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Propofol inhibits invasion and enhances paclitaxel-induced apoptosis in ovarian cancer cells through the suppression of the transcription factor slug

P. WANG, J. CHEN[1], L.-H. MU, Q.-H. DU, X.-H. NIU, M.-Y ZHANG

Department of Anesthesiology, Provincial Hospital Affiliated to Shandong University, Shandong University, Jinan, Shandong Province, China.
[1]Department of Anesthesiology, People's Hospital of Huaiyin District, Jinan, Shandong Province, China.

Abstract. – BACKGROUND AND AIM: Propofol is one of the most commonly used intravenous anaesthetic agents during cancer resection surgery. It has recently found that propofol has the effect to inhibit cancer cell migration and invasion and sensitize cancer cells to chemotherapy. However, the role of the propofol on the ovarian cancer cells is unknown. In the present study, we explored the effect of propofol on invasion and chemosensitization of ovarian cancer cells to paclitaxel.

MATERIALS AND METHODS: The paclitaxel sensitivity of ovarian cancer cell lines HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 were determined by MTT assays. The Slug levels in the cell lines and the effects of propofol on Slug levels in the cell lines were determined by western blot assays. The effect of propofol on invasion, migration and paclitaxel-induced ovarian cancer apoptosis was determined by Boyden chamber assays, cell MTT, TUNEL assays.

RESULTS: The results showed that the cell lines COC1, H0-8910 and ES-2 were sensitive, whereas HO-8910PM, OVCAR-3, SKOV-3, were resistant to paclitaxel. Significant correlation was observed between basal Slug levels and paclitaxel sensitivity. Paclitaxel treatment increased Slug levels. Treatment with propofol induced apoptosis and increased paclitaxel killing of all paclitaxel-sensitive and -resistant ovarian cancer cells followed by significant decrease in the Slug levels. Treatment with propofol inhibits invasion and migration.

CONCLUSIONS: These data suggest a new mechanism by which the propofol inhibits invasion and metastasis,enhances paclitaxel-induced ovarian cancer cell apoptosis through suppression of Slug.

Key Words:

Ovarian cancer, Metastasis, Chemotherapy, Transcription factor.

Introduction

Ovarian cancer (OVCA) is the most fatal gynecological malignancy that has frustrated both clinicians and researchers for several decades. It is the fifth leading cause of cancer-related death among women, with estimated 21,990 newly diagnosed cases and 15,460 deaths occurring in the United States in 2011 (http://seer.cancer.gov/statfacts/html/ovary.html). This is primarily due to the lack of methods for an early detection of the disease leading to rapid, aggressive peritoneal dissemination of cells from the primary tumor, which results in an adverse prognosis for most patients[1]. The exact molecular events leading to metastases of ovarian tumor cells have not as yet been well elucidated, although it is recognized that the acquisition of capacity for migration and invasiveness would be a necessary prerequisite.

Chemotherapeutic drug resistance is a critical problem in cancer therapy as many tumors are intrinsically tolerant to some of the cytotoxic agents used, while others, although they are initially sensitive, recur and eventually acquire resistance to subsequent treatment with antineoplastic agents[2]. In the ovarian cancer, after optimal surgical debulking of the tumor and standard chemotherapy, patients with advanced disease experience 5-year survival rate[3]. Despite the relative sensitivity of ovarian cancer to chemotherapy, clinical chemotherapeutic treatment often encounters drug resistance[4]. Development of this acquired resistance represents the major limitation to successful treatment. Consequently, there is a pressing need to identify the mechanisms underlying resistance in order to develop novel drugs to re-sensitize tumor cells to primary chemotherapy.

Corresponding Author: Meng-Yuan Zhang Ph.D; e-mail: slyyzmy@126.com

Recent work in esophageal squamous cell carcinoma, bladder cancer pancreatic cancer and ovarian cancer[5-8], suggests that the transcriptional factor Slug are important effectors of the process of invasiveness and tumorigenecity. In cholangiocarcinoma cells, Slug silencing could increase cell sensitivity to cisplatin and radiation[9-10]. In the ovarian cancer, Slug could also mediate radioresistance and chemoresistance[11-12]. We, therefore, suggested that Slug may be a effective gene target.

