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ORIGINAL ARTICLE

Low-dose radiation reverses cisplatin resistance in ovarian cancer cells by changing Survivin and Caspase-3 expression

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Abstract

Objective Cisplatin (DDP) is the main chemotherapy drug for ovarian cancer. However, ovarian cancer cells tend to develop cisplatin resistance in the clinical setting. Tumor cells are sensitive to low-dose radiation (LDR). LDR therapy can improve the effects of chemotherapy drugs on ovarian cancer, but the underlying mechanisms are not clear. In this study, we explored the impact of low-dose radiation on Survivin and Caspase-3 levels in SKOV3/DDP ovarian cancer cells that are resistant to cisplatin.

Methods Cell viability was examined by cell counting kit-8 (CCK-8) assay, and quantitative PCR was used to detect Caspase-3 and Survivin transcript levels. Flow cytometry was used to detect and quantify apoptotic cells.

Results Cell viability was lower when cells were treated with LDR and cisplatin than when cells were treated with conventional radiation and cisplatin, or cisplatin alone ($P < 0.05$). The IC_{50} of cisplatin in the LDR, no-radiation control, and conventional-dose groups was 3.837 ± 0.16, 9.467 ± 0.17, and 9.389 ± 0.17, respectively. The level of Caspase-3 mRNA was higher and the level of Survivin mRNA was lower in the LDR group compared to that in the other two groups ($P < 0.05$).

Conclusion LDR reverses cisplatin resistance in SKOV3/DDP cells, and may do so by suppressing Survivin expression and increasing Caspase-3 expression.

Key words: SKOV3/DDP; LDR; Caspase-3; Survivin

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Ovarian cancer is the most lethal cancer of the gynecologic malignancies [1]. In 2012, it was estimated that 238,719 cases were diagnosed, and 151,905 women died from this disease worldwide [2]. In Poland, ovarian cancer is the second most frequent invasive malignancy of the female genital tract after cancer of the uterine corpus, with an estimated 3,600 cases diagnosed annually [3]. Ovarian cancer is one of the most frequent gynecological malignancies worldwide, and the fifth leading cause of cancer mortality among women. Due to the asymptomatic nature of the early stages of the disease, ovarian cancer is usually diagnosed at an advanced stage [4]. Current chemotherapies for ovarian cancer patients are only transiently effective, because patients with advanced disease eventually develop resistance despite significant initial responses. The current standard therapy for ovarian cancer is surgical resection and adjuvant chemotherapy [5]. However, the therapeutic efficacy is hindered by tumor recurrence and chemoresistance [6]. Disease that relapses six months after the completion of platinum therapy is considered platinum-resistant. Effective treatments are limited in this setting, although novel targeted therapies are rapidly emerging. Therefore, it is important to find effective methods to reverse ovarian cancer cisplatin (DDP) resistance.

Low-dose radiation (LDR) is characterized by a low linear energy transfer (LET) radiation dose of less than 0.2 Gy, or a high LET radiation dose of less than 0.05 Gy but at a dose rate higher than 0.05 mGy/min. LDR can induce a general adaptation reaction, indicating that LDR can induce DNA damage, chromosomal damage, gene mutation, cell death, immune function restraint, and tumorigenesis [7–8]. LDR can enhance the antitumor effects of conventional radiation, and this combination can in-

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crease apoptosis in tumor tissues by decreasing the expression of P53 and Bcl-2 [9]. Overall, LDR has clinical significance as a supporting radiotherapy [9]. We wanted to investigate whether LDR might reverse DDP resistance in ovarian cancer. To test this possibility, we used SKOV3/DDP ovarian cancer cells and studied how LDR affected their response to cisplatin treatment. Further, to provide new theoretical support for the clinical application of LDR, we investigated the molecular mechanisms of these effects by testing the impact of LDR on Survivin and Caspase-3 expression.

Recently, a correlation between chemoresistance and Survivin expression has been reported. Survivin is a small anti-apoptotic protein normally expressed only in embryonic and fetal tissues. However, high Survivin levels have been detected in many cancer tissues, especially in advanced stages. The over-expression of Survivin has been associated with poor prognosis and tumor aggressiveness. In advanced ovarian carcinomas, it has been found that the expression of Survivin directly correlates with resistance to taxane chemotherapy. Treatments that suppress Survivin expression can induce apoptosis, inhibit cancer growth, and enhance the sensitivity of cancer cells to chemotherapy and radiotherapy. In the future, new strategies based on the inhibition of Survivin in tumor tissues should represent a powerful tool to enhance chemo-sensitivity in patients with drug-resistant ovarian cancer [10].

