96-well plates, each well of which contained 100 μl PRMI-1640 medium supplemented with 10% FBS at 5 × 10^4 cells/well. Then cells were treated with 1 ug/ml cisplatin. After 24 h, 36 h or 48 h incubation, 10 μl Cell Counting Kit-8 (CCK-8) was added and culture was continued for 1 h in humid atmosphere containing 5% CO_2. Absorbancies at 450 nm were measured by Microplate Reader (Bio-Tech Company).

2.5. Apoptosis analysis by flow cytometry

Cells (1 × 10^6) were washed twice with Hepes-buffered saline, treated with trypsin, and fixed in cold 70% ethanol at 4 °C for 30 min. Cell pellet were collected and incubated in a solution containing 5 μl Annexin V-FITC and 1 μl of PI (50 μg/ml). Flow cytometric evaluation was conducted within 5 min. The cells were analyzed by flow cytometry using an EPICS XL-MCL FACScan (Becton–Dickinson, Mountain View, CA, United States). The data was analyzed with the MultiCycle Software for Windows (Phoenix Flow Systems, San Diego, CA, United States).

2.6. Western blot analysis

Western blot analyses were performed as previously described [12]. Briefly, cell lysates were prepared in a buffer containing 50 mM Tris pH 8.0, 150 mM NaCl, 1% NP-40, 0.5% DOC and 0.1% SDS. Protein quantitation was performed with Lowery protein assay, and equal amounts of proteins were separated by electrophoresis on SDS-polyacrylamide gel and blotted to a nitrocellulose membrane. The membrane was incubated with antibodies against MDR1 (1:3000) and MRP1 (1:1500), or anti-GAPDH as a control, and then incubated with a peroxidase-linked secondary antibody (1:1000) after washed with TBST. Enhanced chemiluminescence was used to visualize the antigen–antibody complexes.

2.7. Quantitative real-time PCR

Total RNA was extracted using the Trizol reagent according to the manufacturer's instructions. After quantification by spectrophotometry, 1 μg total RNA was used to synthesis first-strand cDNA with the RevertAidHMinus First Strand cDNA synthesis kit (Fermentas,USA). Real-time PCR (RT-PCR) reactions were carried out on an Mx3000P real-time PCR system (Stratagene USA). To correct for the experimental variations between samples, glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as the internal control. PCRs were performed with the following primer sets: PVT1 primers were sense: 5′-CAGCACTCTGGACGGAC-3′ and antisense: 5′-CAACAGGAGAAGCAAACA-3′. MDR1 primers were sense: 5′-ACC AAG CGG CTC CGA TAC A-3′ and antisense: 5′-TCA TTG GCG AGC CTG GTA GTC-3′. MRP primers were sense: 5′-GGA CCT GGA CTT CGT TCT CA-3′ and antisense: 5′-CGT CCA GAC TTC ATC CG-3′. mTOR primers were sense: 5′-CCC GAG ACA GCC TTG GCA GTT GG-3′ and antisense: 5′-CAG GAC TCA GGA CAC AAC TAG CCC-3′. HIF-1α primers were sense: 5′-CTA TGG AGG CCA GAA GAG GGT AT-3′ and antisense: 5′-CCC ACA TCA GGT GGC TCA TAA-3′. GAPDH primers were sense: 5′-ACC ACA GTC CAT GCC ATC AC-3′ and anti-sense: 5′-TCA CCA CCC TGT TGC TGT A-3′). All mRNA levels were calculated using the $2^{-\Delta\Delta Ct}$ method. The results were analyzed by Mx3000P real-time PCR software version 2.00.

2.8. Statistical analysis

Data are expressed as mean ± SD. One-way analysis of variance (ANOVA) was used to determine the statistical significance. Statistical analysis were carried out using Origin 7.5 software programs. A value of $P < 0.01$ was considered as statistically significant.

3. Results

3.1. PVT1 is associated with the development of cisplatin resistance

To investigate whether PVT1 involves the development of cisplatin resistance in gastric cancer tissue, we examined the mRNA levels of PVT1 in the gastric cancer tissues of cisplatin-sensitive patients ($n = 10$) and cisplatin-resistant patients ($n = 10$). As a result, significantly elevated mRNA level of PVT1 was observed in the cancer tissues of cisplatin-resistant patients comparing to cisplatin-sensitive patients (Fig. 1A). To verify this differential expression of PVT1, we detected the PVT1 expression in two kinds of cisplatin-resistant cells BGC823/DDP and SGC7901/DDP, which were developed from the parental BGC823 cells and SGC7901 cells, respectively. Consistent with the results in gastric cancer tissues, PVT1 was overexpressed in cisplatin-resistant cells BGC823/DDP and SGC7901/DDP (Fig. 1B). These results indicated that PVT1 may be associated with the development of cisplatin resistance in gastric cancer.

