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Targeted Blockage of CXCR4 on the Epithelial-Mesenchymal Transition Effect between Epithelial Ovarian Cancer

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Abstract

To investigate the effect of targeted blockage of CXCR4 on EMT and tumour invasion and metastasis in epithelial Ovarian cancer (OC). The expression of CXCR4 was detected using SP immunohistochemistry in 55 cases of OC and 35 cases of benign tissue. CXCR4 and EMT markers, correlation analysis of the related factors, CXCR4 protein expression and the clinicopathological characteristics of patients with OC; The CXCR4 antagonist AMD3100, OVCAR3 detection by western blot CXCR4 and the expression of EMT-related protein; MTT method, real ability experiment and Transwell experiment were used to detect the invasion of OC cell proliferation and cell clone formation, cell clone formation ability and invasion ability. The expression of CXCR4 and EMT-related proteins in OC was significantly higher than in the control group. The expression of CXCR4 in patients with tumour grade, FIGO staging, lymph node metastasis, and ascites had a close relationship ($P < 0.05$). After AMD3100 treatment, cell proliferation, colony formation, and invasion abilities were significantly inhibited in OVCAR3 cells. AMD3100 inhibited proliferation, invasion, and metastasis of OC by blocking CXCR4 and regulating the expression of EMT-related proteins. CXCR4 promoted the proliferation of OC, and the invasion and metastasis process may be related to the pathogenesis of EMT. Therefore, CXCR4 may be a new target for the treatment of OC.

Keywords

Ovarian Cancer, CXCR4, EMT, Targeted Blockage

1. Introduction

Ovarian cancer (OC) is one of the most common gynaecological malignant tumours. Its mortality rate is the highest among all gynaecological tumours. Epithelial ovarian cancer (EOC) is the most common ovarian cancer. The recurrence and distant metastasis are closely related to the survival of ovarian cancer staging [1]. Because of the lack of typical symptoms and effective screening strategies, in approximately 75% of women with ovarian cancer, ovarian cancer cells spread to the abdominal cavity, even reaching an advanced stage of disease [2]. Studies have shown that a high CXC chemokine receptor 4 (CXCR4) expression in EOC is closely related to the prognosis [3]. In addition, CXCR4 is the most common tumour cell and the only expressed chemokine receptor of the chemokine family in ovarian tumours. It plays a vital role in tumour invasion, metastasis, and prognosis [4]. However, the CXCR4-mediated mechanism of invasion and metastasis of ovarian cancer cells is not precise. Epithelial-Mesenchymal Transition (EMT) is one of the main ways of development of a malignant epithelial tumour [5], playing an essential role in the invasion and metastasis of various tumours, including breast, prostate, pancreatic, and lung cancers [6]-[9].

In recent years, several studies have shown that the interaction between CXCR4 and EMT plays a vital role in the invasion and metastasis of tumours, indicating the importance of CXCR4 and EMT in the process of tumour development. At present, CXCR4 has become a therapeutic target for blocking tumour invasion and metastasis. Thus, the expression of CXCR4 on tumour cells is essential in the diagnosis and prognosis of tumours. In recent years, immunotherapy for ovarian neoplasms using small interfering RNA (siRNA)-mediated gene silencing has been investigated. However, at present, the studies on the mechanism of targeted blocking the action of CXCR4 and EMT in EOC are scarce. Therefore, to further explore the role of CXCR4 in the occurrence of EMT in ovarian cancer and the mechanisms involved in the invasion and metastasis, we used CXCR4-specific inhibitor AMD3100 to block CXCR4 in ovarian cancer cells. The expression of CXCR4 and EMT-related proteins was measured, and their correlation was analysed. This study helped in further understanding the relationship and interaction between CXCR4 and EMT in ovarian cancer.