Tumor growth and metastasis are known to be angiogenesis-related processes. Caspases have been shown to be activated during apoptosis in many cells, and they play critical roles in both the initiation and execution of apoptosis [11]. Among the caspase family, Caspase-3 is a well-established apoptosis mediator. Caspase-3 is highly expressed in normal ovarian cells. In this study, we tested the effect of LDR on the expression of Caspase-3 in SKOV3/DDP cells, in the hope that LDR might represent a new method for overcoming cisplatin resistance in the treatment of ovarian cancer.

Materials and methods

Materials

SuperReal PreMix and FastQuant RT Kit (with gDNase) were purchased from Tiangen Biotech Co. Ltd. (Beijing, China). Fetal bovine serum (FBS) was purchased from Gibco BRL (Grand Island, NY, USA). The CCK-8 cell counting kit was acquired from Beyotime Inst. Biotech (Haimen, China) and maintained at –20°C. Annexin V-FITC Apoptosis Detection Kit was acquired from Jiamay Biotech Co. Ltd. (Beijing, China). RPMI 1640 medium was purchased from HyClone China Ltd. (Shanghai, China). EASYspin cell RNA rapid extraction kit was purchased from Aidlab Biotechnologies Co. Ltd. (Beijing, China). Survivin, Caspase-3, and GAPDH were purchased from Sangon Biotech Co., Ltd. (Beijing, China).

Cell culture

The human epithelial ovarian cancer cell line SKOV3/DDP was purchased from the Cell Bank of the Chinese Academy of Sciences (Beijing, China). Cells were cultured in RPMI 1640 medium supplemented with 10% heat-inactivated FBS and antibiotics (100 units/mL of penicillin and 100 μg/mL streptomycin) in a humidified atmosphere of 95% air and 5% carbon dioxide at 37 ℃. The cells were treated with 0.5 μg/L cisplatin to maintain drug resistance.

CCK8 (cell viability) assay

The growth inhibitory effect of drugs was assessed by CCK8 assay. Cells were seeded in each well of a 96-well microtiter plates (104 cells per well). After 24 h, the culture media was replaced with new media containing various concentrations of cisplatin (0, 0.625, 1.25, 2.5, 5, or 10 μg/mL). After a 48-h incubation, 20 μL of CCK-8 solution was added to each well and the plate was subsequently incubated for 3 h at 37 ℃, after which the optical density (OD) at 480 nm was recorded. The control group was treated as described. The conventional irradiation group was treated with 2 Gy of radiation, and various concentrations of cisplatin (0, 0.625, 1.25, 2.5, 5, or 10 μg/L), and incubated for 24 h after radiation. After that, the growth inhibitory effect of conventional radiation was measured compared to that of the control group. The LDR group was exposed to 0.5 Gy of radiation for 0, 8, 16, or 24 h, with a total dose of 2 Gy. The cisplatin concentrations were the same across all groups, and cell viability was assayed as described. The survival rate of cells was calculated as a percentage by subtracting the blank OD value from the experimental group OD value, and dividing this by the control group OD value with the blank OD value subtracted. The percent inhibition of cell proliferation was calculated as 100 minus the survival rate. The half-maximal inhibitory concentration (IC_{50}) was calculated using the weighted linear regression method with SPSS 19.0 software. Each experiment was repeated three times.

Analysis of apoptosis

Cell apoptosis was detected using a commercially available apoptosis assay kit. Cells were seeded in each well of a six-well microtiter plate, and cultured in RPMI 1640 medium for 24 h. Each treatment was repeated in three wells. The culture media was replaced with new media containing various concentrations of cisplatin (0, 0.625, 1.25, 2.5, 5 or 10 μg/L) and cells were further incubated for 24 h. Cells were harvested and washed with cold phosphate buffered saline (PBS) twice, and 300 μL of 1× Binding Buffer was added to resuspend the cells. The harvested cells were incubated with 5 μL of fluorescein

isothiocyanate (FITC)-conjugated Annexin V for 15 min at room temperature in the dark. PI was added (5 μL) to the harvested fresh cells for five min before detection. The 1× Binding Buffer (200 μL) was added to each sample tube, and the samples were analyzed on a FACSCalibur flow cytometer using Cell Quest Research Software (BD Biosciences, San Jose, CA, USA). The experiment was repeated three times. The conventional irradiation group was treated with 2 Gy of radiation and the LDR group was treated with 0.05 Gy of radiation four times before the assay, and then cultured as described.

