miR-215 functions as a tumor suppressor in epithelial ovarian cancer through regulation of the X-chromosome-linked inhibitor of apoptosis

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Abstract. Epithelial ovarian cancer (EOC) accounts for 90% of all ovarian cancer, which is the third most common gynaecological malignancy worldwide. Dysregulation of miRNAs is involved in the development of different types of EOC. The present study was designed to investigate the role of abnormal expression of miR-215 in the development of EOC and to elucidate the possible molecular mechanisms. mRNA expression of miR-215 was significantly decreased in EOC tissues and cell lines. Upregulation of miR-215 inhibited cell proliferation, promoted apoptosis and increased sensitivity to chemotherapy drugs in EOC cells. In contrast, downregulation of miR-215 increased cell proliferation, inhibited apoptosis and decreased sensitivity to chemotherapy drugs in EOC cells. In addition, the X-chromosome-linked inhibitor of apoptosis (XIAP) expression was significantly increased in EOC tissues and cell lines. Downregulation of XIAP inhibited cell proliferation, promoted apoptosis and increased sensitivity to chemotherapy drugs in EOC cells. Upregulation of miR-215 notably inhibited the expression of XIAP. Moreover, overexpression of XIAP significantly inhibited miR-215-exerted decrease of proliferation, increase of apoptosis and increase of sensitivity to chemotherapy drugs. In conclusion, we identified miR-215 as a potential tumor suppressor in patients with EOC downregulating expression of the oncogenic regulator XIAP. The data demonstrate that miR-215/XIAP pathway may serve as novel therapeutic targets and prognostic markers in patients with EOC.

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Introduction

Ovarian cancer is believed to be the third most common gynaecological malignancy worldwide (1,2). Among them, epithelial ovarian cancer (EOC) accounts for 90% of all ovarian cancer, representing the most fatal gynecological malignancy among women (1,2). EOC is a highly heterogeneous tumor, consisting of several different histotypes with distinct characteristics (3). It was estimated that EOC resulted in 21,980 new cases and 14,270 deaths in 2014 (2). However, the molecular mechanism of EOC is far from completely understood. Further understanding of the molecular pathogenesis and biomarkers of ovarian cancer would facilitate early detection and reduce mortality, as well as useful in identifying therapeutic targets, reducing chemoresistance and prolonging survival at advanced-stage disease (4).

MicroRNAs (miRNAs) are a group of single-stranded, non-coding, small RNAs (20-24 nucleotides) (5-7). These miRNAs play important roles in various biological processes through regulating gene expression by repressing translation or facilitating degradation of the target mRNA by partially binding to the 3' untranslated region of the target mRNA (8,9). Accumulating results have shown that approximately one-third of all mammalian genes were targeted and regulated by miRNAs (10,11). Moreover, miRNAs are believed to function as important regulators in the pathogenesis of various types of tumors (12-14). miRNAs can act as oncomiRs or tumor suppressor miRNAs depending on the functions of their gene targets in cancer development and progression (15). In particular, dysregulation of miRNAs is involved in the development of different types of ovarian cancer (8,16,17). Vaksman *et al* (18) performed miRNA array analysis and compared ovarian cancer effusions and primary ovarian cancer, identifying several differentially expressed miRNAs. Zou *et al* (19) identified potential microRNAs associated with drug resistance in ovarian cancer through web-available microarrays. In our preliminary experiments, we found that abnormal expression of miR-215 was associated with the development of ovarian cancer. However, the extract role of miR-215 in the pathogenesis of ovarian cancer is unclear.

The present study was designed to investigate the role of abnormal expression of miR-215 in the development of EOC

Table I. Clinical features of EOC patients.