Propofol (2,6-diisopropylphenol), one of the most commonly used intravenous anesthetic agents producing smooth induction and rapid recovery from anesthesia, has gained wide acceptance since its introduction in the late 80s[13]. Apart from its multiple anesthetic advantages, propofol exerts a number of non-anesthetic effects[14]. In lung cancer cells, propofol inhibits MMP-2 and -9 mRNA and protein expressions, resulting in suppression of invasion and migration *in vitro*[15]. Propofol could inhibit the invasion ability of cancer cells by modulating Rho A and suggested that this agent might be an ideal anesthetic for cancer surgery[16]. In the colon carcinoma cells, propofol stimulation inhibits cancer cell invasion and that the effect is partly due to ERK1/2-dependent down-regulation of MMPs[17]. However, in gallbladder cancer, propofol induces proliferation and promotes invasion through activation of Nrf2[18]. We have recently reported inactivation of NF-κB signaling pathway by propofol could abrogate gemcitabine-induced active activation of NF-κB resulting in the chemosensitization of pancreatic tumors to gemcitabine[19].

In the present study, we examined the effect of propofol on cell invasion and apoptosis induction *in vitro* using paclitaxel-sensitive and -resistant ovarian cancer cell lines. We found that propofol treatment inhibits invasion and promotes apoptosis, and increased paclitaxel killing of all paclitaxel-sensitive and -resistant ovarian cancer cells. Significant correlation was observed between basal Slug levels and paclitaxel sensitivity. Paclitaxel treatment increased Slug levels. Our study demonstrates that propofol inhibits invasion and metastasis, enhances paclitaxel-induced ovarian cancer cell apoptosis through suppression of Slug.

Materials and Methods

Cells and cell culture

Human ovarian cancer cell lines HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 were purchased from American Type Culture Collection (ATCC, Manassas, VA, USA). SKOV-3 and OVCAR-3 cells were grown in DME medium (Sigma-Aldrich, Oakville, ON, Canada) supplemented with 10% heat-inactivated fetal bovine serum, 50 μg/mL gentamicin and 1 mmol/L sodium pyruvate.HO-8910PM, H0-8910, COC1 and ES-2 were purchased from American Type Culture Collection (ATCC, Shanghai China) and cultured in RPMI with 10% FBS (fetal bovine serum), 1% penicillin/streptomycin and 1% L-glutamine. All the cells was at 37°C in a humidified atmosphere containing 5% CO_2.

Drug exposure

Cells were plated in 96-well plates, 5 x 10^3 cells/well. After 24 h incubation, the medium was aspirated and replaced with MEM with 5% FBS containing a range of concentrations of paclitaxel (0.01-10 μM) or propofol (0.1-10 μg/ml) and incubated for an additional 72 h for does-dependent assay. For time-dependent assay, 5 x 10^3 cells/well was incubated with 10 μM paclitaxel or 5 μg/ml propofol for 24-72h. Relative numbers of viable cells remaining were determined using the MTT assay. Apoptotic cells were detected by TUNEL staining assay.

Chemosensitivity Assays

Cells were plated in 96-well plates, 5 x 10^3 cells/well. After 24 h incubation, the medium was aspirated and replaced with MEM with 5% FBS containing 5 μg/ml propofol for an additional 24 h, then the cells were exposed to 0.1 μM paclitaxel for 48 h. Relative numbers of viable cells remaining were determined using the MTT assay. Apoptotic cells were detected by TUNEL staining assay.

MTT assays

5 x 10^3 cells/well were treated above for indicating time, after which 10 μl MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added to each well and cells were left for 4 hours. After incubation, 150 μl MTT solvent (0.1 N HCl in anhydrous isopropanol) was added to each well and mixed thoroughly by pipetting until all formazan crystals were dissolved. Colorimetric change was measured at 570 nm and background absorbance at 690 nm. Final values were obtained by subtracting OD690 nm from OD570 nm.

TUNEL assay

1 x 10^4 cells above in the indicated time were cultured on chamber slides for 24 h. Apoptosis of

the cells was evaluated on the basis of the TUNEL assay according to the manufacturer's instructions. All assays were performed in quadruplicate.