Evaluation of Survivin and Caspase-3 mRNA expression by qPCR

The cells of control group, conventional dose group, and LDR group were cultured and treated as described previously. Total RNA was isolated from the cells using the RNeasy kit according to the manufacturer's instructions. For reverse transcription, 2 μL of 5× gDNA Buffer, 4 μL of total RNA, and 4 μL of RNAse-free water were incubated for three min and placed on ice. Next, 2 μL of 10× Fast RT Buffer, 1 μL RT Enzyme Mix, 2 μL FQ-RT Primer Mix, and 5 μL RNAse-free water were added. The reaction mixture was incubated at 42 ℃ for 15 min, then 95 ℃ for 3 min. After that, the cDNA was placed on ice. The Survivin primers were 5'-AGGACCACCGCATCTCTACA-3' (forward), and 5'-TTTCCTTTGCATGGGGTCGT-3' (reverse). The Caspase-3 primers were 5'-CTCTGGTTTTC GGTGGGTGT-3' (forward) and 5'-CGCTTCCATGTAT GATCTTTGGTT-3' (reverse). The GAPDH internal control primers were 5'-TCAGATCATTGCTCCTCCTG-3' (forward) and 5'-CTGCTTGCTGATCCACATCTG-3' (reverse). All custom primers were designed using the Invitrogen OligoPerfect™ Designer to have 50%–60% GC-content, annealing temperatures near 60 °C , and lengths of nearly 20 base pairs. The PCR reaction was as follows: Initial denaturation at 95 ℃ for 15 min, followed by cycles of denaturation at 95 °C for 10 s, and annealing extension at 60 ℃ for 32 s. A total of 41 cycles were performed per reaction. The change in mRNA levels was determined by the formula 2–(ΔΔCT), where ΔCT is the value from the threshold cycle (CT) of the treated sample subtracted from the CT value of untreated or zero time-point control sample. The relative expression levels are expressed as a percentage of the indicated control.

Exposure conditions

The media depth of the cell culture dishes was 1.5 cm. The area of radiation field was 10 × 15 cm. The Varian 23EX Electron linear accelerator and 6 MV X-ray was used and the dosage rate was 300 cGy/min. The distance from the radiation source to the surface of the cell was 100 cm. Cells were divided into a low-dose group, conventional-dose group, and a control no-dose group. The low-dose group was treated with 0.5 Gy of radiation for 0, 8, 16, or 24 h, to a total dose of 2 Gy. The conventional-dose group was exposed to 2 Gy of radiation at one time. The control group was given no radiation. All the cells were treated with various concentrations of DDP as described above.

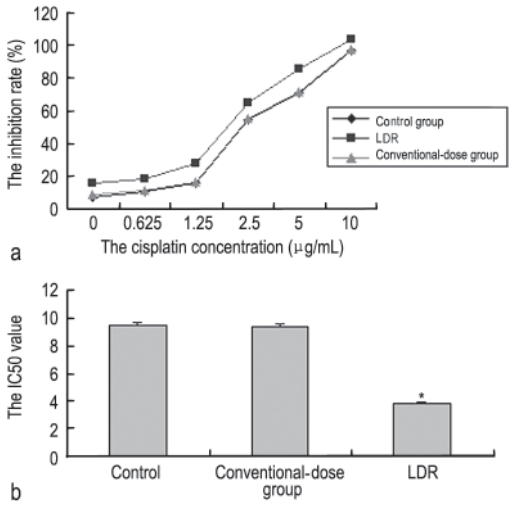

Fig. 1 (a) The inhibition rate of each groups. The inhibition rate of LDR group was higher than any other two groups; (b) The IC_{50} of each groups. The cell viability was determined using the CCK8 assay. The results are presented as the mean ± SD, mean of 6 replicates. Each cell viability experiment was repeated 3 times. The asterisk indicates a significant difference compared to the control group (ANOVA, * $P < 0.05$)

Statistical analysis

Statistical analyses were carried out using SPSS 17.0 software. Comparisons between treatments were made using a paired Student's *t*-test, or one-way ANOVA for multiple group comparisons. A $P < 0.05$ was considered statistically significant.

