

# Low-dose radiation enhances susceptibility to cisplatin in resistant ovarian cancer cells via downregulation of ERCC1 and Bcl-2

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## Abstract

**Objective** Ovarian cancer is one of the leading causes of mortality in patients with malignant gynecological tumors. After surgical intervention for ovarian cancer, cisplatin (DDP)-based chemotherapy is the first-line treatment. However, a major challenge to treating ovarian cancer is the development of chemoresistance. Thus, the first aim of this study was to determine whether low-dose radiation could enhance the susceptibility of resistant ovarian cancer cells to DDP. The second aim was to provide new strategies for treating DDP-resistant ovarian cancer by examining its mechanism.

**Methods** A cell counting kit-8 (CCK8) assay was performed to measure cell proliferation. Flow cytometry was utilized to quantify the apoptosis of DDP-resistant ovarian cancer cells (SKOV3/DDP) using Annexin V and propidium iodide staining. Real-time quantitative (qPCR) was used to analyze the messenger RNA (mRNA) expression levels of excision repair cross complementing-group 1 (ERCC1) and B-cell lymphoma 2 (Bcl-2) in SKOV3/DDP.

**Results** The  $IC_{50}$  values of the control, conventional-dose, and low-dose groups were  $9.367 \pm 0.16$ ,  $9.289 \pm 0.16$ , and  $3.847 \pm 0.15$ , respectively ( $P < 0.05$  vs control group and conventional-dose group). Compared with the control and conventional-dose groups, low-dose radiation resulted in significantly more apoptosis, as detected by flow cytometry ( $P < 0.05$ ). The relative mRNA expression of ERCC1 and Bcl-2 in the low-dose group was significantly lower than that in the control group and conventional-dose group ( $P < 0.05$ ).

**Conclusion** Low-dose radiation enhanced the sensitivity of resistant ovarian cancer cells to DDP, possibly by decreasing the DNA repair capacity of tumor cells and promoting apoptosis.

**Key words** Low-dose radiation; ovarian cancer; resistance; SKOV3/DDP; excision repair cross complementing-group 1 (ERCC1); B-cell lymphoma 2 (Bcl-2)

Received: 16 September 2015  
Revised: 24 November 2015  
Accepted: 25 January 2016

Ovarian cancer is the seventh most common cancer in women worldwide and is one of the leading causes of mortality among gynecological malignancies [1–2]. The American Cancer Society estimates that in 2014, approximately 21,980 new cases of ovarian cancer were diagnosed and 14,270 women died of ovarian cancer in the US [3]. Treatment for ovarian cancer patients involves surgery, which typically includes a combination of hysterectomy, bilateral salpingo-oophorectomy, and omentum removal, followed by chemotherapy [4–5]. In ovarian cancer chemotherapeutics, cisplatin (DDP) has a central role as the first-line treatment option and is typically administered in combination with taxanes [6]. Although ovarian

cancer is a relatively chemosensitive disease, 20%–30% of patients show resistance to DDP-based chemotherapy [7–8]. Moreover, even after efficient clearance of the tumor cells in response to standard therapy, many patients (70–90%) suffer from relapse within months to years and the relapsed tumors typically acquire resistance to DDP [7–9]. Currently, DDP resistance can be classified into two categories. The first is increased tolerance toward DNA–platinum adducts, while the other is enhanced DNA repair capacity of tumor cells [10–11]. Thus, it is important to identify novel targets and develop new therapeutic strategies.

The United Nations Scientific Committee on the Effects of Atomic Radiation states that low-dose radiation

refers to the low linear energy transfer radiation within the dose of 0.2 Gy, or the high linear energy transfer irradiation that the agent is within 0.5 Gy and the dose rate is within 0.05 Gy/min<sup>[12]</sup>. In recent years, a number of studies showed that low-dose radiation reduced the expression of the protein products of antiapoptotic genes in immune organs and increased the expression of the protein products of pro-apoptotic gene, as well as promoted the maturation, differentiation, and signal transmission of immune cells, eventually reducing the apoptosis of immune cells<sup>[13]</sup>.

