Original Article

Low Programmed Cell Death 5 Expression is a Prognostic Factor in Ovarian Cancer

Li Gao[1], Xue Ye[1], Rui-Qiong Ma[1], Hong-Yan Cheng[1], Hong-Jing Han[2], Heng Cui[1], Li-Hui Wei[1], Xiao-Hong Chang[1]

[1]Gynecology Oncology Center, Peking University People's Hospital, Beijing 100044, China
[2]Center for Reproductive Medicine, Peking University People's Hospital, Beijing 100044, China

Abstract

Background: Ovarian cancer is a leading gynecological malignancy. We investigated the prognostic value of programmed cell death 5 (PDCD5) in patients with ovarian cancer.

Methods: Expression levels of PDCD5 mRNA and protein were examined in six ovarian cancer cell lines (SKOV3, CAOV3, ES2, OV1, 3AO, and HOC1A) and one normal ovarian epithelial cell line (T29) using reverse transcription polymerase chain reaction, Western blotting, and flow cytometry. After inducing PDCD5 induction in SKOV3 cells or treating this cell line with taxol or doxorubicin (either alone or combined), apoptosis was measured by Annexin V-FITC/propidium iodide staining. Correlations between PDCD5 protein expression and pathological features, histological grade, FIGO stage, effective cytoreductive surgery, and serum cancer antigen-125 values were evaluated in patients with ovarian cancer.

Results: PDCD5 mRNA and protein expression were downregulated in ovarian cancer cells. Recombinant human PDCD5 increased doxorubicin-induced apoptosis in SKOV3 cells (15.96 ± 2.07%, vs. 3.17 ± 1.45% in controls). In patients with ovarian cancer, PDCD5 expression was inversely correlated with FIGO stage, pathological grade, and patient survival ($P < 0.05$, $R = 0.7139$ for survival).

Conclusions: PDCD5 expression is negatively correlated with disease progression and stage in ovarian cancer. Therefore, measuring PDCD5 expression may be a good method of determining the prognosis of ovarian cancer patients.

Key words: Ovarian Cancer; Poor Prognosis; Programmed Cell Death 5

Introduction

Ovarian cancer is a leading gynecological malignancy, second only to cervical cancer. It is the most lethal gynecological malignancy, accounting for more deaths than endometrial and cervical cancers combined.[1] Ovarian cancer is typically asymptomatic during the early stages; this, together with its deep pelvic location, multiple morphologies, and characteristic genetic factors, frequently results in late diagnosis. Approximately, 70% of ovarian cancer patients are diagnosed at an advanced stage. Although the surgery is the primary treatment for early-stage ovarian cancer, cytoreductive surgery with platinum-based chemotherapy is the only option for advanced-stage cancer. Although cytoreductive surgery with chemotherapy can significantly prolong patient survival, 5-year survival rates are <30% in patients with advanced-stage ovarian cancer, apparently as a result of either primary or acquired drug resistance by cancer cells. Therefore, increasing the sensitivity of cancer cells to chemotherapeutic regimens may improve prognoses.

Programmed cell death 5 (PDCD5), also called TF-1 cell apoptosis-related gene-19, was discovered at the Peking University Human Disease Center.[2] The PDCD5 gene is located on chromosome 19; its cDNA comprises 559 nucleotides. PDCD5 is highly conserved evolutionarily and is expressed in most tissues. Although PDCD5 overexpression does not induce strong cellular effects, it can enhance apoptosis when triggered by certain stimuli. For example, one study showed PDCD5 gene transfer to sensitize K562 cells to idarubicin-induced apoptosis.[3]

Programmed cell death 5 expression was found to be downregulated in gastric cancer,[4] hepatocellular, carcinoma,[5] breast cancer,[6] acute and chronic myeloid leukemia,[7] and glioma.[8] However, the role of PDCD5 protein in ovarian cancer progression is not widely reported.[9] In this study, we investigated PDCD5 expression in ovarian cancer cell lines and tissue to explore the relationship between PDCD5 and ovarian cancer. We also investigated

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Address for correspondence: Prof. Xiao-Hong Chang, Gynecolog Oncology Center, Peking University People's Hospital, Beijing 100044, China
E-Mail: changxiaohong@pkuph.edu.cn

whether PDCD5 overexpression enhances apoptosis induced by chemotherapeutic regimens in ovarian cancer.