Results

Effect of low-dose radiation on the proliferation of cisplatin-treated SKOV3/DDP cells

SKOV3/DDP cell viabilities were determined using CCK8 assay at 480 nm. Fig. 1a shows the control group, conventional-dose group, and LDR group cell proliferation rates following treatment with various concentrations of cisplatin. After four rounds of irradiation with low-dose radiation of 0.5 Gy per dose, the growth inhibition rates of the LDR group cells were increased significantly compared to that of the other two groups. As shown in Fig. 1b, the IC_{50} of cisplatin in the LDR treatment group was lower than that of cisplatin in the other two treatment groups ($P < 0.05$). There was no obviously

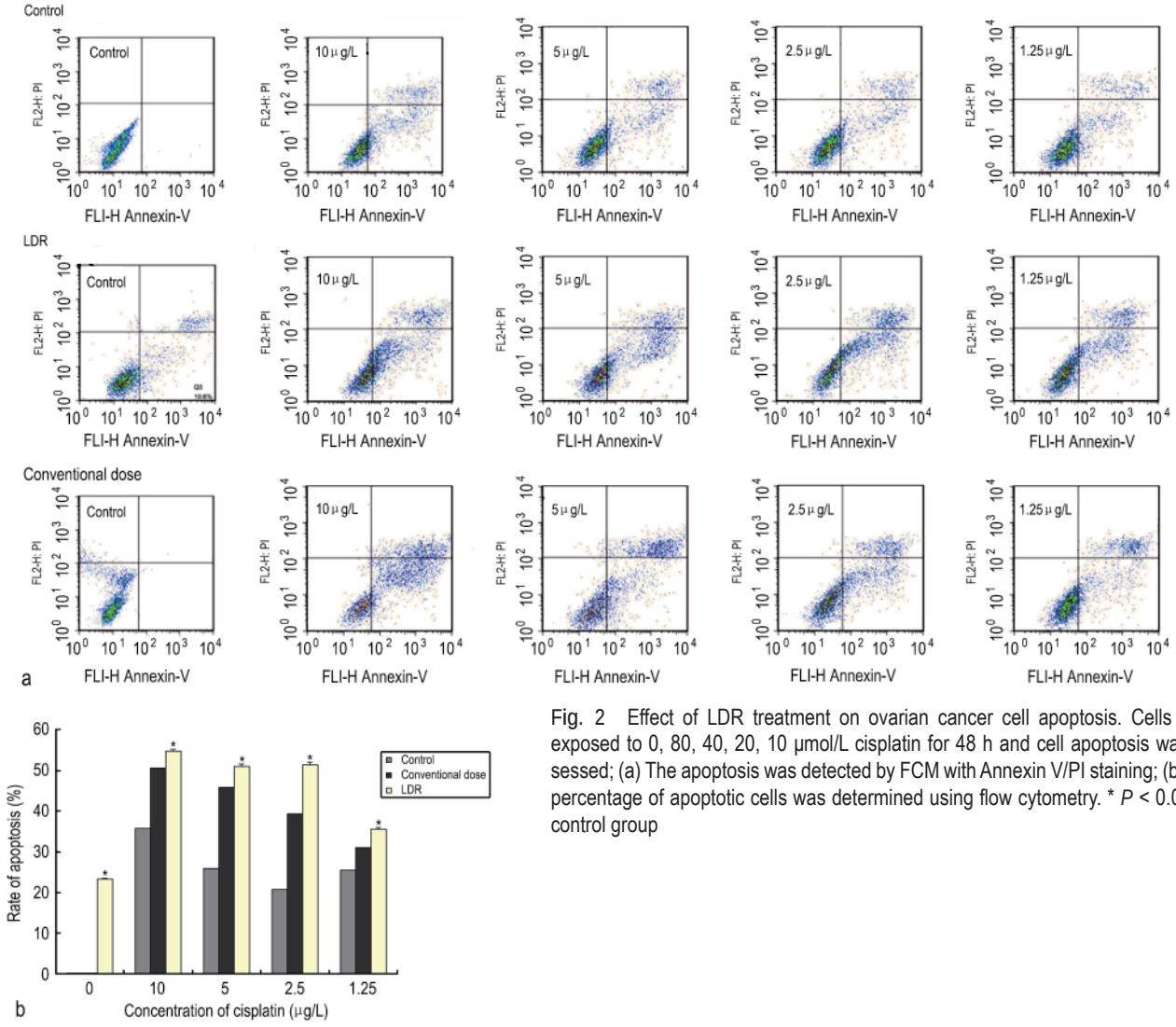

Fig. 2 Effect of LDR treatment on ovarian cancer cell apoptosis. Cells were exposed to 0, 80, 40, 20, 10 μmol/L cisplatin for 48 h and cell apoptosis was assessed; (a) The apoptosis was detected by FCM with Annexin V/PI staining; (b) The percentage of apoptotic cells was determined using flow cytometry. * $P < 0.05$ vs. control group

difference between control group and conventional-dose irradiation group. This result shows that low-dose radiation can increase the effectiveness of cisplatin at inhibiting SKOV3/DDP cell growth.

Effect of low-dose radiation on the frequency of apoptosis in cisplatin-treated SKOV3/DDP cells

Apoptotic cells are characterized by major features such as DNA fragmentation and loss of plasma membrane integrity. To further investigate calycosin-induced apoptosis, flow cytometry was used to quantify apoptotic SKOV3/DDP cells after co-treatment with no radiation, conventional radiation, or low-dose radiation for 48 h Apoptosis was detected based on double staining with