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Review Article

The New Trends in Ovarian Cancer and the Effect of Chemokine as a Therapeutic Target

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Abstract

Ovarian cancer is one of the highest fatal case ratios recorded in gynecological cancers. It is the fourth among female malignancies and the common cause of death of women with cancers of gynecological origin. Early stage ovarian cancer is more likely treatable solid tumors that respond to surgery and cytotoxic agents, mainly when the disease is still confined within the ovary. The inflammation of the female peritoneum associated with ovarian micro-metastases and stromal invasion has been subjected to elevated interleukin-8 (IL-8) expression. However, the up-regulation of tumor-regulated IL-6, IL-8 and IL-1 β are related to inflammatory networking, angiogenesis, promotion of tumor genesis and metastasis in cancers. Chemokine (CXC motif) promotes angiogenesis via interaction with epithelial cells of ovarian cancer (EOC), and tumor-derived vascular endothelial growth factor revealed to also encourage angiogenesis. Chemokine ligand 1 (CXCL1) is a small cytokine belonging to the CXC chemokine family that binds and activate the G-Protein-coupled receptor (GPCR). The phosphatidylinositol 3-kinase (PI3-K) signaling pathway is activated in EOC to increase the rate of cell survival and proliferation of several components. Our studies show that chemokine receptor-specific monoclonal antibodies can be used as a potential targeted therapy such as CXCR5 etc. has been developed for an effective treatment for cancer. We, therefore, confirmed that blocking CXCR4/CXCL12 pathways will serve as a potential therapy for patients with ovarian cancer.

Keywords: *Epithelial Ovarian Cancer; Targeting Therapy; Cytokines and Chemokine; GPCRs; Gynecology*

Introduction

G-protein-coupled receptor (GPCR) is the largest family classes of protein found in the human genome. The specific physiological function of GPCR is the regulation of chemosensation and neurotransmission. However, GPCR maintains its characteristics effects by acting as guanine nucleotide exchanges (GEFs) on G protein α subunit via translation of extracellular stimuli into intracellular signal cascades. It was reported as having an important role in ovarian cancer [1]. Ovarian cancer was recognized as the most treated solid tumors because the majority is able to respond temporarily to surgery and cytotoxic agents, and also known for its ability to frequent persistence and reoccurrences. It is one of the highest fatal cases of cancers recorded among gynecological cancers, and it represents fourth of the malignancies of the female genital tract but common cause of death in those women with cancers of gynecological origin. Ovarian cancer carcinomas represent the 4% of all woman having cancer in the United State, accounting very close to malignant neoplasms of the breast,

colon uterus and lung [2]. In 2009, epithelial ovarian cancer is the most lethal gynecologic malignancy among women in the United States, while other countries account 22,000 new cases of approximately 15,000 deaths. Moreover, 90% of ovarian cancer patients diagnosed at an early stage are prone to survive [3]. Ovarian cancer is the second most common gynecological cancer and regards as one of the highest mortality gynecological cancers. This is due to aggressive but asymptomatic progression of cancer cells in the peritoneal cavity, which accounts more than 70% of patients diagnosed with the advance or metastatic stage. The endocrine hormones can be classified into three superfamilies; such as GPCRs, nuclear receptors and cytokine receptors that are responsible for the development of malignant gynecological neoplasms, and which fertility drugs or androgens can act upon. Some hormones play a vital role in the replacement therapies and been recognized as a risk factor for gynecological cancers. The physiological function of an ovary is regulated by the reproductive hormones and receptors of the HPG axis. The receptor signaling cascades were found not only in the ovary but also in ovarian tumors which suggest that ovarian cancer development is connected with deregulated hormone cancer cells [4]. Autocrine and paracrine loop in the epithelial ovarian cancer (EOC) regarded as the most lethal gynecological malignancy can mediate the aberrant activation of GPCR endothelin (ETAR) by endothelin-1 (ET-1). Pleiotropic activities aids in function which includes survival, migration, invadopodia formation, cell proliferation, chemoresistance, epithelial-mesenchymal transition (EMT), neovascularization, and this was achieved via the activation of different signaling as a result of the cell to cell communication. On the other hand, aberrant activation of autocrine and paracrine signaling by ET-1 binding to its receptors were reported as to regulate pleiotropic functions such as the dynamic interactions between the tumor cells and the host microenvironment so as to stimulate metastatic dissemination [5]. Receptors of hormones, chemokines, neuropeptides, neurotransmitters, autocrine and paracrine signaling molecules have the ability to interact with heterotrimeric G proteins to perform functions on target cells and these receptors can be regarded as GPCRs. Heterotrimeric G protein is made up of α-subunit capable of binding and hydrolyzing guanosine-5 triphosphate (GTP), β- or γ- subunits to form an indissociable complex. It was also learnt that GPCRs carries extracellular signals into the cell by binding and activating different intracellular signaling proteins known as G protein (Gβγ with family members called Gi, Gs, Gq/11, G12/13) or arrestins [6] which are selectively associated with ligand activation to initiate a potential downstream signaling pathway [7]. The paracrine interactions between chemokines produced by the ovarian cancer cells and chemokine receptors expressed by the endothelial cells have been shown to stimulate angiogenesis. Angiogenesis stimulation is one of the popular features of ovarian carcinoma whereby the growing peritoneal metastasis requires constant oxygen and nutrients supply to be able to promote their fastest growth. Chemokines receptors are made up of two receptors known as CXCR1 and CXCR2 receptors expressed by the endothelial cells, and they are responsible for mediating angiogenesis response. However, stromal cells in the tumor microenvironment are the major factor for regulation of malignant phenotype and their mechanism mediated by the chemokine-receptor network. The primary tumor cells are responsible for the production of cytokine lymphotoxin thereby releasing chemokine CXCL11 from the neighbouring stromal fibroblast [8].