Features of patients	Patients
No. of patients	85
Age, year (median, range)	57, (21-88)
Surgery	
Primary debulking	71
Interval debulking	14
FIGO stage (I + II/III + IV)	28/57
Histological type (serous/endometrial/mucinous/clear cell/others)	41/7/20/5/12
Histological grade (G1 + G2/G3)	22/63
Lymph node metastasis (yes/no)	66/19
Chemotherapy (platinum-based/non-platinum-based/none)	67/2/4
Elevated CA125 levels, U/ml ($<5x10^5/\geq5x10^5$)	16/69
Relapse (yes/no)	20/65

and to elucidate the possible molecular mechanisms. Our results showed that miR-215 was decreased in EOC tissues and cell lines, and functioned in EOC cell proliferation, promoted apoptosis and sensitivity to chemotherapy drugs through inhibition of the X-chromosome-linked inhibitor of apoptosis (XIAP).

Materials and methods

Chemicals and materials. β-actin and XIAP antibodies were purchased from Santa Cruz Biotechnology Inc. (Santa Cruz, CA, USA). Paclitaxel was procured from Sigma. All of the other chemicals used were of the highest grade available commercially.

Ethics statement, patients and tissue samples. All patients provided their informed consent, and the present study was approved by the Ethics Review Committee of The First Affiliated Hospital of Xi'an Jiaotong University, and complied with the Declaration of Helsinki. Tissue samples were collected from 85 subjects who underwent surgery from September 2012 to June 2014 for the treatment of epithelial ovarian cancers at the Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xi'an Jiaotong University. All EOC patients had been histopathologically diagnosed with primary ovarian cancer. The histological diagnosis was evaluated by two independent pathologists according to the WHO classification. The International Federation of Gynecology and Obstetrics (FIGO) staging system was used to stage cases. The patient features are summarized in Table I. Samples from 63 cases involving other ovarian tumors or ovarian cystadenomas were collected as controls.

Cell lines and culture. Human EOC cell lines, OVCAR3, CAOV3, SKOV3 and HEY cells were purchased from the American Type Culture Collection (ATCC; Manassas, VA, USA). These cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Gibco-BRL, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS; Gibco-BRL), 100 U/ml penicillin, and 100 μg of streptomycin at 37˚C in 5% CO_2. Normal human ovarian surface epithelial (HOSE) cells were purchased from ScienCell Research Laboratories (Carlsbad, CA, USA) and maintained in ovarian epithelial cell medium supplemented with 1X ovarian epithelial cell growth supplement (ScienCell Research Laboratories). All cell lines were maintained at 37˚C in a humidified incubator containing 5% CO_2.

Cell transfection. The miR-215 mimics, inhibitors and negative miRNA control, and XIAP overexpression and shRNA lentivirus were synthesized by Shanghai GenePharma Co., Ltd. (Shanghai, China). Transient transfection was performed using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) system according to the manufacturer's protocols. Transfection of XIAP shRNA lentivirus and stable knockdown of XIAP was conducted according to the manufacturer's protocols.

RNA isolation and real-time PCR. Total RNA was isolated from EOC tissues or cell lines using a commercial assay kit (Tiangen Biotech Co., Ltd., Beijing, China) according to the manufacturer's instructions. RNA (1 μg) was reversely transcribed to make cDNA using the First Strand cDNA synthesis kit (Takara, Tokyo, Japan). Quantitative real-time polymerase chain reaction (PCR) was used to precisely quantify miR-215 and XIAP. Real-time PCR was performed using SYBR-Green reagents (Takara) in a real-time PCR system from Bio-Rad Biosystems. The $2^{-\Delta\Delta CT}$ method was used to evaluate gene expression compared with the endogenous controls (β-actin or U6 non-coding small nuclear RNA). Amplification was performed with an initial step at 94˚C for 5 min, followed by 40 cycles of denaturation at 94˚C for 30 sec, annealing at 63˚C for 30 sec and then extension at 72˚C for 10 sec.