Cell invasion assay

For invasion assay, BD BioCoat™ Matrigel™ invasion chambers (BD Biosciences, Mississauga, Canada) was used. Briefly, HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 cells were treated with 0.1-10 μg/ml propofol for 72 hours, or 5 μg/ml propofol for 24-72 h. Then the 2 x 10^3 cells above in serum-free media were added to the interior of each insert. Plates were incubated for 24 hours at 37°C in 5% CO_2, and media removed from the insert, which was then washed with phosphate buffered saline (PBS). Insert membranes were fixed with cold methanol for 10 minutes, stained with 0.5% Crystal Violet in 25% methanol for 10 mins and rinsed with water to remove excess dye. Membranes were removed from the insert, placed under a microscope and the number of cells that migrated through the porous membrane was counted.

Western blot analysis

For Western blot analysis, cells were rinsed in ice-cold PBS twice and lysed in cell lysis buffer (10 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1% sodium deoxycholate, 1% Nonidet P-40, 1 μg/ml aprotinin, 1 μg/ml leupeptin, 50 mM NaF, 2 mM Na_3 VO_4, 2 mM EGTA: ethylene glycol tetraacetic acid, 2 mM EDTA, and 0.25 mM PMSF: phenylmethylsulfonyl fluoride) for 30 min. Samples were sonicated for 30 s and centrifuged for 20 min at 12,000 x g at 4°C. Samples were electrophoresed on a 12% SDS-polyacrylamide gel and electrophoretically blotted on nitrocellulose membrane. Membranes were blocked in TBS/Tween-20 with 5% milk and incubated with primary Abs (antibodies) diluted in TBS/Tween-20/BSA (bovine serum albumin) overnight at 4°C. The following primary was anti-slug. All blots were incubated with secondary Abs conjugated to horseradish peroxidase (HRP) (1/2000) and developed using the enhanced chemiluminescence (ECL) method. Protein concentration was determined using bicinchoninic acid assay (Pierce, Rockford, IL, USA).

Statistical Analysis

Statistically significant differences were determined by two-tailed unpaired Student's *t* test and one-way ANOVA and were defined as $p < 0.05$. All experiments were repeated independently at least three times.

Results

Ovarian cancer (OC) cell lines vary in resistance to paclitaxel

We examined the relative sensitivity of six OC cell lines (HO-8910PM, H0-8910, SKOV-3,OVCAR-3, COC1 and ES-2) to paclitaxel *in vitro*. Cells were treated with different concentrations of paclitaxel for 72 hours and the number of surviving cells was analyzed by MTT assay (Figure 1). Whereas the paclitaxel LD50 was >10 μM for the HO-8910PM, OVCAR-3 and SKOV-3 cells, the LD50 was around 0.1 μM for H0-8910, COC1 and ES-2 cells.The same sensitivities were obtained when the effects of paclitaxel were analyzed on apoptosis using TUNEL assay (data not shown). These data supported the classification of the HO-8910PM, H0-8910 and SKOV-3 cell lines as paclitaxel-resistant and the OVCAR-3, COC1 and ES-2 cell lines as paclitaxel-sensitive.

Slug levels in OC cell lines

To test the hypothesis that Slug basal levels could predict paclitaxel sensitivity, we initially evaluated slug levels in the OC cell lines by western blot assay. Highest levels of slug protein were observed with HO-8910PM, OVCAR-3 and SKOV-3 cells, and lowest slug protein level was

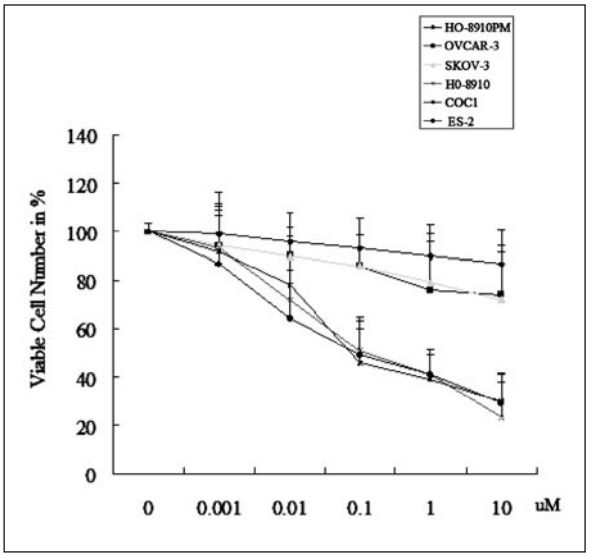


Figure 1. Ovarian cancer cells have differing levels of native resistance to paclitaxel. Human OC cell lines HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 were treated with increasing concentrations of paclitaxel (0-10 μM) for 72 h. The viabilities indicated on the y axis were determined by MTT assays and normalized to control. Data shown are means ± SE for n = 3 independent experiments.