Various cellular and molecular mechanisms are activated following high doses of radiation. The effects of low-dose radiation include cell apoptosis, cell cycle regulation, and the repair of double-stranded DNA breaks. The B-cell lymphoma 2 (Bcl-2) family plays a key role in apoptosis. Under low-dose radiation, the Bcl-2 gene is the most widely studied among apoptosis-related genes, and the messenger RNA (mRNA) and protein expressions of Bcl-2 gene have been shown to be reduced by low-dose radiation. Head and neck squamous carcinoma cell lines SCC-61 and SQ-20B were exposed to 0.5 Gy radiation every time, for a total dose of 2 Gy. Next, the Bcl-2 protein was detected by western blotting, which revealed reduced expression compared to before radiation<sup>[14]</sup>. Additionally, numerous studies suggested that the nucleotide excision repair (NER) pathway is an essential mechanism for the repair of DNA-platinum adducts<sup>[15]</sup>. The excision repair cross complementing-group 1 (ERCC1) gene plays an important role in the NER pathway because of its damage recognition and excision abilities<sup>[16–17]</sup>. However, whether low-dose radiation can increase the sensitivity of SKOV3/DDP to DDP remains unclear. Thus, we examined whether low-dose radiation could enhance the susceptibility of SKOV3/DDP to DDP and investigated its mechanism by detecting the levels of the ERCC1 and Bcl-2 genes.

## Materials and methods

### Materials and reagents

Fetal bovine serum was purchased from Gibco BRL (USA). RPMI 1640 medium was purchased from HyClone (USA). The cell counting kit (CCK8, Beyotime Inst. Biotech, China) was stored at -20 °C. The Annexin V-FITC Apoptosis Detection Kit was purchased from Jiamay Biotech (China). The EASYspin cell RNA rapid extraction kit was purchased from Aidlab Biotechnologies (China). The FastQuant RT Kit (with gDNase) and SuperReal PreMix Plus (SYBR Green) was purchased from Tiangen Biotech (China). Bcl-2, ERCC1, and GAPDH were purchased from Sangon Biotech (China).

### Cell lines and culture

Human ovarian cancer SKOV3/DDP cell lines were purchased from the Cell Bank of the Chinese Academy of Sciences (China). SKOV3/DDP cells were resistant to DDP and were additionally cultured with 0.5 g/L DDP to maintain drug resistance. The cells were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum and 100 U/mL streptomycin/penicillin, incubated in a 5% CO<sub>2</sub> incubator at 37 °C. Cells were passaged every 2–3 days when the cells were at approximately 80–90% confluence.

#### *Radiation conditions*

A Varian 23EX Electron linear accelerator and 6MV X-ray were used. The distance from the radiation source to the cell surface was 100 cm. The cell culture bottles contained medium at a depth of 1.5 cm. The area of the radiation field was 10 × 15 cm. The dosage rate was 300 cGy/min. The cells were divided into a low-dose group, conventional-dose group, and control group. The low-dose group was given 0.5 Gy radiation every 8 h for a total of 4 times. The total dose was 2 Gy. The conventional-dose group was given 2 Gy radiation once. The control group was given no radiation.

#### *CCK8 assay*

SKOV3/DDP cells were seeded into 96-well plates (5 × 10<sup>3</sup> cells each well) and cultured for 24 h. Next, the culture medium was replaced with new medium containing various concentrations of DDP (0, 1.25, 2.5, 5, 10 and 20 µg/mL). A blank group included no drugs and cells. Each treatment was repeated in five wells. After incubation for 48 h, 20 L CCK-8 was added to each well and cultured at 37°C and 5% CO<sub>2</sub> for approximately 3 h. A microplate reader was used to calculate the optical density (OD) at 480 nm. The survival rate of cells (%) = (experimental group OD value – blank group OD value)/(control group OD value – blank group OD value), while the inhibition rate of cell proliferation (%) equaled 100% minus the survival rate. The half-maximal inhibitory concentration (IC<sub>50</sub>) was calculated using the weighted linear regression method with SPSS 19.0 software (USA). Each experiment was repeated three times.