Methods

Ethics statement

This study was carried out in accordance with the *Declaration of Helsinki* of the World Medical Association. It was approved by Peking University People's Hospital (Beijing, China). All patients provided informed written consents.

Cell lines and cell culture

The human serous cystadenocarcinoma cell line SKOV3 was kindly provided by the Memorial Sloan Kettering Cancer Center. CAOV3 ovarian serous cystadenocarcinoma samples were purchased from the China Military Science Center. HOC1A cells (immortalized ovarian cancer cells) were derived in our laboratory from metastatic nodules of the left abdominal wall of ovarian cancer patients. OV1 cells, a low-grade ovarian adenocarcinoma cell line, were kindly provided by Peking University Oncology Institution. The 3AO low-grade ovarian mucinous cell line was purchased from the China Science and Technology Cell Bank. The ES-2 human low-grade clear-cell line was a gift from Dr. You-Ji Feng at Fudan University. The T29 human immortalized ovarian epithelial cell line was a gift from Dr. Jin-Song Liu at the MD Anderson Cancer Center.

All cells were cultured at 37°C in an atmosphere containing 5% CO_2. SKOV3, ES-2, 3AO, OV1, and OV2 cells were cultured in RPMI1640 medium containing 15% fetal calf serum. T29 and HOC1A cells were cultured in MCDB medium containing M199 plus 15% fetal calf serum. CAOV3 cells were cultured in Dulbecco's modified Eagle's medium containing 15% fetal calf serum. All media contained 1% penicillin and streptomycin.

Tissue samples

A total of 127 ovarian cancer samples, 48 ovarian benign tumors, and 33 normal ovarian tissue samples were obtained during surgical procedures at the Department of Gynecology, Peking University People's Hospital from January 2000 to March 2006. All samples were examined by two pathologists to confirm patient diagnoses before experiments were performed. None of the patients had received neoadjuvant therapy, such as radiation or chemotherapy, prior to surgery.

Real-time reverse transcription polymerase chain reaction

Samples were frozen at −80°C in liquid nitrogen. RNA was extracted from 24 samples (5 normal ovarian tissues, 8 benign tumors, and 11 ovarian cancer tissues) using a modified TRIzol one-step extraction method. RNA concentrations were determined by their absorbance at 260 nm. Total RNA (3 μg) was reverse transcribed to cDNA using oligo-dT primers and M-MLV transcriptase (Promega, USA). Real-time polymerase chain reaction (PCR) was performed using a SYBR Green Master Mix (Toyobo, Japan) and primers specific to PDCD5 (sense: 5'-GTGATGCGGCCCAACAG-3', antisense: 5'-GTGATGCGGCCCAACAG-3') and GAPDH (sense: 5'-TGCACCACCAACTGCTTAGC-3', antisense: 5'-GGCATGGACTGTGGTCATGAG-3'). The PCR protocol comprised of 30 cycles at 94°C for 30 s, 58°C for 30 s, and 72°C for 30 s; followed by a final extension at 72°C for 7 min. Human GAPDH was used as an internal control. Samples were analyzed in triplicate in three independent experiments using Bio-Rad MJ Mini and MiniOpticon (Bio-Rad, USA). PDCD5 expression was calculated using the $2^{\Delta\Delta Ct}$ method.

Western blotting

Tissue samples and ovarian cell lines were treated with RIPA lysis buffer (pH 7.4) containing ×1 protease inhibitor cocktail (M221; Amresco, Solon, OH, USA). After centrifugation for 15 min at 12,000 r/min, the supernatant was used for the whole protein lysate samples. Protein concentrations were determined using the BCA standard method. Protein extracts were diluted in loading buffer (1 mmol/L Tris-HCl, 3% sodium dodecyl sulfate [SDS], 60% glycerol, and 75 mmol/L dithiothreitol), and samples were analyzed by SDS-polyacrylamide gel electrophoresis) using 15% gels, followed by transfer to polyvinylidene fluoride membranes. Membranes were then incubated with mouse anti-human PDCD5 (1:1000 dilution; Beijing University Human Disease Center, Beijing, China) or rabbit anti-human GAPDH (1:2000 dilution; Cell Signaling Technology Company, USA) antibodies at room temperature overnight. This was followed by incubation with horseradish peroxidase (HRP)-conjugated secondary antibodies (1:10,000 dilution; ZB-2301, Zhongshan Golden Bridge Biotechnology, Beijing, China). Immunoreactive bands were visualized using the enhanced chemiluminescence method according to the manufacturer's instructions (Applygen Technologies, Beijing, China).