Protein extraction and western blot analysis. Total proteins were collected from EOC cell lines using RIPA lysis buffer according to the manufacturer's protocols. Cell lysates were washed with cold PBS and incubated on ice in lysis buffer for 30 min. The lysates were centrifuged at 25,000 x g for 30 min

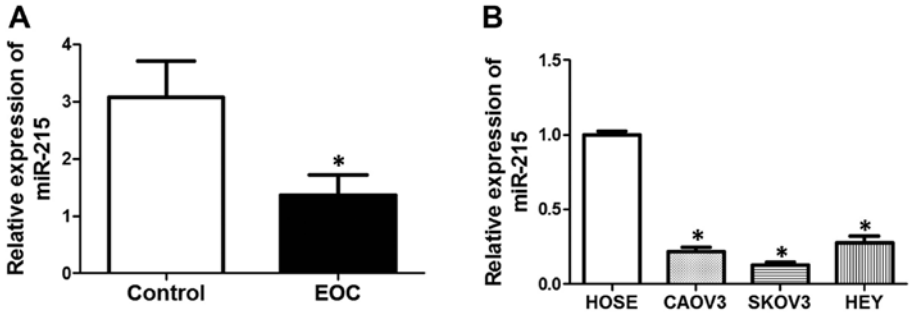

Figure 1. Expression of miR-215 in EOC tissues and cell lines. (A) Relative expression of miR-215 in all samples of EOC and controls. (B) Relative expression of miR-215 in HOSE, CAOV3, SKOV3 and HEY cell lines. *P<0.05, compared with control.

at 4˚C and the protein concentrations in supernatants were measured using a Bradford protein assay kit (Pierce, Rockford, IL, USA). Approximately 50 μg of protein was separated using SDS-PAGE. Then, proteins were transferred to PVDF membrane (Millipore, Billerica, MA, USA), which was blocked with 5% non-fat milk. Membranes were incubated overnight at 4˚C with primary antibodies. After washing, the membrane was incubated with a horseradish peroxidase-conjugated secondary antibody (Pierce) at 37˚C for 1 h. Protein bands were visualized with the ECL and captured using Bio-Rad Imaging Systems (Bio-Rad Laboratories, Hercules, CA, USA).

Cell viability and proliferation. Cell viability was examined using MTT assay. Absorbance was measured at 570 nm using a microplate reader (Bio-Rad Laboratories). Determination of cell proliferation was conducted using a Cell Counting kit-8 (CCK-8) assay according to the manufacturer's instructions. Absorbance was detected at 450 nm using a microplate reader (Bio-Rad Laboratories).

TUNEL assay. TdT-mediated dUTP nick end labeling (TUNEL) staining was used to detect apoptosis in cells. TUNEL assay was conducted using a commercial kit (Roche) according to the manufacturer's protocols. The total number of cells and the number of TUNEL-positive stained cells were counted in 6 random fields in a 'blinded' manner. Results were expressed as percentage of apoptotic cells.

Statistical analysis. The data are shown as the means ± SEM, and P<0.05 was considered significant. All experiments were conducted at least in triplicates. Data analysis was performed using the SPSS 16.0 software (SPSS, Inc., Chicago, IL, USA). One-way analysis of variance (ANOVA) was used to measure the significance between more than two groups. The significance of differences between two groups was analyzed by Student's t-test.

Results

miR-215 is downregulated in EOC tissues and cell lines. To determine the expression of miR-215 in EOC tissues and cell lines, we conducted real-time PCR. As shown in Fig. 1A, mRNA expression of miR-215 was significantly decreased in EOC tissues, compared with controls. The patient characteristics are shown in Table I. Moreover, we also compared the expression of miR-215 between normal human ovarian surface epithelial (HOSE) cells and the human EOC cell lines, CAOV3, SKOV3 and HEY. The results showed that mRNA expression of miR-215 was notably decreased in EOC cell lines, compared with that in HOSE cells.