#### *Flow cytometry analysis of apoptosis*

SKOV3/DDP cells were cultured in 6-well plates (1 × 10<sup>6</sup> cells each well), incubated overnight, and then exposed to different concentrations of DDP (0, 1.25, 2.5, 5, 10, and 20 µg/mL) for 48 h. Each treatment was repeated in three wells. Cells were harvested by trypsin and washed with PBS. The cells were resuspended in binding buffer and then stained sequentially with Annexin V-FITC and propidium iodide (PI) according to the manufacturer's instructions. Apoptotic cells were analyzed using a flow cytometry (BD FACSCalibur, BD Biosciences, USA). Twenty thousand events were measured and results were expressed as the percentage of early apoptotic cells (high

**Table 1** Real-time fluorescent qPCR for detecting mRNA expression of ERCC1 mRNA (mean  $\pm$  SD)

Groups	$\Delta Ct$	$2^{-\Delta\Delta Ct}$
Control group	$9.00 \pm 0.62$	1.00
Conventional-dose group	$9.20 \pm 0.34$	$0.97 \pm 0.49$
Low-dose group	$10.26 \pm 0.70$	$0.42 \pm 0.07^*$

FITC and low PI signal) and the very late apoptotic cells which had lost membrane integrity (high FITC and high PI signal).

### qPCR detection of Bcl-2 and ERCC1 mRNA

Total RNA was extracted from SKOV3/DDP cells following the manufacturer's protocol for the EASYspin cell RNA rapid extraction kit. For mRNA quantitative analysis, total RNA was reverse-transcribed using the FastQuant RT Kit according to the manufacturer's instructions. The resulting complementary DNAs were used for quantitative real-time reverse-transcriptase PCR using a SYBR Green Kit according to the manufacturer's protocol. The negative control contained all PCR components without template DNA to ensure that the reagent mix was free of contamination. Real-time PCR and data collection were performed on a Real-Time PCR Instrument (FTC-3000, Funglyn Biotech, China). These experiments were performed in triplicate. The primers used were as follows. Bcl-2, 5'-TTCTTTGAGTTCGGTGGGGTC-3' (forward) and 5'-TGCATATTTGTTTGGGGCAGG-3' (reverse), with an anticipated size of 304 bp. ERCC1, 5'-TCGATCCCTCTGCAGTCTTT-3' (forward) and 5'-ATTGC-GCAGAACTTCAGTA-3' (reverse), with an anticipated size of 447 bp. GAPDH served as an internal reference, and the primers used were as follows: 5'-CTACAAT-GAGCTGCGTGTGGC-3' (forward) and 5'-CAGGTC-CAGACGCAGGATGGC-3' (reverse), with an anticipated size of 271 bp. The conditions for PCR were as follows: pre-denaturation at 95 °C for 15 min; 40 cycles of denaturation at 95 °C for 10 s, annealing at 60 °C for 20 s, and extension at 72 °C for 30 s. The increase in fluorescence intensity was measured and used to delineate the amplification curve, according to which the Ct value (Ct value reflects the fluorescence intensity) and  $\Delta Ct$  (Ct sample-Ct GAPDH) were determined, followed by analysis of the relative expression levels using the  $2^{-\Delta\Delta Ct}$  method. In this study, a gene Ct value of  $\leq 32$  was considered to indicate positive expression.

### Statistical analysis

All statistical analyses were performed using SPSS19.0 software. The data were expressed as the mean values  $\pm$  SD for three independent experiments. Student's *t*-test and analysis of variance were used to test for statistically significant differences between two groups or among

more groups, respectively.  $P < 0.05$  was defined as statistically significant.

## Results

### Low-dose radiation enhanced the sensitivity of SKOV3/DDP to DDP

The SKOV3/DDP cells in the low-dose group, conventional-dose group, and control group were exposed to various doses of DDP for 48 h. Cell viability was measured using the CCK-8 assay. The inhibition rates of SKOV3/DDP were plotted on curves (Fig. 1a). The  $IC_{50}$  values of different groups were shown in Fig. 1b. The  $IC_{50}$  value of DDP was significantly reduced in the low-dose group, compared to the cells in other groups ( $P < 0.05$ ). While there was no statistical significance between the  $IC_{50}$  values of the control group and conventional-dose group, there was a clear increase in drug sensitivity in SKOV3/DDP cells in the low-dose group. Low-dose radiation increased the sensitivity of SKOV3/DDP to DDP.