Immunohistochemistry

Formalin-fixed, paraffin-embedded tissue sections from normal ovary tissue and serous tumors were cut into 4–6-μm sections and transferred to slides. Samples were deparaffinized in xylene and rehydrated via an ethanol gradient (100%, 95% ×2, 85%, 75% ×2, 50%, and distilled water). Slides were then washed, endogenous peroxidase activity was blocked by incubation in 3% H_2O_2, and samples were preincubated with 10% goat serum, and then with monoclonal mouse anti-PDCD5 antibody (1:1000) for 1 h at room temperature in a humid chamber. Secondary staining with HRP-conjugated anti-mouse IgG (Zhongshan Golden Bridge Biotechnology, Beijing, China) was performed using a DAB peroxidase substrate kit (Zhongshan Golden Bridge Biotechnology, Beijing, China). Nuclei were counterstained with hematoxylin. In negative controls, the primary antibody was replaced with an isotype control. All staining was evaluated using the Leica Q550CW software system (Germany) and Qwin image analysis software. We randomly selected five independent fields from each slide; the average density of positive cells these five fields was calculated as the PDCD5 expression level.

Annexin v-FITC/propidium iodide staining and flow cytometry

SKOV3 cells were centrifuged, resuspended in 1× binding buffer at a density of 4.0×10^5 cells/ml and transferred to a 12-well dish (1 ml suspension/well). Cells were incubated in triplicate with PBS (control), 20 μg/ml recombinant human PDCD5 (rhPDCD5; P20; Beijing University Human Disease Center, Beijing, China), 0.1 μg/ml taxol (T0.1), 0.5 μg/ml doxorubicin (A0.5), or P20 plus T0.1 or A0.5. After 24 h, cells were collected, centrifuged, and incubated with conjugated Annexin V (2.5 μl; Pharmingen) and 1 μl propidium iodide (Pharmingen) for 15 min at room temperature in the dark. Next, 400 μl ×1 Annexin binding buffer was added to each cell sample, and the cells were analyzed by flow cytometry (BD Influx, Becton Dickinson) using Cell Quest Research Software (Becton Dickinson).

Survival time and follow-up

The mean follow-up period for patients was 49.6 months (range: 6–133 months; median: 45.5 months). The survival time of ovarian cancer patients enrolled in this study was defined as the time from primary surgery to death or last follow-up. Of the 94 patients at Stages III and IV, 22 were lost to follow-up before the time of death could be recorded. Therefore, only 72 patients were included in the survival analysis.

Statistical analysis

We used χ^2 and Fisher's exact tests to determine correlations between PDCD5 levels and clinical parameters. The cumulative survival time was calculated by the Kaplan–Meier method and analyzed using the log–rank test. Cox proportional hazard regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (*CIs*) between groups in univariate and multivariate settings. A $P < 0.05$ was considered significant. All calculations were performed using SPSS 17.0 statistical software (SPSS Inc., USA).

Results

Human ovarian epithelial cells and cancer cell lines had different programmed cell death 5 mRNA and protein expression levels

Programmed cell death 5 mRNA and protein expression levels were analyzed in T29 cells and various ovarian cancer cell lines using real-time PCR and western blotting, respectively. PDCD5 mRNA levels were highest in normal ovarian epithelial cells (T29). Among the ovarian cancer cell lines examined, PDCD5 mRNA expression was highest in CAOV3 cells, moderately expressed in OV1 and 3AO cells, and lowest in HOC1A, SKOV3, and ES2 cells [Figure 1a]. The pattern of PDCD5 protein expression in these cell lines, as analyzed by western blotting [Figure 1b] and flow cytometry [Figure 1c], reflected their mRNA expression (i.e., T29 > CAOV3 > 3AO = OV1 > Hoc1A = SKOV3 = ES2).

PDCD5 mRNA and protein expression in human ovarian tissues

We next determined PDCD5 mRNA and protein expression levels in tumor tissues and compared them with levels in normal ovarian tissue. Benign ovarian tumor samples were used as controls. Reverse transcription-PCR showed that PDCD5 mRNA expression was less in epithelial malignancies ($n = 11$) than in normal tissue ($n = 5$) or benign ovarian tumors ($n = 8$). Immunohistochemical analysis showed PDCD5 protein expression in these tissues was consistent with their mRNA expression. Similarly, PDCD5 expression was lowest in epithelial cancer tissues ($n = 127$), higher in benign ovarian tumor tissue ($n = 48$), and highest in normal ovarian tissue ($n = 33$; Table 1 and Figure 2). Compared with normal ovaries, the expression of PDCD5 mRNA and protein in benign ovarian tumors and epithelial malignancies are significantly decreased [Table 1].