2. Materials and Methods

2.1. Tissue Selection

In this study, we included 55 cases of EOC (experimental group) in our hospital from 2009 to 2013. The inclusion criteria were as follows: patients with complete clinical and pathological data; the first treatment and were not receiving preoperative chemotherapy, radiotherapy, hormone, and anti-inflammatory treatment; surgery for cytoreductive surgery (the whole uterus and double appendix resection of the pelvic and para-aortic lymph node dissection selective greater omentum resection appendectomy). Select the same period because ovarian masses underwent surgical resection, and the postoperative pathological diagnosis was a be-

nign ovarian epithelial tumour. Overall, 35 cases were included in the control group. All samples were routinely fixed in formaldehyde solution and embedded in paraffin after immunohistochemical detection.

2.2. Material

DMEM high glucose, trypsin digestion liquid, PBS buffer, double-antibody (HyCLONE), PAN Serum (Germany), Pakistan Straw, culture bottle, centrifuge tube, freezing tube (Corning), Ovarian cancer cell line OVCAR3 (purchased from cell bank centre of Kunming Medical University), Four methyl thiazolyl tetrazolium (MTT) assay, Transwell BD board. Rabbit anti-human CXCR4 polyclonal antibody was purchased from Wuhan Boster Company. AMD3100, anti-human rabbit Snail monoclonal antibody, mouse anti-human E-cadherin monoclonal antibody, vimentin monoclonal antibody, and SP immunohistochemistry kit were purchased from Beijing Zhongshan Company.

2.3. Immunohistochemical Analysis

Paraffin, 4-μm serial sections, xylene dewaxing, gradient ethanol hydration, high-temperature boiling antigen repair (citrate buffer, pH 6). Hydrogen peroxide (3%) was used to block endogenous peroxidase and close the liquid nonspecific antigen. Add the primary antibody and incubate overnight at 4˚C. Subsequently, add the secondary antibody and incubate for 1 hour at room temperature, followed by DAB staining, haematoxylin staining, dehydration and mounting. The negative control was PBS. The double-blind method determines the semi-quantitative integral method. In the nucleus, cell membrane or cytoplasm yellow particles for positive, each section at high magnification in 10 fields, each field counting 100 cells, The percentage of positive cells less than 5% to 0, From 5% to 25% to 1 point, 2 points from 26% to 50%, From 51% to 75% for 3 points, more than 76% to 4 points. Staining was light yellow count 1, yellow-brown for 2 points, 3 points. The product was above two scores 3 points for the negative, more than 3 points as positive.

2.4. Cell Culture

Ovarian cancer cell line OVCAR3 was cultured in high-glucose DMEM containing 10% foetal bovine serum and 1% penicillin-streptomycin with 5% CO_2 and 37% saturated humidity. The cells were washed with PBS 2 - 3 times, digested using trypsin, and passed through 0.25% routine. All the cases in the experimental group were divided into 3 groups: negative control, AMD3100 10 μg/mL, and AMD3100 100 μg/mL groups.

2.5. Cell Proliferation Assay

Single-cell suspensions were prepared in 3 groups of cells. The cells were seeded in 96-well plates at a density of 2×10^5 cells per well. Each cell volume was about 200 L, with 6 wells for each group. Cell culture, transfection, colour, microplate colourimetric. Absorbance was detected at 490 nm. The formula used for calculation was as follows.

$$\text{Inhibition ratio} = (1 - \text{treatment group/control group}) \times 100\%. \quad (1)$$

2.6. The Clone Formation Assay

Cells in the logarithmic growth phase were digested with 0.25% trypsin and triturated into single cells. After gradient dilution, the cells were inoculated into a dish containing 10 mL of pre-warmed medium (37˚C), then incubated in an environment with 37˚C, 5% CO_2, and saturated humidity. After terminating the culture, the cells were gently rinsed twice with PBS and fixed with methanol for 15 minutes. With appropriate Giemsa, applications were dyed for 10 - 30 min and then washed to remove the stain. After drying with the naked eye, counting cloning, the meter measures cell clone formation rate.