3.2. PVT1 knockdown reverses the cisplatin resistance in cisplatin-resistant GC cell lines

On the basis of above results, we examined the effect of PVT1 knockdown on cisplatin-induced cytotoxicity and apoptosis in BGC823/DDP and SGC7901/DDP cells. Pvt1 small RNA significantly decreased the expression of PVT1 in BGC823/DDP and SGC7901/DDP cells, as shown in Fig. 2A. After transfected siPvt1, BGC823/DDP and SGC7901/DDP cells were treated with cisplatin for 24 h, 36 h and 48 h, and CCK-8 assay was performed to detect the cell viability. As shown in Fig. 2B and C, cells transfected siPvt1 had a significantly lower survival rate than that in control group, and cell viability clearly decreased with time of cisplatin treatment. Furthermore, we detected the percentage of apoptotic tumor cells in cells. After stained with Annexin V and PI, BGC823/DDP and SGC7901/DDP cells transfected siPvt1 and treated with cisplatin were analyzed by flow cytometry. On the dual parameter fluorescent dot, plots in the lower-left quadrant present the viable cells and in the right quadrant present the apoptotic cells. Increased apoptotic cells are observed in siPvt1 group than that in control group (Fig. 2D and E). These results indicate that siPvt1 reverses the cisplatin resistance in cisplatin-resistant GC cell lines.

3.3. Overexpression of PVT1 inhibits apoptosis in GC cell lines

We further examined the effect of PVT1 overexpression on cell apoptosis in GC cell lines. Transfection of LV-PVT1-GFP into BGC823 and SGC7901 cells led to marked enhancement of PVT1 mRNA (Fig. 3A). Densitometry analysis indicated that PVT1 mRNA levels in the BGC823 and SGC7901 cells both transfected LV-PVT1-GFP were approximately 3.8- and 6-fold higher, respectively, than those in the control cells ($P < 0.05$). These results confirmed that BGC823 and SGC7901 cells transfected with LV-PVT1-GFP showed the up-regulation of PVT1 mRNA expression. We next examined the effect of LV-PVT1-GFP expression on the apoptosis of GC cells. The results of flow cytometry revealed that BGC823 and SGC7901 cells transfected LV-PVT1-GFP exhibited a significantly decreased apoptosis index compared to the control groups ($P < 0.01$) (Fig. 3B and C). Together, these data indicate that overexpression of PVT1 inhibits cisplatin-induced apoptosis in BGC823 and SGC7901 cells.

3.4. PVT1 influenced the expression of MDR1 and MRP1

Multidrug resistance (MDR) to cancer chemotherapy was known to be the major obstacle to successful treatment of GC. To investigate the mechanism by which PVT1 enhance the cisplatin resistance of GC cells, we examined the expression levels of several MDR-related proteins (MDR1, MRP1, mTOR and HIF-1α) by qRT-PCR. The mRNA level of MDR1, MRP, mTOR and HIF-1α in BGC823 and SGC7901 cells transfected LV-PVT1-GFP were significantly higher than that in control (Fig. 4A–D). To better understand the function of PVT1, we detected the protein levels of MDR1 and MRP1 with western blotting. We found that the protein level of MDR1 and MRP1 increased in BGC823 and SGC7901 cells transfected LV-PVT1-GFP than that in control (Fig. 4E).

4. Discussion

The development of multidrug resistance (MDR) is a crucial problem of therapy failure in gastric cancer, which results in disease recurrence and metastasis. Cisplatin, as an important drug used in gastric cancer chemotherapy, could trigger apoptosis by inducing DNA damage through crosslinking of the DNA [1]. However, cancer cells often develop multiple mechanisms to cause cisplatin resistance. The mechanism for drug resistance involves a series of pathological changes. Nevertheless, the exact mechanism of MDR is an ongoing need to pinpoint.