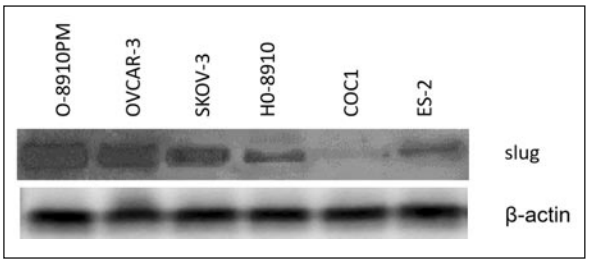


Figure 2. Expression of endogenous Slug in OC cell lines by western blot assay. β-actin is shown as a loading control. Highest levels of slug protein were observed with HO-8910PM, OVCAR-3 and SKOV-3 cells, and lowest slug protein level was observed with H0-8910, COC1 and ES-2 cell.

observed with H0-8910,COC1 and ES-2 cell (Figure 2). Thus, OC cells exhibited elevated slug, and there was consistent pattern of slug in the resistant versus sensitive cell lines. Consistent difference was noted between slug in paclitaxel -sensitive versus paclitaxel-resistant cells.

Paclitaxel treatment increases Slug expression in sensitive but not resistant cells

HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 cells were treated with 0.001, 0.01, 0.1, 1, 10 μM paclitaxel for 24 hours, and slug were measured using western blot assay. Paclitaxel treatment for 24 hours with 0.001-10 μM had no significant effect on slug levels in the paclitaxel-resistant HO-8910PM, OVCAR-3, SKOV-3 cells (Figure 3). However, in the paclitaxel-sensitive H0-8910, COC1 and ES-2 cells, paclitaxel treatment for 24 hours with 0. 1 μM had significant increase in slug levels (Figure 3).

Propofol treatment inhibits cell invasion in resistant but not sensitive cells

The target plasma concentrations of propofol for general anesthesia are between 3 and 8 μg/ml[20]. In the present study, HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 cells were treated with 0.1-10 μg/ml propofol for 72 hours, or 5μg/ml propofol for 24-72 h. Propofol inhibits invasion in dose- (Figure 4A) and

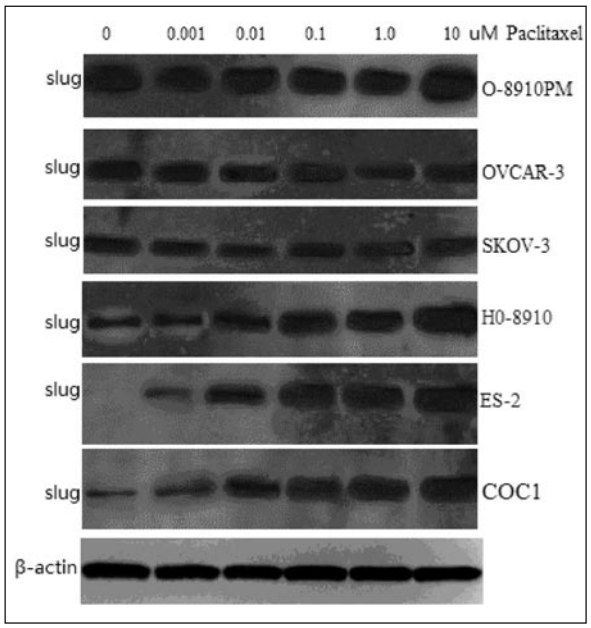


Figure 3. Expression of Slug in OC cell lines after treatment with paclitaxel by western blot assay. Paclitaxel treatment for 24 hours with 0.001-10 μM had no significant effect on slug levels in the paclitaxel-resistant HO-8910PM, OVCAR-3, SKOV-3 cells In the paclitaxel-sensitive H0-8910, COC1 and ES-2 cells, paclitaxel treatment for 24 hours had significant increase in slug levels.

time- (Figure 4B) dependent manners in the paclitaxel-resistant HO-8910PM, OVCAR-3, SKOV-3 cells 5-10 μg/ml concentrations of propofol were sufficient to suppress the invasion ability of cancer cells. No significant effect was found in the paclitaxel-sensitive H0-8910, COC1 and ES-2 cells (Figure 4A-B).