2.7. Matrigel Invasion Assay

The basement membrane was hydrated before use. The ovarian cancer cells were digested after cell suspension preparation. Digestion was terminated after adjusting the cell density to 5×10^5/mL. Join the Transwell chamber (24-well plate) Orifice room under the general culture medium added 600 L containing 20s, cell culture: Cultured 12 - 48 h. Statistics the results, count the "Adherent" cell, remove the Transwell chamber, and discard the culture medium in the hole. The cells were washed twice with calcium-free PBS and fixed with methanol to dry. After 30 min, the cells were stained with 0.1% crystal violet for 20 min. Sign gently wipe with cotton without upper cell migration. The cells were washed thrice with PBS and observed under 400× magnification. Five random fields were chosen to determine the cell count.

2.8. Western Blotting Analysis

OVCAR3 cells in the logarithmic growth phase were cultured in a serum-free medium overnight. The total proteins were extracted and separated after degreasing. Room temperature closed 2 h after adding antibody, 4˚C TBST after rinsing overnight, adding two anti-TBST after rinsing, adding DAB colour liquid, and then waiting for the positive zone colour to clear after being photographed.

2.9. Statistical Analysis

SPSS 17 statistical software was used for statistical analysis. The values were expressed as mean ± standard deviation (SD). The normal distribution and homogeneity of variance case. Two groups were compared using a t-test, and multiple groups were compared using one-way ANOVA. Count data using the χ^2 test. Correlation analysis was performed using Spearman's correlation coefficient. $P < 0.05$ was considered significant.

3. Results

3.1. The Expression of CXCR4 with E-Cadherin, Snail, and Vimentin Immunohistochemistry, in EOC and Control Groups

CXCR4 is expressed in the cytoplasm of cells. E-cadherin is located on the cell

membrane. Snail is expressed in the nucleus and cytoplasm. Vimentin is located in the cytoplasm. In EOC, the cells were positive for CXCR4 and vimentin. The differences in expression were significant compared with ovarian benign tumour tissue ($P < 0.05$). Low or no expression of E-cadherin was observed in EOC, and its high expression was observed in benign tissues. The expression of Snail was not significantly different in experimental and control groups (Figure 1). The expression of vimentin was positively correlated with CXCR4, whereas E-cadherin and CXCR4 were negatively correlated, which was significant compared with the control group ($P < 0.05$; Table 1). The expression of CXCR4 correlated with tumour grade, FIGO staging, lymph node metastasis, and metastatic ascites ($P < 0.05$). Regardless of the age factor ($P = 0.595$; Table 2).