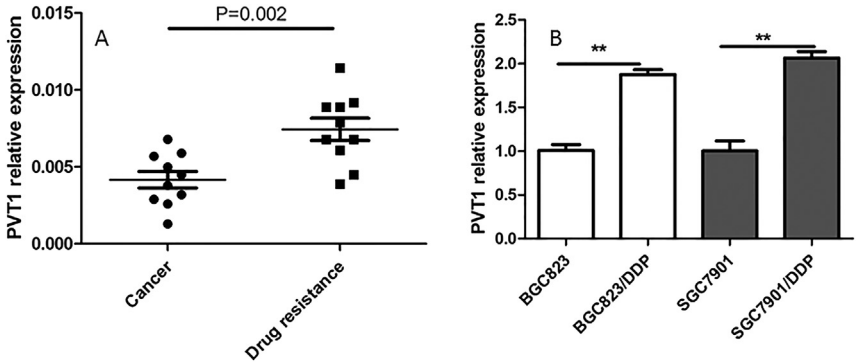

Fig. 1. PVT1 is associated with the cisplatin-resistance. (A) The mRNA levels of PVT1 in gastric cancer tissue of cisplatin-sensitive patients and cisplatin-resistant patients. (B) The mRNA levels of PVT1 in the cisplatin-resistant BGC823/DDP cells and SGC7901/DDP cells. All values are mean ± SD. ** vs control, $p < 0.01$.

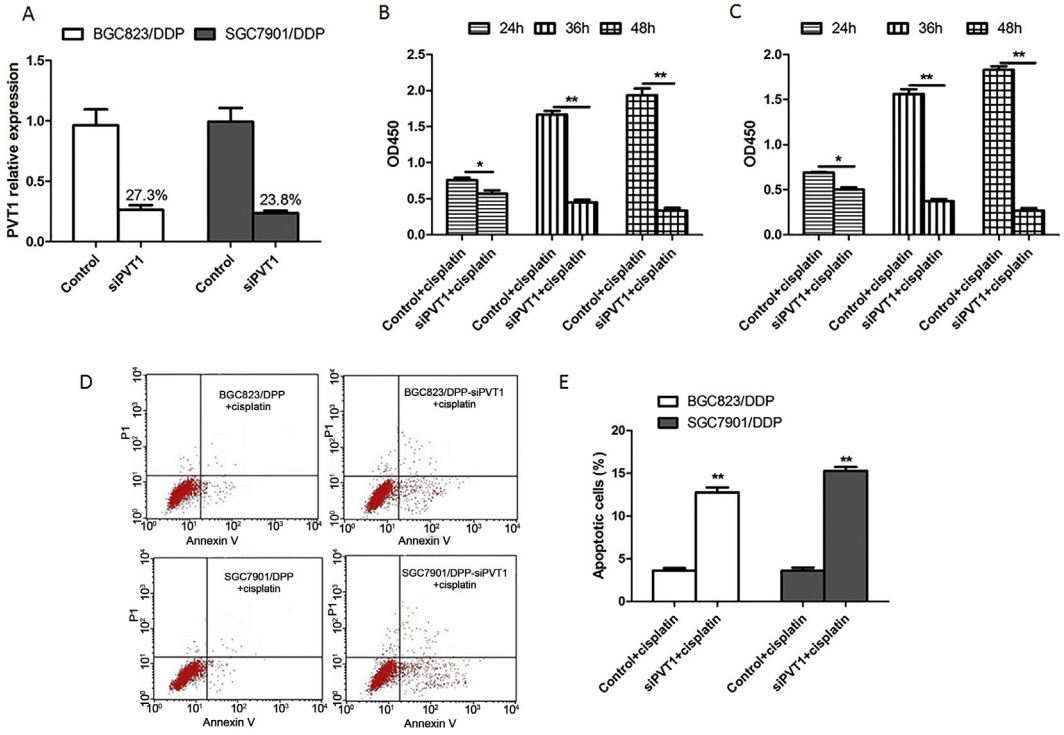

Fig. 2. PVT1 knockdown reverses the cisplatin-resistance in cisplatin-resistant gastric cancer cells. (A) The efficiency of Pvt1 small RNA on the mRNA level of Pvt1. (B) The effect of PVT1 knockdown on cell viability of BGC823/DDP cells transfected with siPVT1 and treated with cisplatin. (C) The effect of PVT1 knockdown on cell viability of SGC7901/DDP cells transfected with siPVT1 and treated with cisplatin. (D) (E) Percentage of apoptotic cells was analyzed by flow cytometry. All values are mean ± SD. **vs control, $p < 0.01$.