Upregulation of miR-215 inhibited cell proliferation, promoted apoptosis and increased sensitivity to chemotherapy drugs. To examine to role of downregulation of miR-215 in the development of EOC, human EOC cell line SKOV3 was transfected with miR-215 mimics. As shown in Fig. 2A, miR-215 expression was significantly increased after the transfection of miR-215 mimics. Cell proliferation of SKOV3 cells overexpressing miR-215 was determined and the results showed that overexpression of miR-215 markedly inhibited cell proliferation in SKOV3 cells (Fig. 2B). In addition, we evaluated the effect of miR-215 upregulation on apoptosis. We showed that overexpression of miR-215 significantly increased TUNEL-positive cell numbers (Fig. 2C), indicating that miR-215 promoted apoptosis in SKOV3 cells. Moreover, we examined the effect of overexpression of miR-215 on the sensitivity to chemotherapy drugs. The results showed that incubation of 400 ng/ml paclitaxel for 48 h significantly decreased cell viability (Fig. 2D). Overexpression of miR-215 markedly promoted paclitaxel-induced decrease of cell viability (Fig. 2D).

Downregulation of miR-215 promotes cell proliferation, inhibits apoptosis and decreases sensitivity to chemotherapy drugs. SKOV3 was transfected with miR-215 inhibitors to investigate the effect of downregulation of miR-215 on cell proliferation and apoptosis in SKOV3 cells. As shown in Fig. 3A, miR-215 expression was significantly decreased after the transfection of miR-215 inhibitors. The effect of downregulation of miR-215 on SKOV3 cell proliferation was detected and the results showed that downregulation of miR-215 markedly promoted cell proliferation in SKOV3 cells (Fig. 3B). Moreover, we evaluated the effect of miR-215 downregulation on apoptosis. We showed that downregulation of miR-215 significantly decreased TUNEL-positive cell numbers (Fig. 3C), indicating that downregulation of miR-215 inhibited apoptosis in SKOV3 cells. We examined the effect of downregulation of miR-215 on the sensitivity to chemotherapy drugs, and the inhibition of miR-215 markedly blocked paclitaxel-induced decrease of cell viability (Fig. 3D).