Propofol treatment inhibits cell proliferation and promotes apoptosis in resistant but not sensitive cells

HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 cells were treated with 0.1-10 μg/ml propofol for 24, 48 and 72 hours. Propofol decreased paclitaxel-resistant HO-8910PM, OVCAR-3,SKOV-3 cells proliferation in a time-(Figure 5B) and dose-dependent (Figure 5A) manner by MTT assay. Apoptosis analysis using

Figure 5. Propofol treatment on cell proliferation and apoptosis in OC cells. ***A,*** HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 cells were treated with 0.1-10 μg/ml propofol for 72 hours. ***B,*** HO-8910PM, H0-8910, SKOV-3,OVCAR-3, COC1 and ES-2 cells were treated with 5 μg/ml propofol for 24,48 and 72 hours. The viabilities indicated on the y axis were determined by MTT assays and normalized to control. Data shown are means ± SE for n = 3 independent experiments; $^{*}p <$ 0.05. ***C,*** HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 cells were treated with 0.1-10 ug/ml propofol for 72 hours. ***D,*** HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 cells were treated with 5 μg/ml propofol for 24,48 and 72 hours. The apoptosis cell indicated on the y axis were determined by TUNEL assays and normalized to control. Data shown are means ± SE for n = 3 independent experiments $^{*}p < 0.05$.