### Low-dose radiation enhanced DDP-induced apoptosis in SKOV3/DDP

Flow cytometry analysis was used to quantify the apoptotic SKOV3/DDP cells that were double-stained with Annexin V-FITC and PI after treatment with different concentrations of DDP (0, 1.25, 2.5, 5, 10, and 20 g/mL) for 48 h. As shown in Fig 2a, compared with the control group and conventional-dose group, the low-dose radiation group showed significantly higher apoptosis. Furthermore, Annexin V-FITC/PI staining revealed that the apoptotic ratio of the low-dose group was higher than in the other groups at each concentration of DDP (Fig. 2b). The apoptosis rates of the control group and conventional-dose group were not statistically significant ( $P > 0.05$ ). The results also suggested that apoptosis increased in a dose-dependent manner with increasing concentrations of DDP.

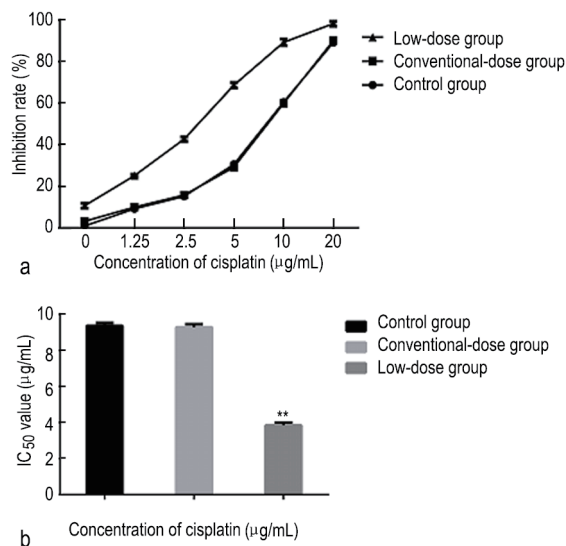
### mRNA expression of ERCC1 and Bcl-2 in SKOV3/DDP of each group

After qPCR and delineation of the kinetic curves following PCR amplification, the relative mRNA expression levels of ERCC1 and Bcl-2 were calculated. As shown in Table 1, Table 2, and Fig. 3, the mRNA expression of ERCC1 and Bcl-2 in the low-dose group was significantly lower than that in the control group and conventional-dose group ( $P < 0.05$ ). However, ERCC1 and Bcl-2 expression in the conventional-dose group did not significantly decrease compared with the control group.

**Table 2** Real-time fluorescent qPCR for detecting mRNA expression of Bcl-2 mRNA (mean  $\pm$  SD)

Groups	$\Delta$ Ct	$2^{-\Delta\Delta$ Ct
Control group	8.72 $\pm$ 0.22	1.00
Conventional-dose group	8.88 $\pm$ 0.08	0.91 $\pm$ 0.19
Low-dose group	10.36 $\pm$ 0.73	0.34 $\pm$ 0.13*

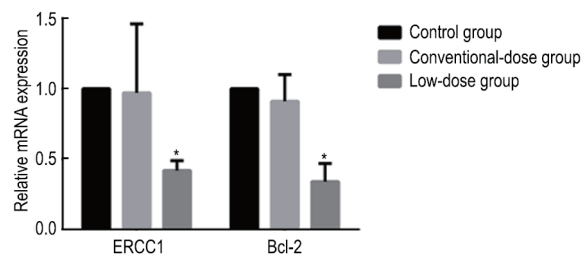
$\Delta$ Ct = Ct gene - Ct GAPDH,  $\Delta\Delta$ Ct =  $\Delta$ Ct treat -  $\Delta$ Ct control. ERCC1 and Bcl-2 expression in the low-dose group were significantly decreased, \*  $P < 0.05$  vs control group and conventional-dose group



**Fig. 1** Low-dose radiation enhanced the sensitivity of SKOV3/DDP to DDP. Cells were incubated with various concentrations of DDP for 48 h, and cell viability was measured by the CCK8 assay. (a) The inhibition rate of each group showed that SKOV3/DDP cells in the low-dose group were more sensitive to DDP than were the other cells; (b) The IC<sub>50</sub> values of the control group, conventional-dose group, and low-dose group were 9.367  $\pm$  0.16, 9.289  $\pm$  0.16, and 3.847  $\pm$  0.15, respectively. Low dose radiation clearly increased the sensitivity of SKOV3/DDP to DDP. Data were shown as the mean  $\pm$  SD. \*\*  $P < 0.05$  vs control group and conventional-dose group