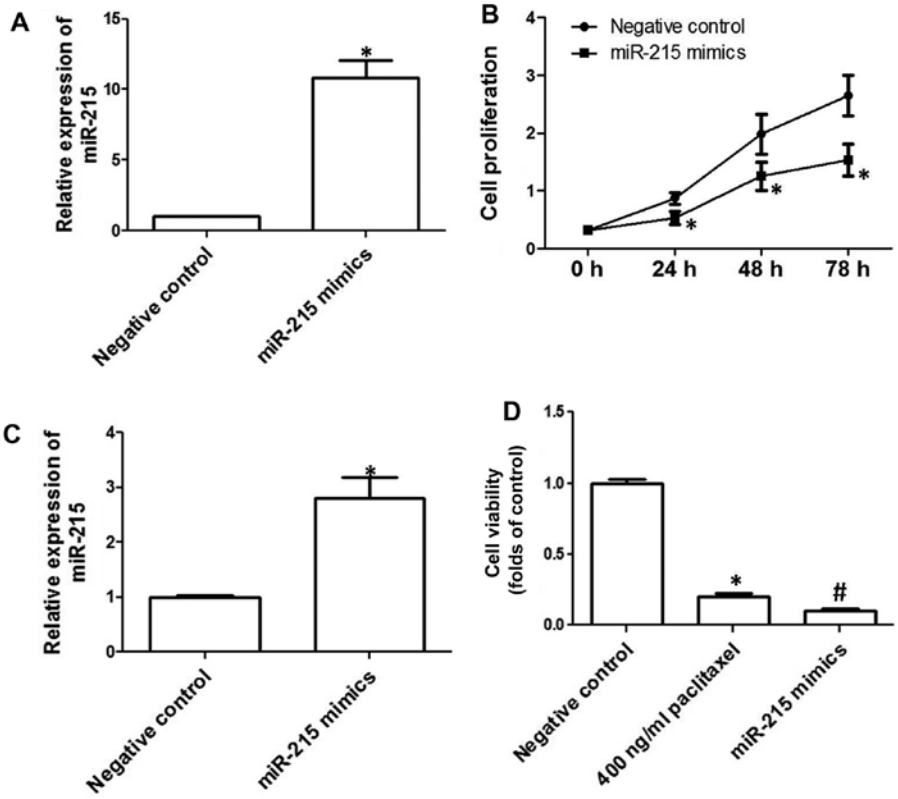

Figure 2. Effect of upregulation of miR-215 on cell proliferation, apoptosis and drug resistance in SKOV3 cells. SKOV3 cells were transfected with miR-215 mimics. (A) miR-215 expression was determined by real-time PCR. (B) Cell proliferation was measured by a commercial kit. (C) Apoptosis was detected by a TUNEL assay kit. (D) OVCAR3 cells were transfected with miR-215 mimics and treated by 400 ng/ml paclitaxel for 48 h, and then cell viability was evaluated by MTT. *P<0.05, compared with control. #P<0.05, compared with paclitaxel treatment.

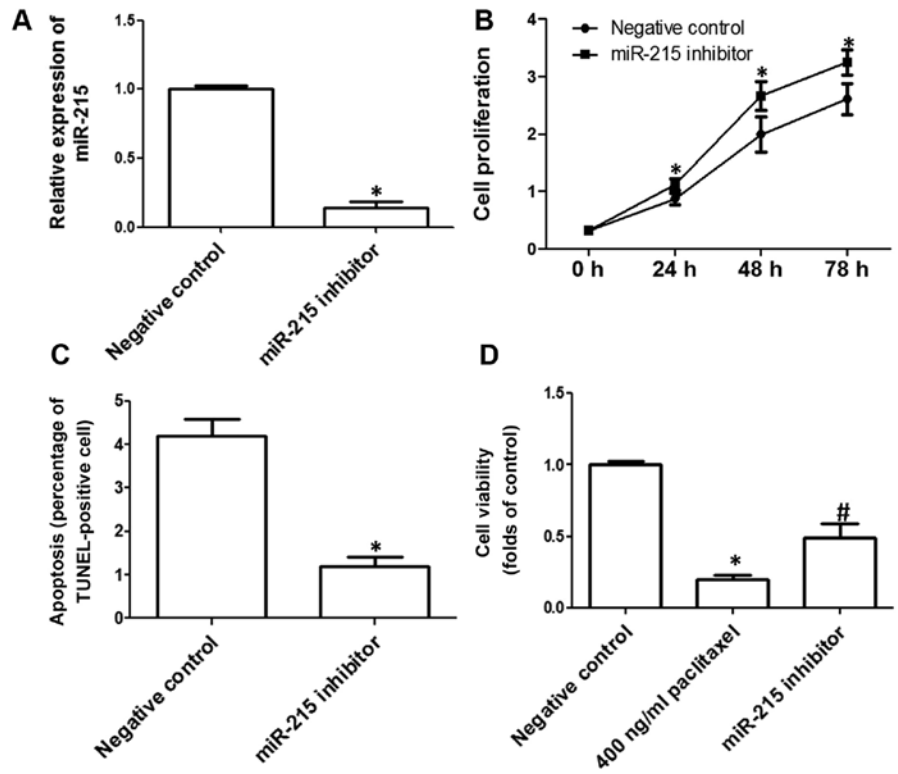

Figure 3. Effect of downregulation of miR-215 on cell proliferation, apoptosis and drug resistance in SKOV3 cells. SKOV3 cells were transfected with miR-215 inhibitors. (A) miR-215 expression was determined by real-time PCR. (B) Cell proliferation was measured by a commercial kit. (C) Apoptosis was detected by a TUNEL assay kit. (D) OVCAR3 cells were transfected with miR-215 inhibitors and treated by 400 ng/ml paclitaxel for 48 h, and then cell viability was evaluated by MTT. *P<0.05, compared with control. #P<0.05, compared with paclitaxel treatment.