Effects of recombinant programmed cell death 5 on apoptosis in skov3 cells

We next analyzed the effect of recombinant PDCD5 on apoptosis. Treatment of SKOV3 cells with 20 μg/ml recombinant PDCD5 (P20) did not alter basal apoptosis compared with controls (3.6 ± 0.7% vs. 3.2 ± 1.5%, respectively). However, PDCD5 did enhance taxol- and doxorubicin-induced apoptosis. Treatment with 0.1 μg/ml taxol increased apoptosis (11.1 ± 0.8%) compared with buffer control and P20-treated controls. However, treatment with P20 + 0.1 μg/ml taxol resulted in even higher levels of apoptosis (21.9 ± 1.9%). Similarly, P20 treatment enhanced doxorubicin-induced apoptosis (16.0 ± 2.1%; Figure 3).

Study participants

Baseline demographic and disease characteristics of the 127 patients are shown in Table 2. Their median age was 52 years (range: 24–72 years). Their ovarian cancer types included serous (84; 66.14%), mucinous (13; 10.24%), endometrioid (14; 11.02%), clear cell (9; 7.08%), and other types (7; 5.51%). Of the 127 patients, 62 (48.82%) had cancer antigen-125 (CA-125) expression levels >500 IU/ml, while the remaining 65 (51.18%) had CA-125 levels <500 IU/ml.

Relationship between programmed cell death 5 expression and clinical parameters of epithelial ovarian cancer

To determine the clinical significance of reduced PDCD5 expression in carcinoma, we examined relationships between

Table 1: PDCD5 mRNA and protein expression in normal human ovaries and ovarian tumors

Tissues	*n*	Relative mRNA expression*†	*n*	Relative protein expression†‡
Normal	5	1.00 ± 0.00	33	0.36 ± 0.03
Benign	8	0.72 ± 0.19§	48	0.31 ± 0.03‖
Epithelial cancer	11	0.49 ± 0.21‖	127	0.28 ± 0.04‖

*Measured by RT-PCR, †Mean ± SD; ‡Measured by signal density after immunostaining; §$P<0.05$; ‖$P<0.001$. PDCD5: Programmed cell death 5; RT-PCR: Reverse transcription-polymerase chain reaction; SD: Standard deviation.