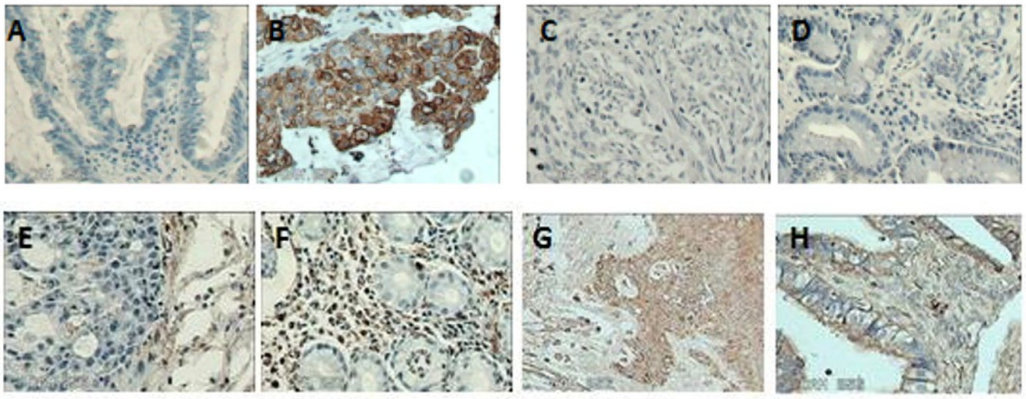

Figure 1. Expression of CXCR4 and EMT-related proteins E-cadherin, snail, EOC, and vimentin in benign tissues of the ovary (A, C, E, and G were control groups. B, D, F, and H were experimental groups, SP ×200). Serum levels of CXCR4 (A-D) and CXCL12 (E) in endometrial cancer. CXCR4 was not expressed in normal endometrium (A), weakly expressed in simple hyperplasia endometrium (B) and atypical hyperplasia endometrium (C) and strongly expressed in endometrial adenocarcinoma (D). (DAB, original magnification ×200).

Table 1. Correlation between expression of CXCR4 and EMT in EOC tissues.

Variable	CXCR4, *n* (%)		*R*	*P*
	Positive	Negative		
E-cadherin				
Positive	6 (10.91)	15 (27.27)		
Negative	26 (47.27)	8 (14.55)	−0.472	<0.001
Snail				
Positive	25 (45.46)	11 (20.00)		
Negative	9 (16.36)	10 (18.18)	0.216	0.113
Vimentin				
Positive	26 (47.27)	8 (14.55)		
Negative	6 (10.91)	15 (27.27)	0.472	<0.001

*$P < 0.05$ as compared to normal ovarian tissues.

Table 2. The relationship between CXCR4 expression and clinicopathological features.

Clinicopathological features	(*n* %)	CXCR4		χ^2	*P*
		Positive	Negative		
Age (years)					
≤47	24 (43.64)	13	11		
>47	31 (56.36)	29	12	0.282	0.595
FIGO stages					
I, II	16 (29.09)	14	2		
III, IV	39 (70.91)	20	19	6.305	0.012*
Tumor grade					
I	21 (38.18)	10	11		
II, III	34 (61.82)	26	8	4.779	0.029*
Lymphatic metastasis					
Yes	16 (29.09)	27	8		
No	39 (70.91)	7	13	9.577	0.002*
Abdominal dropsy					
Positive	37 (67.27)	25	10		
Negative	18 (32.73)	8	12	5.238	0.022*

*$P < 0.05$ as compared to normal ovarian tissues.

3.2. Effect of AMD3100 on Ovarian Cancer Cell Proliferation

The effect of AMD3100 on cell proliferation was observed after 6, 24, 48, and 72 h. At 24 h, no difference in cell proliferation was observed between the groups. Cell proliferation was significantly inhibited at 48 h, compared with the control group ($P < 0.05$). Cell proliferation was inhibited with the increase in AMD3100 concentration. At 48 h, the effect of 100 μg/mL AMD3100 on cell proliferation was significantly lower than that of 10 μg/mL AMD3100 ($P < 0.05$; **Figure 2**).

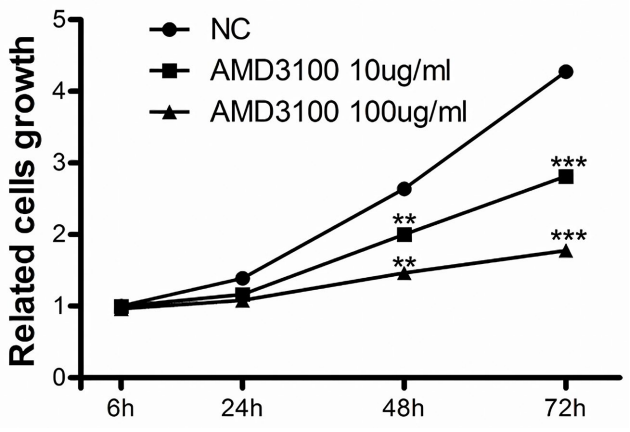

Figure 2. Effect of AMD3100 on the proliferation of OVCAR3 cells (**$P < 0.001$; ***$P < 0.0001$ compared with control group).