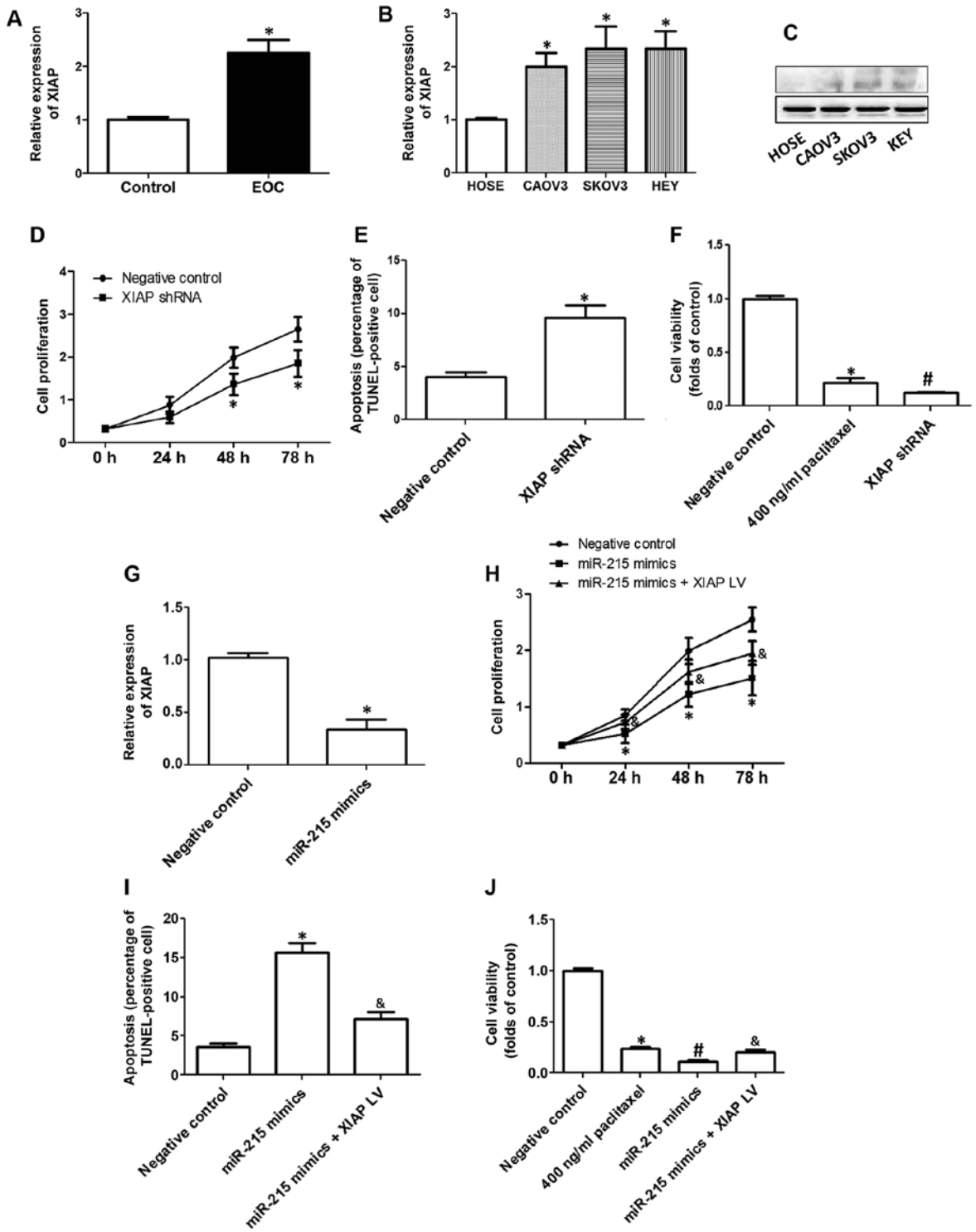

Figure 4. Regulation of XIAP was involved in miR-215-induced regulation of cell proliferation, apoptosis and sensitivity to chemotherapy drugs. (A) Relative expression of XIAP in all samples of EOC and controls. (B and C) mRNA and protein expression of XIAP in HOSE, CAOV3, SKOV3 and HEY cell lines. (D and E) SKOV3 cells were transfected with XIAP shRNAs. (D) Cell proliferation was measured by a commercial kit. (E) Apoptosis was detected by a TUNEL assay kit. (F) OVCAR3 cells were transfected with XIAP shRNAs and treated by 400 ng/ml paclitaxel for 48 h, and then cell viability was evaluated by MTT. (G) SKOV3 cells were transfected with miR-215 mimics and mRNA expression of XIAP was determined by real-time PCR. (H and I) SKOV3 cells were transfected with lentivirus overexpressing XIAP and miR-215 mimics. (H) Cell proliferation was measured by a commercial kit. (I) Apoptosis was detected by a TUNEL assay kit. (J) OVCAR3 cells were transfected with lentivirus overexpressing XIAP and miR-215 mimics, and treated by 400 ng/ml paclitaxel for 48 h, and then cell viability was evaluated by MTT. *P<0.05, compared with control. $^{\&}$P<0.05, compared with paclitaxel treatment. $^{\#}$P<0.05, compared with miR-215 mimic treatment.

Regulation of XIAP is involved in miR-215-induced regulation of cell proliferation, apoptosis and sensitivity to chemotherapy drugs. Previous results have shown that the X-chromosome-linked inhibitor of apoptosis (XIAP) could be regulated by miR-215 (20). In the present study, we further testing the role of XIAP in miR-215-exhibiting regulation of cell prolifera-