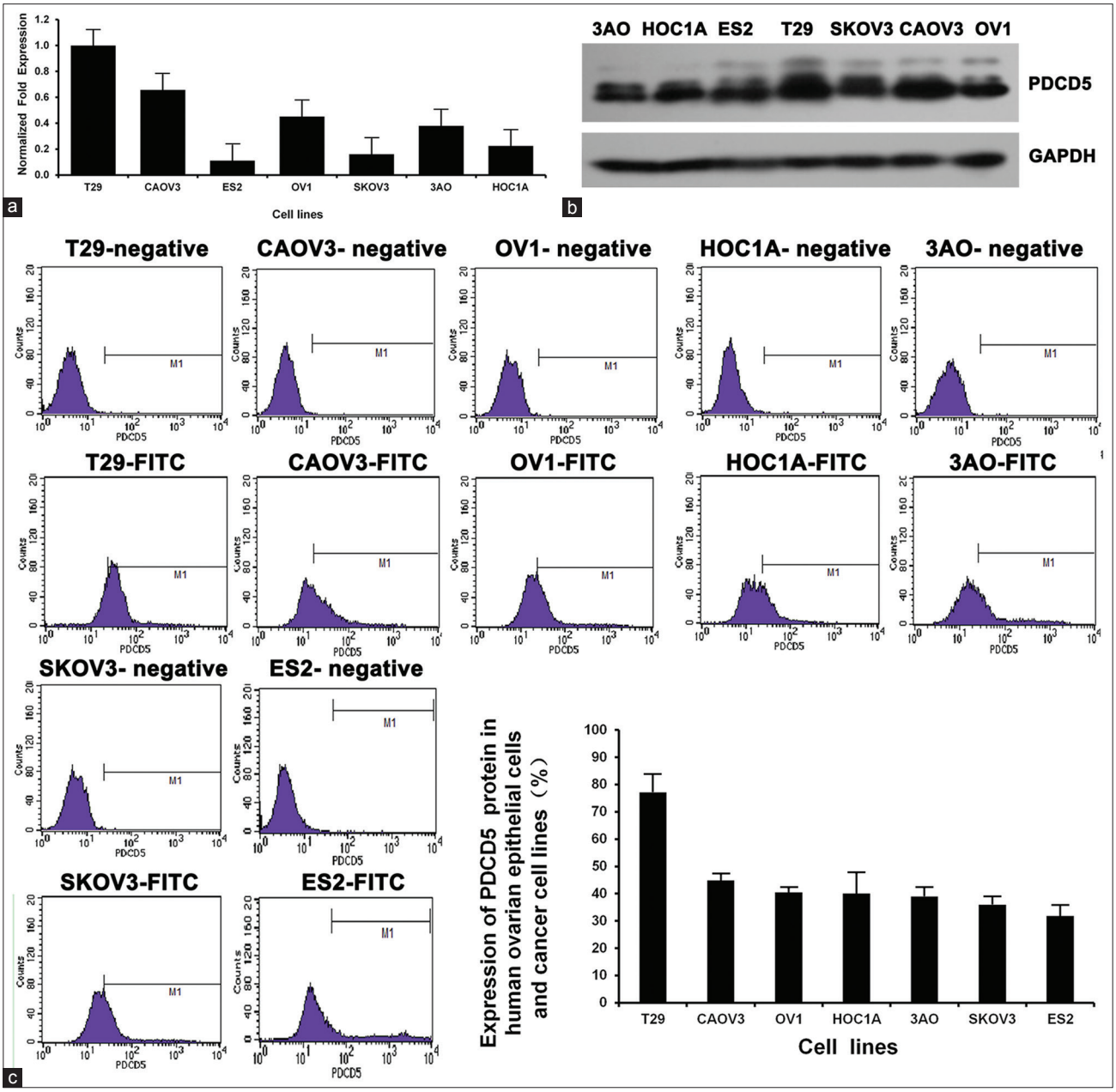

Figure 1: Expression of programmed cell death 5 (PDCD5) in human ovarian epithelial cell lines and cancer cell lines. (a) Real-time reverse transcription polymerase chain reaction shows PDCD5 mRNA expression in different cell lines, standardized to GAPDH mRNA; (b) Western blotting shows PDCD5 protein levels in different cell lines; (c) Flow cytometry shows analysis of cells labeled with anti-PDCD5 antibody; lower right: Relative PDCD5 protein data.

PDCD5 expression and various clinical parameters of epithelial ovarian cancer. PDCD5 expression significantly differed by FIGO stage, pathological grade, whether tumor cytoreduction surgery was satisfactory or unsatisfactory, metastasis, ascites, and CA-125 level ($P < 0.05$; Table 2). PDCD5 expression was significantly reduced in different ovarian cancer subtypes, and was lower in patients with FIGO Stage III–IV tumors (0.2745 ± 0.0342, $n = 94$) than in those with Stage I–II tumors (0.3092 ± 0.0257, $n = 33$). PDCD5 expression was inversely related to pathological grade and significantly lower in grade three tumors than in Grade 1 tumors ($P < 0.0001$).

Risk factor analysis and patient prognosis

We next examined the association between PDCD5 expression and patient survival. We collected survival data from 72 of the 94 Stage III–IV ovarian cancer patients at follow-up [Table 3], and divided the patients into low PDCD5 expression (<median value) and high PDCD5 expression (>median value) groups, according to their immunohistochemical analyses. Median overall survival was 19.5 months (95% *CI*: 13.63–25.37 months) for the low-PDCD5 group versus 63.5 months (95% *CI*: 61.15–65.85 months) for the high-PDCD5 group ($P < 0.001$). Multivariate Cox regression analysis