3.3. The Clone Formation Ability Experimental Detection of the Effect of Ovarian Cancer Cell Clone Formation after AMD3100

In AMD3100 100 μg/mL and AMD3100 10 μg/mL groups, cell clone forming ability was significantly inhibited compared with control group ($P < 0.0001$) in a concentration-dependent manner. AMD3100 10 ug/ml group and AMD3100 group compared to 100 ug/ml cell clone formation was significantly reduced, the difference was statistically significant ($P = 0.0012$; Figure 3).

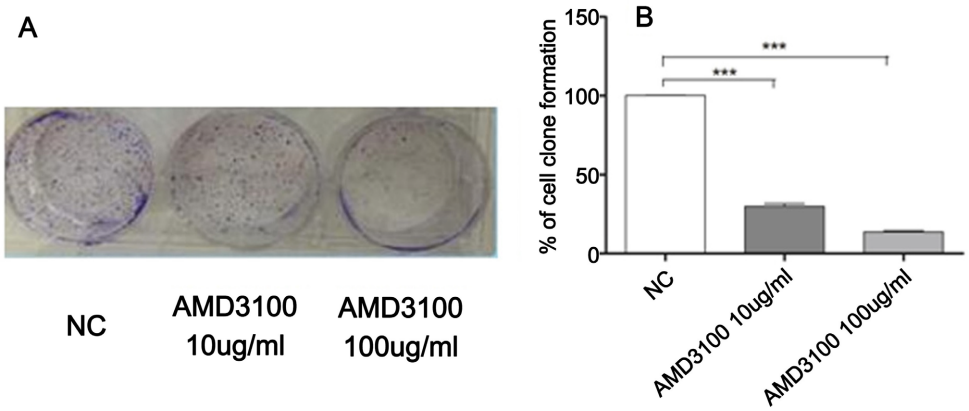

Figure 3. Effect of AMD3100 on ovarian cancer cell clone forming ability of the 3. (A) The ability of cell clone formation; (B) The number of colony-forming cells (***$P < 0.0001$).

3.4. Transwell Assay Was Used to Detect Different Concentrations of AMD3100 after Treatment Detects the Effect on Invasion of Ovarian Cancer Cells

After the addition of 10 or 100 μg/mL AMD3100, cell invasion and metastasis significantly decreased compared with control group ($P < 0.0001$; Figure 4), whereas AMD3100 10 μg/mL and AMD3100 100 μg/mL groups showed no significant difference ($P = 0.0645$).

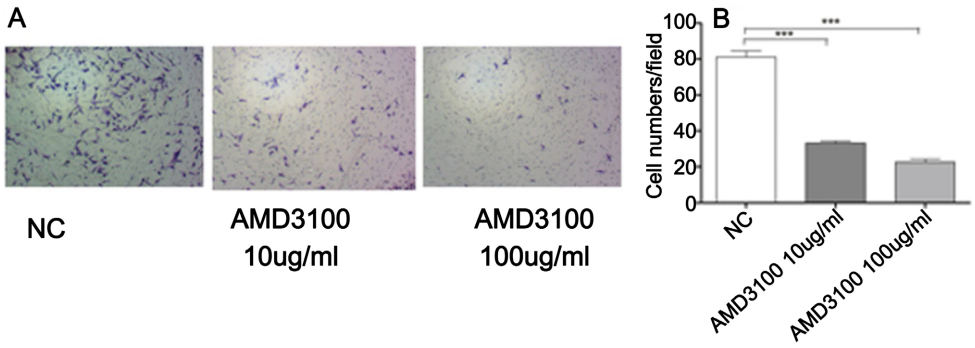

Figure 4. Effect of various concentrations of AMD3100 on the invasion of ovarian cancer cells. (A) Cell invasion assay (HE ×200); (B) The number of cell invasions (***$P < 0.0001$).