## Discussion

Ovarian cancer is one of the leading gynecologic malignancies [18]. The mainline treatment for ovarian cancer is cytoreductive surgery followed by DDP-based chemotherapy, which is the first-line chemotherapeutic agent for ovarian cancer [19, 20]. DDP exerts its cytotoxic effect predominantly by causing intra-strand cross-linking of DNA, which blocks transcription and DNA replication, leading to cell apoptosis [21]. However, the major challenge in treating ovarian cancer is the development of chemoresistance. Although the mechanism of DDP resistance *in vivo* has not been clearly defined, studies of tumor tissues and cell lines showed that increasing NER of DDP-caused DNA damage and impaired DDP-induced apoptosis play crucial roles in the development of the DDP-resistance

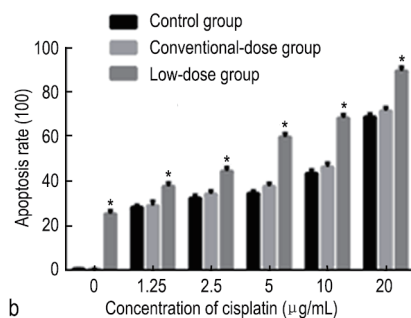
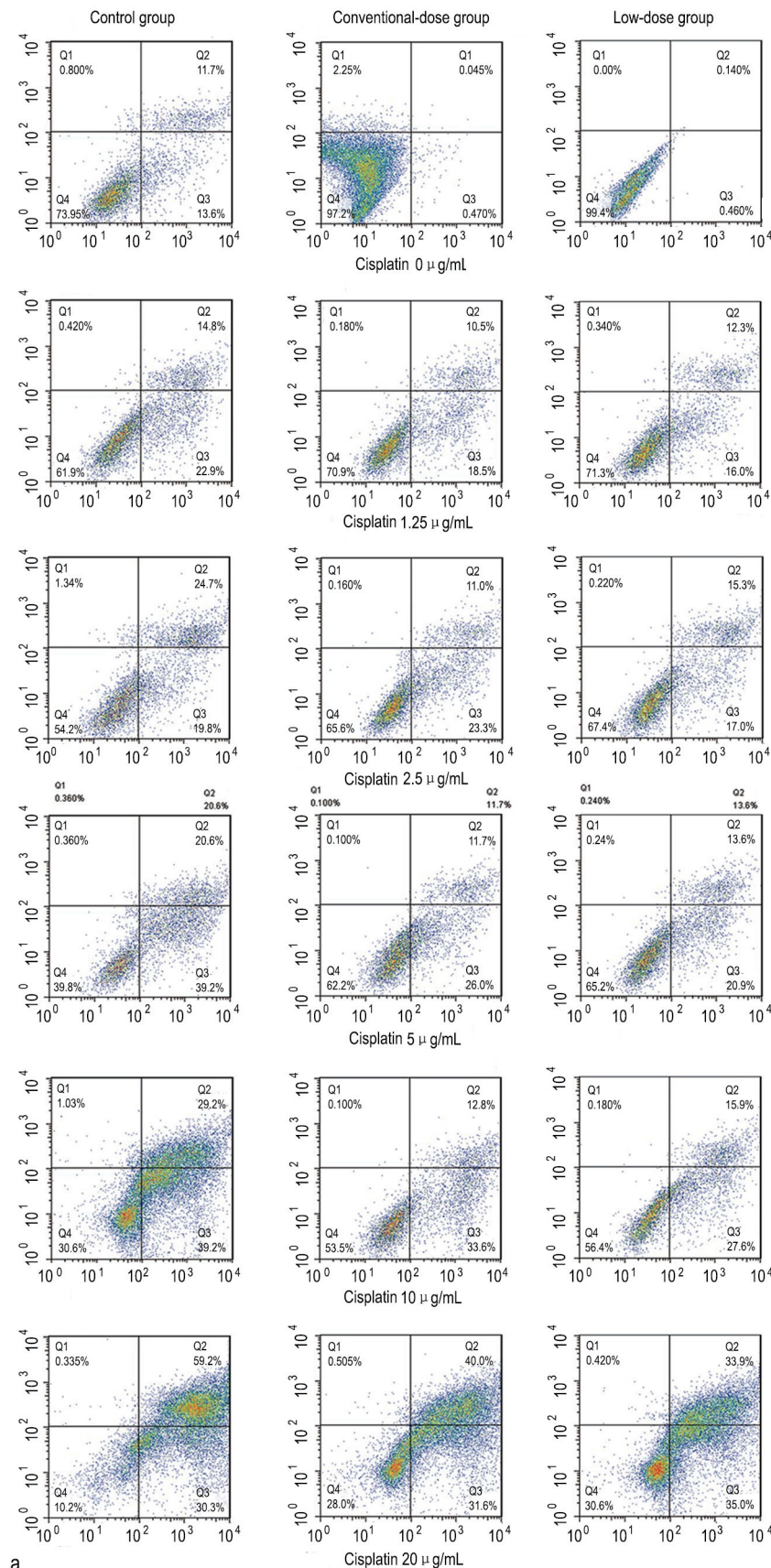