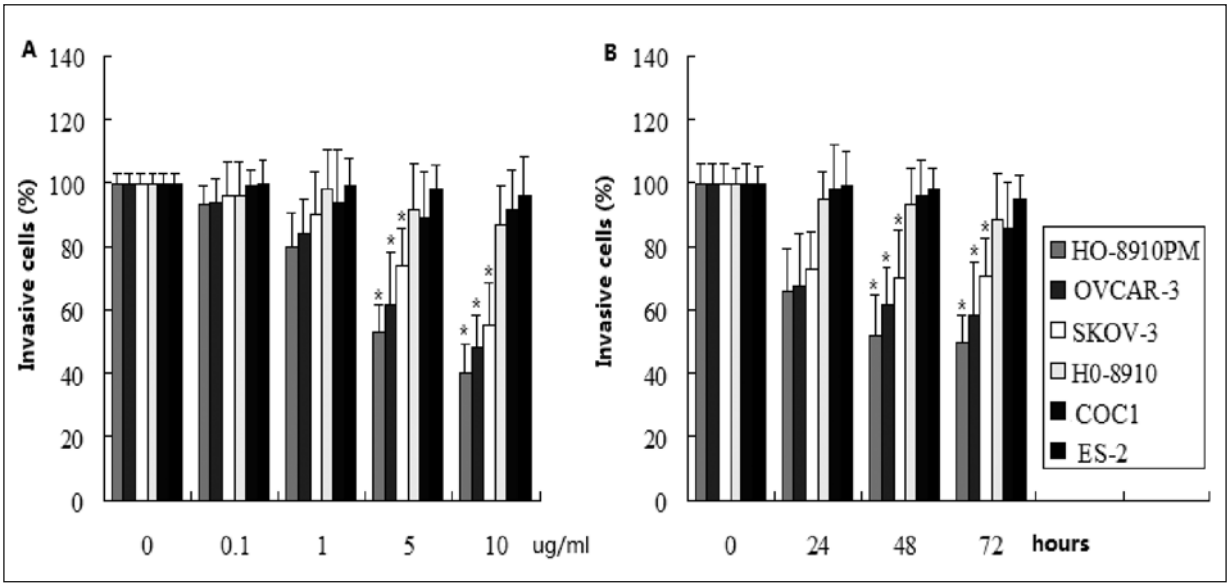
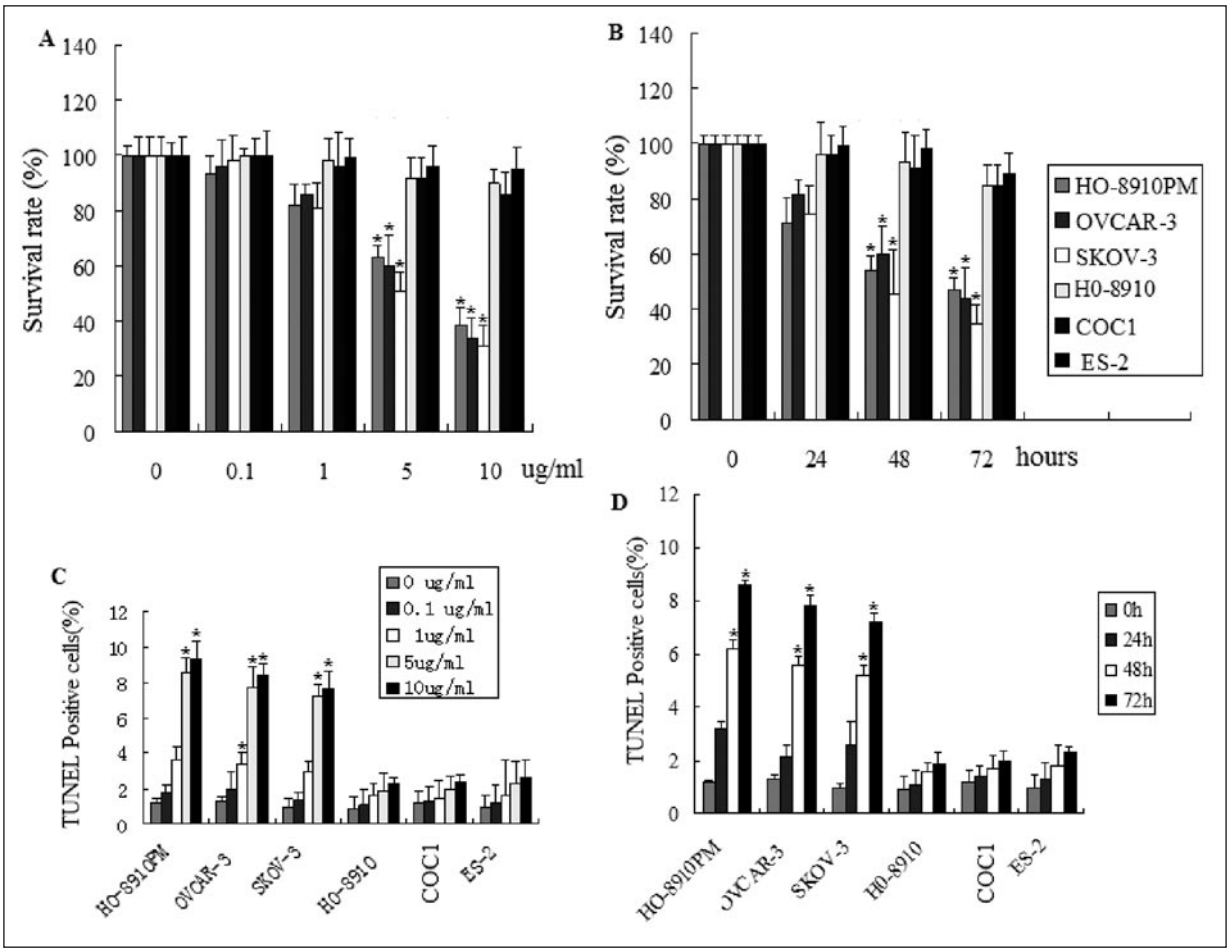


Figure 4. Propofol treatment inhibits cell invasion in resistant but not sensitive cells. ***A,*** HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 cells were treated with 0.1-10 μg/ml propofol for 72 hours. ***B,*** HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 cells were treated with 5 μg/ml propofol for 24,48 and 72 hours. Results are mean ± SD and statistically significant differences from 0 μg/ml propofol are indicated (*$p < 0{:}05$). Similar results were obtained in at least three different experiments.



TUNEL, propofol promoted the apoptosis in the paclitaxel-sensitive OVCAR-3, COC1 and ES-2 cells (Figure 5 C-D). No significant effect was found in the paclitaxel-sensitive H0-8910, COC1 and ES-2 cells (Figure C-D).