Annexin V-FITC and PI. Fig. 2a shows the apoptosis rates of cells from different radiation treatment groups with various concentrations of cisplatin. As shown in Fig. 2b, apoptosis was higher in LDR treated SKOV3/DDP cells than in cells treated with conventional radiation or no radiation ($P < 0.05$). These results reveal that LDR increases cisplatin-induced apoptosis in SKOV3/DDP cells.

The expression of Survivin and Caspase-3 in low-dose radiation treated SKOV3/DDP cells

Survivin and Caspase-3 expression are associated with drug resistance in ovarian cancer cells, so we tested the Survivin and Caspase-3 mRNA levels of SKOV3/DDP cells by RT-qPCR. The cells were cultured and samples prepared as described in the materials and methods. As Fig. 3a shows, the Survivin mRNA levels were lower in the LDR group than in either of the other two radiation treatment groups ($P < 0.05$). This result suggests that LDR can reduce the levels of Survivin in SKOV3/DDP cells. As shown in Fig. 3b, the Caspase-3 mRNA levels in SKOV3/DDP cells treated with LDR were higher than in the

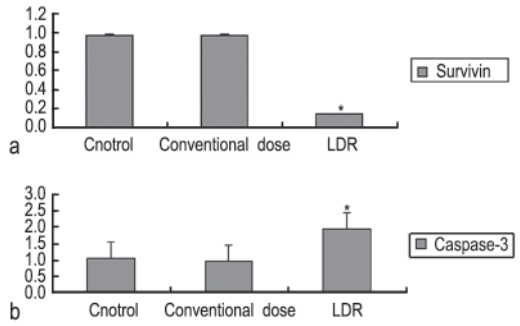

Fig. 3 The expression level of Survivin and Caspase-3 in SKOV3/DDP cell. (a) The expression level of Survivin mRNA in SKOV3/DDP cells of the different groups. LDR group is lower than any other two groups (* $P < 0.05$); (b) The expression level of Caspase-3 mRNA in SKOV3/DDP cells of the three groups. The level of LDR group is higher than any other two groups (* $P < 0.05$)

other two treatment groups. This result shows that LDR upregulates the expression of Caspase-3 in SKOV3/DDP cells. Overall, these results suggest that LDR may reverse cisplatin resistance in ovarian cancer cells by affecting Survivin and Caspase-3 levels.