3.5. The Expression of CXCR4 with Various Concentrations of AMD3100 after Western Blot

Western blot analysis showed that the expression of CXCR4 in ovarian cancer

cells was high. After the addition of 10 or 100 μg/mL AMD3100 in experimental group, the expression of CXCR4 was significantly inhibited ($P < 0.0001$) in a concentration-dependent manner ($P = 0.004$; Figure 5) compared with control group.

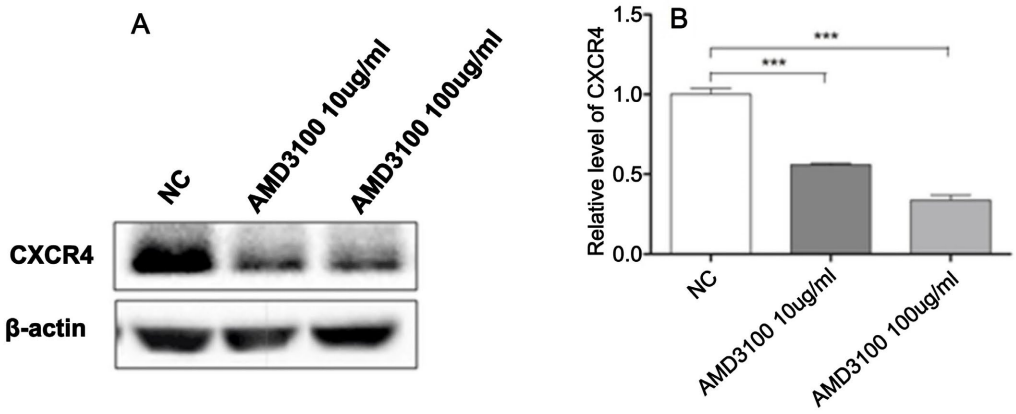

Figure 5. Different concentrations of AMD3100 after the detection of EMT-related markers expression. (A) western blot; (B, C, D) semi-quantitative analysis (*$P < 0.01$; **$P < 0.001$; ***$P < 0.0001$ compared with the other two groups).

4. Discussion

Ovarian cancer is the leading cause of cancer-related deaths worldwide. The clinical prognosis is poor for patients with metastatic disease, with the 5-year survival rate being only 30% [10]. Several studies show that CXCR4 is the only chemokine receptor expressed in ovarian cancer, described in most tumours. It is closely related to the ascites disease progression and metastasis [11]. Chemokines and their receptors play an essential role in cell invasion and metastasis in ovarian cancer. These chemokine receptors can promote tumour growth. Tumour angiogenesis is closely related to formation and metastasis [12]. The aetiology of ovarian cancer is not clear. Despite continuous advances in the technology of surgery and chemotherapy, most of the patients with advanced ovarian cancer face recurrence and progression after treatment. Therefore, the pathogenesis of ovarian cancer and its prognostic factors need to be further clarified to improve the effectiveness of treatment of ovarian cancer and survival.

CXCR4 is a G-protein-coupled receptor, which plays a vital role in the blood vessels, haematopoiesis, and nervous and immune functions [13]. It specifically forms the SDF-1/CXCR4 axis with its ligand SDF-1. Upon activation, this axis mediates various biological behaviors of tumor cells through multiple signaling pathways, including regulating tumor cell proliferation, invasion, and metastasis processes. In the study of endometrial carcinoma in the experiment, siRNA on the role of endometrial carcinoma Ishikawa cells, the expression of CXCR4 mRNA decreased. This showed that the SDF-1/CXCR4 biological axis could enhance tumour invasion and metastasis [4]. The study on endocrine function and epithelial ovarian cancer showed that endocrine disruptors at the physiological level by activating ER and CXCL12-CXCR4 signalling axis hormone enhance the growth