Propofol inhibits slug in both resistant and sensitive cells after paclitaxel treatment

Because 5 μg/ml propofol treatment for 48 hours could significantly inhibits invasion and promotes apoptosis in the OC cells. Therefore, we used 5 μg/ml propofol for 48 hours treatment for further study. HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 cells were treated with 5 μg/ml propofol for 48 hours. Slug protein was significantly or completely inhibited cells (Figure 6). Though paclitaxel treatment for 24 hours with 0.1 μM in the paclitaxel-sensitive H0-8910, COC1 and ES-2 cells significantly increased the slug levels (Figure 3), pretreatment with 5 μg/ml propofol completely inhibited Slug protein after 5 μg/ml paclitaxel treatment for 48 hours (Figure 6).

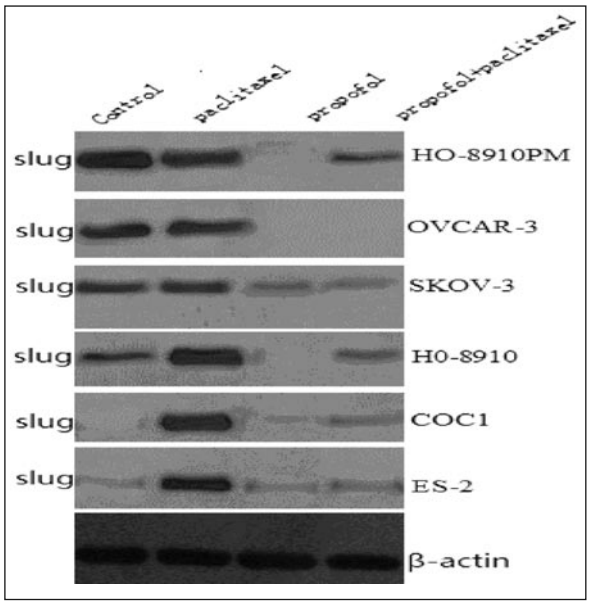


Figure 6. Propofol on slug protein in OC cells after paclitaxel treatment. HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 cells were treated with 5 μg/ml propofol for 24 hours after which the cells were then treated with 0.1 μM paclitaxel for 48 hours. Western blot assay was used to detect slug expression in the OC cells. Slug was completely inhibited in all the cells treated with propofol or/and paclitax-

Propofol enhances paclitaxel-induced apoptosis in both resistant and sensitive cells

To test the hypothesis that propofol treatment would increase the sensitivity of OC lines to paclitaxel-mediated apoptosis, HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 cells were pertreated with 5 μg/ml propofol for 24 hours, then examined the effects alone and with 0.1 concentrations of paclitaxel (Figure 7). Propofol combined with 0.1 concentrations of paclitaxel treatment significantly reduced cell numbers (Figure 7A) and increased apoptosis in vitro of all the OC cells (Figure 7B).

Discussion

Slug is a major component of Epithelial-Mesenchymal Transition (EMT), the process that converts epithelial cells into mesenchymal cells with migratory properties, thereby, contributing to the formation of many tissues during development and to the acquisition of an invasive phenotype in epithelial tumor cells. Accordingly, its amplification has been associated with cancer invasion and dissemination[7-8,21-24]. Furthermore, knockdown of Slug could effectly inhibit invasion in many cancer cells[5-6,25-26]. Recently, it has also found overexpression of Slug could mediate radioresistance and chemoresistance in cancer cells and this effect could be suppressed by interfering of Slug[9-11,27-28]. We therefore suggested slug is a potentially useful gene for cancer treatment. However, how to effectly target slug is the key for cancer treatment.

Propofol is a widely used intravenous anesthetic. In addition to its sedation/hypnotic properties, propofol displays neuroprotective effects due to its effect against neuroal cell apoptosis[29-31]. Propofol has recently been reported to have the ability of influencing the invasion of human cancer cells by different signaling parthway[15-17,32]. Propofol has many targets, such that interpretation of the actions of propofol is quite difficult.

In the present study,we found propofol treatment inhibits invasion and proliferation and promotes apoptosis in paclitaxel resistant OC cells. Of particular significance, our results on the effects of propofol treatment on sensitivity to paclitaxel indicated that natively sensitive but also resistant cells were affected.