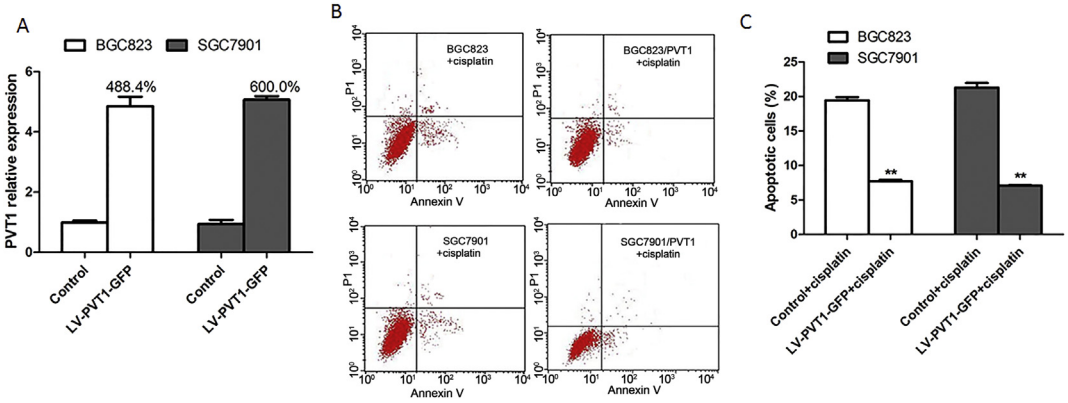

Fig. 3. Overexpression PVT1 inhibits apoptosis in the cisplatin-resistant gastric cancer cells. (A) Cells transfected LV-PVT1-GFP plasmid overexpressed PVT1. (B) (C) Percentages of apoptotic cells were analyzed by flow cytometry. All values are mean ± SD. **vs control, $p < 0.01$.

Several reviews have focused on the biological functions of lncRNAs in human cancers, such as gastric cancer [10], hepatocellular carcinoma [13], renal cancer [14], prostate cancer [15], ovarian cancer [16] etc. LncRNAs exert their effects through regulating gene expression at the level of chromatin modification, transcription and post-transcriptional processing. Dysregulation of lncRNAs were found to affect the clinicopathological appearance, prognosis and outcome of GC [10]. Furthermore, some lncRNAs were also reported to promote the development of MDR in cancers. For example, Ying Wang et al. suggested that lncRNA *MRUL* is a potential target to reverse the MDR phenotype of GC MDR cell sublines [17]. In non-small-cell lung cancer cells, lncRNA AK126698 might regulate A549 cells cisplatin resistance through the canonical Wnt pathway [18]. In this study, we also found that lncRNA PVT1 is associated with the development of cisplatin resistance.

Here, we found the overexpression of PVT1 in gastric cancer tissues of cisplatin-resistant patients and two kinds of cisplatin-resistant cells BGC823/DDP and SGC7901/DDP. In addition, the results of CCK-8 assay and flow cytometry revealed that PVT1 knockdown significantly lowered the survival rate and enhanced the percentage of apoptotic tumor cells in cisplatin-resistant cells transfected siPvt1 and treated with cisplatin, which indicated that PVT1 knockdown reverses the cisplatin resistance of cisplatin-resistant cells. On the other hand, PVT1 overexpression exhibit the antiapoptotic property, which inhibited the apoptosis of BGC823 and SGC7901 cells treated with cisplatin. Notably, cell apoptosis played a critical role in the development of MDR [19]. Several studies have shown that most chemotherapeutic agents exert their anticancer activity by inducing apoptosis or programmed cell death, which is an essential physiologic process