of the ovarian cancer cell line [14]. AMD3100 is a synthetic macrolide specific antagonist of CXCR4, transferred through interaction with signal blocking CXCL12/CXCR4 signalling axis, thereby inhibiting the tumour invasion and metastasis. At the same time, it can be mobilised into the peripheral circulation of some tumour cells in the tumour microenvironment to cause damage. To increase the sensitivity of tumour cells to cytotoxic drugs, promote apoptosis of tumour cells and [15] here. In EMT, epithelial cells lose their polarity and turn into mesenchymal cells, promoting the biological process of invasion and migration. Tumour invasion and metastasis have been extensively studied. Its biological process plays a key role in embryonic development and wound healing. EMT-reactivation can promote tumour development, such as cancer cell migration, invasion, metastasis, and anti-apoptosis resistance [16]. The occurrence of EMT is regulated by the intracellular signal transduction pathway. TGF-B is a regulator of various life activities such as cell proliferation, migration, and apoptosis. The incidence of EMT induced by the SAMD pathway, thereby promoting tumour metastasis [17]. EMT gives characteristics of migration and invasion to the cells and makes tumour cells have the characteristics of stem cells to encourage the production of CSCs, drug resistance, and tumour recurrence [18]. To further understand the role of CXCR4 in ovarian cancer through EMT, we first examined the benign ovarian tissue, the expression of CXCR4 and ovarian cancer cell OVCAR3 CXCR4 and EMT protein in ovarian carcinoma. We found that EOC tissues and cell lines had a high expression of CXCR4. Low or no expression of CXCR4 in benign ovarian tissue was negatively correlated with E-cadherin, Vimentin and Snail expression, which were positively related to relationship analysis of CXCR4, and the clinicopathological features found. The high expression of CXCR4 EOC in ovarian cancer and age, with tumour grade, FIGO staging, lymph node metastasis and ascites metastasis that CXCR4 and EMT play essential roles in carcinogenesis [19]. MTT results showed that with the increase in AMD3100 concentration, cell proliferation was significantly inhibited. CXCR4 played a role in the proliferation of ovarian cancer cells.

The colony-forming ability and transwell experimental results showed that the clone formation ability and invasion ability decreased with the increasing AMD3100 concentration. Therefore, CXCR4 could promote the invasion ability of ovarian cancer cells. In addition, found in the study of related mechanisms in rectal cancer, The expressions of CXCR4 and beta-catenin in colorectal carcinoma, And the high expression of CXCR4 and E-cadherin, N-cadherin, vimentin is closely related, shows that the SDF-1/CXCR4 axis can occur through the regulation of EMT wnt/β-catenin signalling pathway, Promote the metastasis of colorectal cancer invasion [20]. Western blot analysis showed that after AMD3100 treatment, the expression of E-cadherin increased with CXCR4 expression. The expression of Vimentin and Snail was reduced with the reduced expression of CXCR4. In ovarian cancer, CXCR4 can be adjusted by the expression of EMT. To promote the occurrence and development of ovarian cancer cells and ovarian cancer cell invasion

and metastasis play a significant role.

This study suggested that the treatment by targeting the blocking effect on the expression of EMT-related proteins, detected by CXCR4 in ovarian cancer cells, contributes to ovarian cancer. This provided a new target for the treatment of ovarian cancer. CXCR4 is an essential factor in regulating ovarian cancer invasion and metastasis; however, there may be other factors regulating the invasion and metastasis of ovarian cancer. Therefore, further studies are warranted on the mechanism of action of CXCR4 in ovarian cancer and other tumours and their treatment.

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Author Contributions

Conceptualization, Z.D. and W.J.J.; methodology, C.Y.X.; software, W.F.; validation, W.F., Z.Q.Z. and W.F.; formal analysis, C.Y.X.; investigation, W.J.J.; resources, W.J.J.; data curation, W.J.J.; writing—original draft preparation, W.F.; writing—review and editing, W.F.; W.J.J. visualization, W.J.J.; supervision, W.J.J.; project administration, Z.D.; funding acquisition, Y.Y. All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Ethical Approval

Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the Ethics Committee of Guizhou Medical University (ethical code: No.81860460).

Informed Consent

Informed consent was obtained from all individuals included in this study.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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