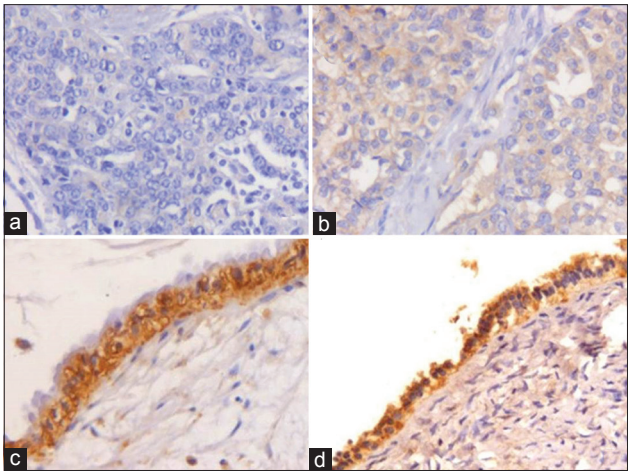

Figure 2: Programmed cell death 5 (PDCD5) protein expression in normal ovaries and ovarian tumors, as detected by immunohistochemistry. (a) and (b) Epithelial ovarian cancer tissues; (c) Benign ovarian neoplasm tissue; (d) Normal ovarian epithelial tissues. Red: PDCD5^{+} cells; magnification: ×200.

showed PDCD5 levels to significantly correlate with survival time (HR: 0.00, 95% *CI*: 0.00–0.00; $P < 0.001$; Table 3). High PDCD5 protein expression was associated with significantly longer survival than for low PDCD5 expression ($P < 0.001$; Figure 4a). Patients with lower PDCD5 levels had significantly shorter disease-specific survival than those with higher expression. Spearman's analysis strongly associated PDCD5 expression with patient survival time ($P < 0.0001$, $R = 0.7139$; Figure 4b).

Discussion

Programmed cell death 5 is a human gene identified via the cDNA-representative differences analysis technique described by Liu *et al*.[2] at Peking University Human Genomic Center. The 6-Kb PDCD5 gene, located on chromosome 19q12–q13.1, contains 6 exons and 5 introns. It encodes a 125-amino acid protein that localizes to both the nucleus and cytoplasm. PDCD5 is expressed in more than 50 human tissues; high expression levels have been