To clarify the mechanism of propofol on invasion, apoptosis and sensitive to paclitaxel, we detected the native Slug expression in the OC cells. The results showed high Slug expression was found in paclitaxel-resistant OC cells. However, in the paclitaxel-sensitive cells, Slug expression

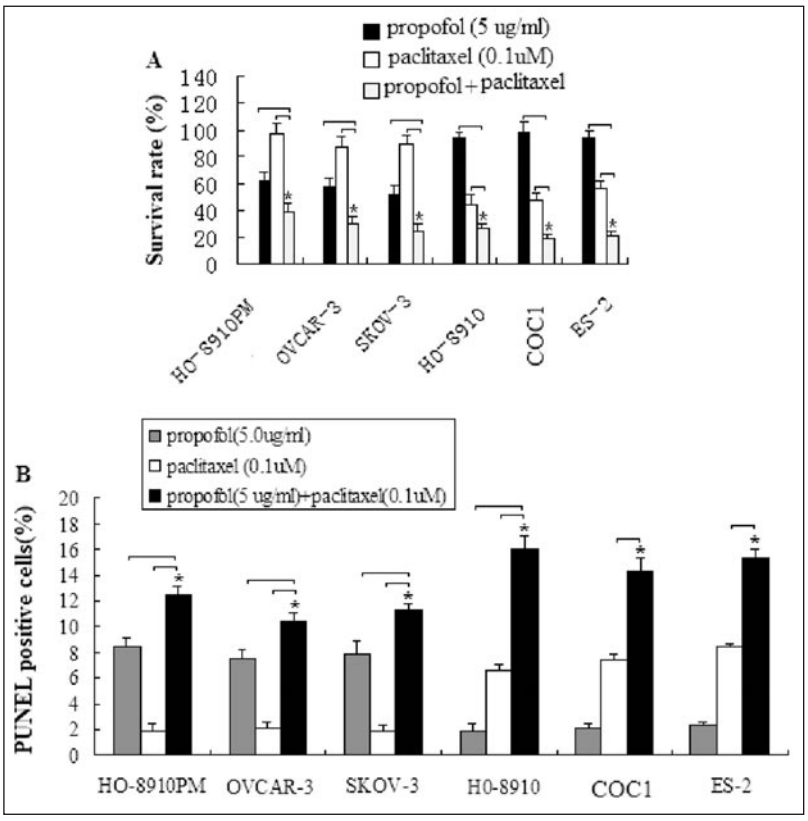


Figure 7. Propofol on cell survival and apoptosis in OC cells after paclitaxel treatment. HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 cells were treated with 5 μg/ml propofol for 24 hours after which the cells were then treated with 0.1 μM paclitaxel for 48 hours. MTT and TUNEL assay was used to detect proliferation and apoptosis. Data shown are means ± SE for n = 3 independent experiments $^{*}p < 0.05$.

was null or very low. This was indicated slug might correlate with sensitivity to paclitaxel. We detected the Slug expression in the OC cells after propofol treatment. In the OC cells with high Slug levels, propofol treatment inhibits invasion, proliferation and promoted apoptosis followed by decreased Slug expression in these cells. However, no significant effect was found on Slug levels after propofol treatment. This was indicated propofol treatment inhibits invasion,proliferation and promoted apoptosis by suppression of Slug.

Drug resistance (both intrinsic and acquired) is thought to be a major reason for the limited benefit of most cancer therapies. In the present study, we found paclitaxel treatment significantly increased slug levels in the OC cells. Propofol treatment inhibits proliferation and promoted apoptosis followed by decreased slug expression paclitaxel-induced in these cells. Although paclitaxel treatment did not significantly increased the Slug levels in the paclitaxel-resistant OC cells, propofol treatment also inhibits proliferation and promoted apoptosis after paclitaxel treatment followed by decreased Slug expression in these cells. This was indicated propofol treatment enhances paclitaxel-induced apoptosis in ovarian cancer cells through the suppression of the transcription factor Slug.

Conclusions

Our findings indicate that propofol inhibites invasion and enhances paclitaxel-induced apoptosis in ovarian cancer cells by effectively inhibiting Slug expression. These results suggest that propofol might be an ideal anesthetic for OC surgery and is potentially useful as a sensitizer in OC therapy.

Conflict of Interest

The Authors declare there was not any possible conflict of interest in this research.

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