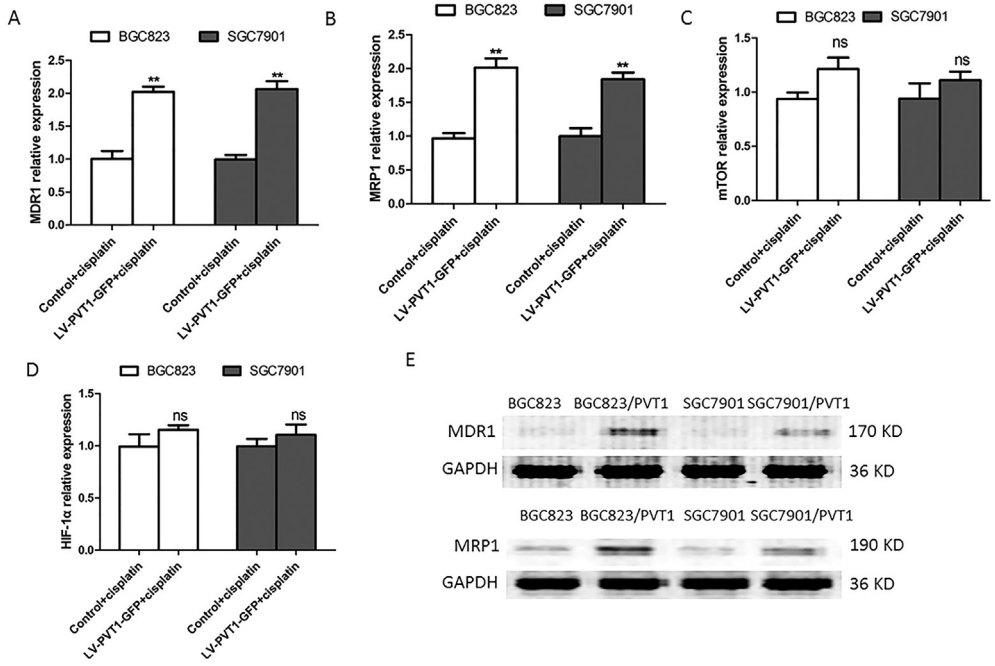

Fig. 4. PVT1 influenced the expression of genes associated with apoptosis and multidrug resistant. (A) The mRNA level of MDR1. (B) The mRNA level of MRP1. (C) The mRNA level of mTOR. (D) The mRNA level of HIFα. (E) The protein level of MDR1 and MRP1. All values are mean ± SD. **vs control, $p < 0.01$.

required to eliminate damaged or abnormal cells [20,21]. Resistance to apoptosis may be a major factor for the ineffectiveness of cancer treatment. Y Takahashi et al. also found PVT1 generated antiapoptotic activity in colorectal cancer [22]. However, a limitation of this current study is that we did not demonstrate a direct molecular function of PVT-1 in apoptosis induction clearly, and further investigation is needed. For example, the key proteins such as p53, Bax, Bcl-2, cytochrome *c* and caspases play an important role in the progress of cell apoptosis [23]. Further study should be carried out to detect the expression of these proteins to verify the role of PVT1-induced apoptosis in MDR.

We further examined the expression of well-known genes involved in multidrug resistant, including MDR1, MRP, mTOR, and HIF-1α. As a results, MDR1, MRP, mTOR and HIF-1α expression were all increased when PVT-1 was up-regulated. Several reports suggested that one of the most important mechanisms being involved in MDR is the expression of P-glycoprotein (P-gp) which acts as an ATP-dependent efflux pump to transport anticancer drugs out of the cells before they reach the cytosol [24,25]. P-gp was encoded by the MDR1 gene [26]. So MDR1 is a well characterized form of drug resistance. Lin-Hai Yan et al. reported in detail that MRP, mTOR, and HIF-1α also involved in P-gp up-regulation and contributed to mediate drug resistance [4,12]. P-gp up-regulation often contributes to a compromised chemotherapy response and prevents the intracellular accumulation of anticancer drugs necessary for cytotoxic activity [17]. Taken together, these results indicated that PVT-1 might promote the development of MDR through regulation of mTOR/HIF-1α/P-gp and MRP1 signaling pathway.

In summary, we demonstrated that PVT-1 knockdown reversed the cisplatin resistance in cisplatin-resistant GC cell lines, while up-regulation of PVT-1 significantly decreased the percentage of apoptotic cells and inhibited the sensitivity of BGC823 and SGC7901 gastric cancer cells to anticancer drugs. Furthermore, we conclude that up-regulation of PVT1 promotes the development of multidrug resistant in gastric cancer via increasing the expression of multidrug resistant related gene (MDR1, MRP, mTOR and HIF-1α). Our results provide evidence that PVT1 may potentially be used as a predictor of chemotherapy response in gastric cancer, and it is a promising therapeutic target in treatment for MDR-gastric cancer.

Competing interests

The authors have no actual or potential conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbrc.2015.04.121.

Transparency document

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