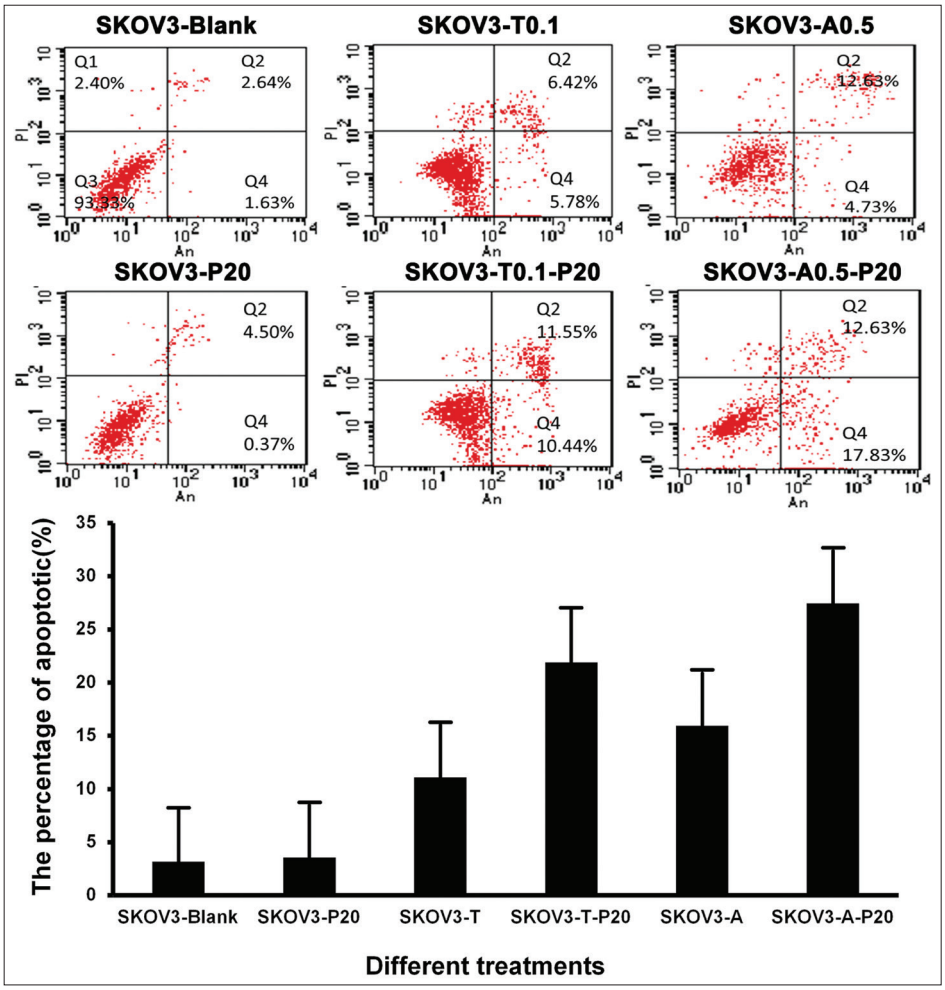

Figure 3: Effects of various treatments on apoptosis in SKOV3 cells. SKOV3 cells were treated with programmed cell death 5 (PDCD5), either alone or combined with taxol or doxorubicin. Apoptotic cells were measured by Annexin V-FITC/propidium iodide staining and flow cytometry. Representative flow cytometry results are shown for each treatment. Lower panel: Data from 3 independent experiments. P20: 20 μg/ml human recombinant PDCD5 protein; T01: 0.1 μg/ml taxol; A0.5: 0.5 μg/ml doxorubicin.

reported in the adult heart, testis, kidney, adrenal glands, and placenta. Expression is significantly lower in embryos. Functional analyses have shown that PDCD5 stimulates tumor cell apoptosis induced by various stimuli.[3-6] When cells undergo apoptosis, PDCD5 mRNA and protein expression are elevated, and PDCD5 protein translocates to the nucleus.[7]

Abnormal PDCD5 expression is associated with many diseases. Importantly, PDCD5 expression is significantly lower in tumor cells than in normal cells and correlates with tumor stage, malignancy, and prognosis.[4-9] Low PDCD5 expression correlates highly with poor prognosis for gastric cancer, clear cell kidney cancer, and chondrosarcoma.[4] These studies indicate that PDCD5 protects against tumorigenesis and tumor progression.

Reportedly, PDCD5 protein modulates both apoptotic and paraptotic cell death in humans and is proposed to positively regulateTip60 histone acetyltransferase and p53 transcription factor to promote apoptosis.[10-12] PDCD5 can also interact with other molecules such as nuclear factor-κB p65 to regulate apoptosis via small heterodimer partner protein[13] and another protein, cytosolic chaperonin containing tailless complex polypeptide one, partly by inhibiting β-tubulin folding.[14]

Recently, Xiao *et al*.[15] revealed that PDCD5 suppresses autoimmunity by modulating the forkhead box P3 (FOXP3)–regulatory T cell (Treg) axis. PDCD5 may thus serve as a guardian of immunological function, and the

Table 2: Relationship between PDCD5 protein expression and clinical prognostic factors in patients with epithelial ovarian cancer

Patient characteristic*†	*n*	PDCD5 expression†	*P*
Median age in years (range)		52 (20-78)	–
Pathology types			
Serous	84	0.2780 ± 0.0365	–
Mucinous	13	0.3110 ± 0.0256	–
Endometrioid	14	0.2937 ± 0.0259	–
Clear cell	9	0.2861 ± 0.0364	–
Others	7	0.2747 ± 0.0348	–
FIGO stage			
Stage I-II	33	0.3092 ± 0.0257	<0.0001
Stage III-IV	94	0.2745 ± 0.0342	
Grades			
1	16	0.3247 ± 0.0252	<0.0001
2	45	0.2870 ± 0.0304	
3	66	0.2711 ± 0.0332	
Tumor cytoreduction surgery			
Satisfactory	74	0.2910 ± 0.0355	0.0045
Unsatisfactory	53	0.2730 ± 0.0332	
Lymph node invasion			
Yes	58	0.2713 ± 0.0354	0.0003
No	69	0.2938 ± 0.0326	
Omentum invasion			
Yes	76	0.2731 ± 0.0351	<0.0001
No	51	0.2990 ± 0.0306	
Ascites			
Yes	92	0.2770 ± 0.0345	0.0007
No	35	0.3006 ± 0.0331	
CA-125 (U/ml)			
≤500	65	0.2942 ± 0.0347	0.0004
>500	62	0.2723 ± 0.0333	

*Total *n* = 127, †Mean ± SD. SD: Standard deviation;
PDCD5: Programmed cell death 5; FIGO: Federation of Gynecology and Obstetrics; CA-125: Cancer antigen-125.