**Fig. 3** Relative mRNA expression of ERCC1 and Bcl-2 in each group. Asterisks denote values that were significantly different from the control group and conventional-dose group (ANOVA, \* $P < 0.05$ )

[22]. However, as described above, many studies suggested that low-dose radiation decreased the expression of anti-apoptotic genes and reduced the repair capacity of DNA. Thus, according to the mechanisms of DDP resistance and low-dose radiation, low-dose radiation may enhance the sensitivity of SKOV3/DDP to DDP. A CCK8 assay was performed to measure cell proliferation, and flow cytometry was utilized to quantify the apoptosis of DDP-resistant ovarian cancer cells (SKOV3/DDP). As expected, the data showed that cells in the low-dose radiation group had higher inhibition and apoptosis rates. Thus, low-dose radiation enhanced the sensitivity of SKOV3/DDP to DDP.

Increasing evidence indicates that NER is responsible for the repair of platinum-caused DNA damage. Repair-defective cells are hypersensitive to DDP. Furthermore, increased repair of DDP-caused interstrand cross-links and intrastrand adducts are associated with resistance in human ovarian cancer cells. ERCC1 is a key DNA repair gene in the NER pathway and a useful biomarker for NER activity in human cells. The overexpression of ERCC1 has been associated with the repair of DDP-induced DNA damage and clinical resistance to DDP [23–27]. Additionally the Bcl-2 family plays a key role in apoptosis and includes proapoptotic and antiapoptotic members; Bcl-2 belongs to the latter group. Overexpression of Bcl-2 can delay cell death. Bcl-2 exerts these anti-apoptotic effects by stabilizing the mitochondrial membrane potential and preventing the release of apoptosis-inducing molecules. DDP has been shown to induce the expression of Bcl-2 to impede apoptosis [28–30]. Thus, to further study how low-dose radiation enhances the sensitivity of SKOV3/DDP to DDP, the ERCC1 and Bcl-2 genes were selected as representative genes based on the mechanism of DDP resistance. By detection of the mRNA expression of ERCC1 and Bcl-2 showed that ERCC1 and Bcl-2 expression in the low-dose group were significantly decreased. This means that low-dose radiation reduced the NER of DDP-induced DNA damage and decreased the expression of anti-apoptotic genes. There is a clear link between this finding and the mechanisms of how low-dose radiation enhances the sensitivity of SKOV3/DDP. Low-dose radiation increased





**Fig. 2** Low-dose radiation enhanced the apoptosis rate of SKOV3/DDP. (a) Apoptotic cells were analyzed by flow cytometry with Annexin V-FITC and PI dual staining; (b) Flow cytometry was performed to measure the total percentage of early and late apoptotic cells. Each value was expressed as the mean  $\pm$  SD. \*  $P < 0.05$  vs the control group and conventional-dose group

susceptibility of ovarian cancer cells to DDP and may exert this effect by decreasing DNA damage repair and promoting apoptosis. Importantly, we showed for the first time that low-dose radiation could be applied to DDP-resistant ovarian cancer cells, offering a new theoretical basis for the clinical treatment of DDP-resistant ovarian cancer.

## Conflicts of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-015-0119-3

Cite this article as: Liu XR, Liang DH, Jiang T, *et al.* Low-dose radiation enhances susceptibility to cisplatin in resistant ovarian cancer cells via downregulation of ERCC1 and Bcl-2. *Oncol Transl Med*, 2016, 2: 84–89.