Discussion

Ovarian cancer is one of the most common female genital malignant tumors, and the conventional treatment is maximal cytoreductive surgery coupled with a platinum-based chemotherapy drug such as cisplatin. Drug resistance is a major obstacle in successful treatment of ovarian cancers. Therefore, overcoming drug-resistance in ovarian cancer would be an important advancement, and should increase treatment efficacy [12].

Radiotherapy functions as an adjuvant therapy for the treatment of ovarian cancer. It is mainly a pre-operative and post-operative adjuvant therapy, or a palliative treatment of advanced ovarian cancer. In recent years, studies on the effects of low-dose radiation (LDR) have attracted the attention of scientists in radiation research [13–14]. *Yu et al* [15] reported that LDR markedly improved the therapeutic efficacy of chemotherapy by reducing damage to the immune systems of tumor-bearing mice. Further, they reported that LDR stimulated the antitumor immune reaction in these mice [15]. Dey *et al* [16] have also found that low-dose ionizing radiation delivered in a fractionated form (ultrafractionation) acts synergistically with chemotherapy *in vitro*. LDR can induce a general adaptation reaction, including DNA damage, chromosome damage, gene mutation, cell death, tumorigenesis, and decreased immune function [17]. In the present study, we explored how LDR changed the effects of cisplatin on SKOV3/DDP cells. We measured SKOV3/DDP cell viability by CCK8 assay, cell apoptosis by flow cytometry, and Survivin and Caspase-3 expression by qPCR. We found that cisplatin treatment coupled with LDR had a greater impact on all three parameters than cisplatin treatment coupled with conventional radiation or no-radiation. These results suggest that LDR can improve cisplatin induced growth inhibition and apoptosis in SKOV3/DDP cells. Further, these results support the feasibility of using LDR to overcome drug resistance in cancer cells.

It is well known that tumor growth and metastasis are angiogenesis-related processes. Caspase-3 is a well-established apoptosis mediator. Wang and colleagues [18] showed that arctigenin-induced apoptosis of ovarian cancer cells required enhanced cleavage of Caspase-3, and that blocking Caspase-3 activity prevented apoptosis of arctigenin-treated cells. The activation of the Caspase-3 apoptotic cascade by arctigenin was also described in non-small cell lung cancer. Although the effect of Caspase-3 has been shown in many tumors, the relationship between Caspase-3 and LDR has not been explored. In this study, we explored whether LDR could reverse cisplatin resistance in ovarian cancer cells by affecting Caspase-3. We evaluated the expression of Caspase-3 in SKOV3/DDP cells by qPCR, and found that the levels were higher when LDR was administered than when conventional-radiation, or no-radiation, was administered. Thus, we have shown that LDR can up-regulate the expression of Caspase-3, which may explain why LDR enhances the sensitivity of SKOV3/DDP cells to cisplatin. Overall, we conclude that LDR can reverse cisplatin resistance in ovarian cancer, likely by changing the levels of Caspase-3.

The majority of studies investigating the influence of Survivin on the prognosis of ovarian cancers have focused on Survivin expression. Survivin over-expression in tumors is associated with advanced disease stage, poorer survival, and chemotherapy or radiotherapy resistance [19–22]. As an apoptosis suppressor gene, Survivin can inhibit apoptosis, promote proliferation, and have an important effect on the initiation and development of malignant tumors [23]. In non-small cell lung cancer, arctigenin enhances chemosensitivity to cisplatin through down-regulation of Survivin expression [18]. Whether LDR can enhance chemosensitivity of SKOV3/DDP cells to cisplatin by suppressing Survivin expression is unclear. In this study, we explored the levels of Survivin mRNA in SKOV3/DDP cells after low-dose radiation. As the data shows, the expression of Survivin in the LDR group was lower than in either of the other two groups. Thus, LDR suppresses the expression of Survivin in an ovarian cancer cell line. Therefore, we conclude that cisplatin resistance in ovarian cancer can be reversed through LDR-induced down-regulation of Survivin.

In this study, we applied LDR to reverse cisplatin resistance in an ovarian cancer cell line. We found that LDR suppressed the expression of Survivin and increased the

expression of Caspase-3. Therefore, LDR is a potential new therapeutic approach for treating ovarian cancer. Given the impact of LDR on the apoptotic resistance of ovarian cancer cells, the use of LDR to improve chemotherapeutic efficacy warrants further investigation.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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