Table 3: Multivariate Cox regression of factors that affect survival time of patients with ovarian cancer

Variables	Wald χ^2	HR	*P*	95% *CI* for Exp (B)
PDCD5	30.1692	0.0000	<0.001	0.00-0.00
Histology	0.1612	0.6880	1.0664	0.78-1.46
Stage	3.7919	0.0515	2.9112	0.99-8.54
Grade	0.0872	0.7678	0.9291	0.57-1.51
Age	0.4495	0.5026	1.0096	0.98-1.04
CA-125 levels	3.8002	0.0512	1.7799	1.00-3.18
Lymph nodes metastasis	1.0278	0.3107	1.3231	0.77-2.27
Omentum	2.7299	0.0985	1.9286	0.89-4.20
Ascites	1.4765	0.2243	0.6033	0.27-1.36
Cytoreductive surgery	0.4231	0.5154	0.9086	0.68-1.21

PDCD5: Programmed cell death 5; *CI*: Confidence interval; HR: Hazard ratio; CA-125: Cancer antigen-125.

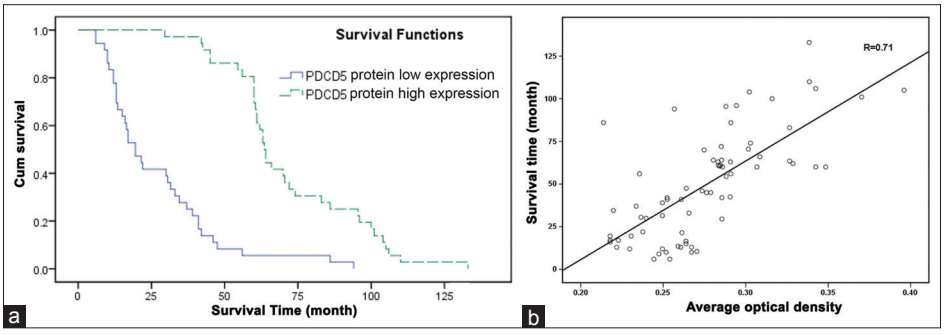

Figure 4: (a) Kaplan–Meier plots of survival times (for all-cause mortality) in patients with ovarian cancer by programmed cell death 5 (PDCD5) protein expression. Loss or reduction of PDCD5 expression is associated with poor prognosis in patients with epithelial ovarian cancer. Patients with low PDCD5 expression have significantly shorter disease-specific survival than do those with high PDCD5 expression; (b) Spearman's analysis of average optical density of PDCD5 protein expression and patients' survival time indicates that PDCD5 expression is highly associated with patient survival time ($P < 0.0001$, $R = 0.7139$).

PDCD5–FOXP3–Treg axis may be a therapeutic target for autoimmunity. These studies indicate the diverse biological activities of PDCD5.

Programmed cell death 5 can enhance apoptotic response to certain stimuli. Recombinant human PDCD5 protein (rhPDCD5) has potent antitumor effects against chronic myelogenous leukemia K562 cells and may be a novel and promising agent for treating chronic myelogenous leukemia.[16] It was also shown to sensitize chondrosarcoma cells to cisplatin-based chemotherapy, by inhibiting cell growth and apoptosis both *in vitro* and *in vivo*. As rhPDCD5 apparently induces cleavage of caspase-9, caspase-3, and poly(ADP-ribose) polymerase, its co-administration with cisplatin is a plausible treatment for chondrosarcoma.[17] In a human breast cancer xenograft model, intraperitoneal rhPDCD5 administration dramatically improved the antitumor effects of paclitaxel, which implies that it could be used therapeutically to enhance sensitivity to paclitaxel in breast cancer cells.[18] PDCD5 is downregulated in chondrosarcoma and might be an independent prognostic factor for overall survival in chondrosarcoma patients.[19]

In this study, we examined PDCD5 expression in normal ovarian tissue, benign tumors, and ovarian cancers, and the relationship between PDCD5 expression and clinical features and prognosis. We found PDCD5 was most highly expressed in normal ovarian tissue; less expressed in benign tumors and had the lowest expression in ovarian cancer tissue. PDCD5 expression was also inversely correlated with FIGO scores. Higher PDCD5 expression was associated with longer survival times for ovarian cancer patients, which accords with the results of Zhang *et al*.[9]

In conclusion, programmed cell death 5 expression is reduced in ovarian cancer and correlates negatively with survival time. Our data indicate that low PDCD5 expression decreases apoptosis in ovarian cancer, thus promoting a poor prognosis. These results imply that PDCD5 could both offer a means of monitoring patient prognosis and be developed on the basis of an anticancer therapy.

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