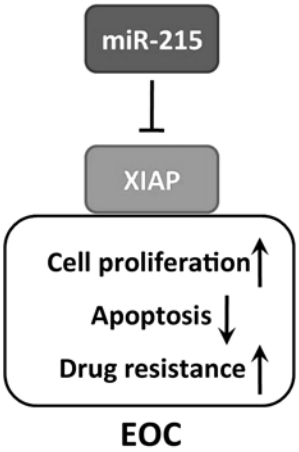

Figure 5. The proposed molecular mechanism underlying the suppressive effect of miR-215 in EOC.

tion, apoptosis and sensitivity to chemotherapy drugs in EOC cells. In Fig. 4A, we show that mRNA expression of XIAP was significantly increased in EOC tissues, compared with controls. Moreover, we also compared the expression of XIAP between HOSE cells and three human EOC cell lines, CAOV3, SKOV3 and HEY cells. The results showed that mRNA (Fig. 4B) and protein (Fig. 4C) expression of XIAP was notably increased in EOC cell lines, compared with that in HOSE cells.

In the next step, we evaluated the role of XIAP in the development of EOC. As shown in Fig. 4D, downregulation of XIAP significantly inhibited cell proliferation in SKOV3 cells. In addition, downregulation of XIAP notably increased the percentage of TUNEL-positive cells in SKOV3 cells (Fig. 4E). Moreover, decrease of XIAP markedly promoted paclitaxel-induced decrease of cell viability in OVCAR3 cells (Fig. 4F).

Furthermore, the results showed that overexpression of miR-215 significantly decreased XIAP expression in EOC cells (Fig. 4G), indicating that miR-215 was a potential target of miR-215. The decrease of cell viability induced by miR-215 mimics was markedly blocked by the transfection of lentivirus overexpressing XIAP (Fig. 4H). Moreover, miR-215 mimic-induced apoptosis was significantly inhibited by the overexpression of XIAP (Fig. 4I). Overexpression of XIAP also inhibited miR-215 mimic-promoted sensitivity to chemotherapy drugs, as reflected by increase of cell viability compared with those cells treated by paclitaxel plus miR-215 (Fig. 4J).

Discussion

Accumulating literature demonstrates that miRNA regulation is associated with the pathogenesis of ovarian cancer (4,16,19,21,22). However, little is known about the role of miR-215. Our previous results indicated that miR-215 is abnormally expressed in EOC samples. In the present study, we investigated the role of miR-215 and the molecular mechanism in the development of EOC.

We found that miR-215 was decreased in EOC tissues and cell lines. Upregulation of miR-215 inhibited cell proliferation, promoted apoptosis and increased the sensitivity to chemotherapy drugs in EOC cells. In contrast, downregulation of miR-215 increased cell proliferation, inhibited apoptosis, and decreased the sensitivity to chemotherapy drugs in EOC cells. Although the literature reporting the relationship between miR-215 and EOC development is limited, there are numerous reports studying the role of miR-215 in other types of cancer (20,23-26). Chen *et al* (23) reported that miR-215 appeared to exhibit oncogenic properties and promote the development of gastric cancer (26). Ye *et al* (20) found that curcumin-activated miR-215 was an important therapeutic target for non-small cell lung cancer. Zhou *et al* (24) regarded the potential of miR-215 as a prognostic predictor for breast cancer with its high expression in cancer tissues. It was also found that the expression level of miR-215 was associated with cervical tumor progression and worse survival rate, suggesting that it may serve as a potential prognostic marker to identify patients at higher risk of recurrence (25). It is suggested that miR-215 plays oncogenic or tumor-suppressive role in different types of tumors. Our results demonstrate that miR-215 functions as a tumor suppressor and a chemotherapy sensitizer of EOC through inhibition of proliferation and promotion of apoptosis.

We also examined the possible molecular mechanism of miR-215-exhibiting inhibition of EOC cell proliferation and promotion of sensitivity to chemotherapy drugs. It was shown that XIAP was a target of miR-215 in the regulation of lung cancer (20). Inhibition of XIAP pathways is involved in the cytotoxicity of EOC cells induced by several different agents (27-31). The anticancer activity of 20(s)-ginsenoside Rg3 in EOC involved inhibition of XIAP pathways and downrgulation of inhibitor of apoptosis protein (IAP) family proteins (27). XIAP expression was correlated with chemoresistance of primary chemotherapy and was identified as a prognostic marker for ovarian clear cell carcinoma (28). DHA2, a synthesized derivative of bisbibenzyl, exerted antitumor activity against ovarian cancer through inhibition of XIAP pathway (29). Bithionol exhibited cytotoxic effects on various ovarian cancer cell lines, in which inhibition of XIAP was involved (30). Farrand *et al* (31) found that the diarylheptanoid hirsutenone sensitized chemoresistant ovarian cancer cells to cisplatin via modulation of XIAP. In the present study, we also evaluated the possible role of XIAP in tumor-suppressive effect of miR-215 in EOC. Consistent with previous results, we found that XIAP acted as an important oncogenic regulator and desensitized factor for chemotherapy. Moreover, we found that overexpression of XIAP significantly inhibited miR-215-exerted decrease of proliferation, increase of apoptosis and increase of sensitivity to chemotherapy drugs. Previous results have also shown that XIAP functioned as the targets of other miRNAs in the regulation of EOC cell proliferation and chemoresistance (20,32). The data demonstrate that XIAP may be an important regulator of EOC development and chemotherapy which is the common downstream target of several tumor-suppressive miRNAs.

In conclusion, we identified miR-215 as a potential tumor suppressor in patients with EOC, and it downregulates expression of the oncogenic regulator XIAP (Fig. 5). Further studies elucidating the molecular pathways of miR-215/XIAP axis are needed. Overall, the data demonstrate that miR-215/XIAP pathway may serve as novel therapeutic targets and prognostic markers in patients with EOC.

Acknowledgements

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