It was reported that the mechanisms of action of GPCR inhibitory effect on cellular activities such as cell proliferation and migration are still unknown. This suggests that the activation of somatostatin receptor 2 was a well recognize inhibitory action on tumor growth [9]. GPCRs has better characteristics such as regulation of several parts of tumorigenesis and many cancer-associated signaling pathways, and for the fact that only a few drugs may be capable to inhibit GPCR is currently used in cancer. GPCRs have been modified in cancer through the genome-wide major analysis of multiple human tumors and could be a potential candidate for cancer drug development, which is very imperative to differentiate between cancer driver genes and bystanders to identify a vital target for personalizes medicine in time to come [7]. It has been shown that heterogeneity of human ovarian cancers with respect to infiltration by immune effectors especially T cells, leads to speculation that ovarian cancer activity in antigen-specific immune response results in killing tumor cells and blocks growth. According to report, the effector T cells associated with ovarian cancers were specific for antigens over expressed in a tumor from Ioannidis and colleagues [10]. Most GPCRs initiate stimulatory effects on cell adhesion, proliferation, migration and invasion, and their mechanism is well studied. Some other GPCR mediates inhibitory effects on cellular activity such as cell proliferation and migration with their mechanism is not yet understood, whereas the activation of somatostatin receptor 2 has a well-documented inhibitory action on tumor growth [9]. Many findings have claimed that the development, progression and responsiveness to treatments in most tumors are

discovered as a result of an imbalance in the stimulatory and inhibitory neurotransmission. Therefore, neurotransmitters adrenaline and noradrenaline plays a very important role in regulating various cellular and tissue functions and promotes tumor growth and metastases through the β-adrenergic receptors (β-AR) which can also be regarded as G-protein-coupled receptors. However, noradrenaline stimulates tumor progression in diverse types of malignancies activating β-AR induces the production of VEGF, interleukin-6 (IL-6) and matrix metalloproteinase [11]. Inflammatory cytokines known as CXCL1 and CXCL8 can enhance tumors cell proliferation and has effects on angiogenesis. The production of these cytokines can be induced by the mutated human cancer oncogene Ras and oncogenic components of the EGFR-Ras-Raf signaling pathway [12].

The effect of chemokine in ovarian cancer

Cancers communicate with a wide diverse stromal microenvironment composed of endothelial, mesenchymal, immunoregulatory and hematopoietic cells to speed up tumor growth and progression [13]. Chemokines are based on the structural classification and group of four families; C, CC, CXC and CX3C depending on the location of cysteine residues near their amino-terminal. It was revealed that most of the chemokine receptor belongs to CC and CXC subgroups. The CXC chemokine ligands were further classified based on the presence or absence of 3 amino acid sequences and glutamic acid-leucine-arginine [14]. Chemokine has three basic characteristics known as small, secreted peptide which controls adhesion and transendothelial migration of leukocytes mainly during inflammatory and immune reactions. The chemokine has NH2-terminal cysteine residues and binds to seven transmembrane domain G protein-coupled receptors. It was also reported that there are two major subfamilies designed as CCR and CXCR. There is no doubt that tumor-derived chemokine regulate the infiltration of cancers by host cells [15]. The chemokine receptors such as CXCR1 and CXCR2 have been reported to play a vital role in the survival of an endothelial cell, angiogenesis and proliferation and IL-8, and GRO-α has potentials in inducing endothelial cell proliferation. The IL-8 and GRO-α effects on endothelial cell proliferation were blocked completely by the CXCR1 and CXCR2 palmitoylated Pepducin (X1/2 pali3 Pepducin) found in the third intracellular loop of the CXCR1 and CXCR2 chemokine receptors [16]. Chemokine is expressed in the cell of tumor microenvironment which is able to immune infiltrate in a tumor and this chemokine is known as CC subfamily and CCL2. According to studies, it is the most expressed in the ovarian cancer histotypes and it reported to be involved in the macrophage recruitment. However, the expression of CCL2 and CCL5 in the epithelial ovarian cancer cell shows a relationship between the existences of CCL2 with immune infiltration. Chemokine system is one of the major signaling pathways in ovarian cancer growth, development and diffusion. This shows that there is complex chemokine network including the autocrine/paracrine mechanism that is essential to the biology of ovarian cells [17]. Bar-Shavit., *et al*. reported that one of the families of the GPCRs that are closely linked to tumor metastasis is the chemokine receptors. The chemokine initiates the motility and survival of cancer cells in the vicinity and milieu of a tumor as a result of the release of paracrine and autocrine into the microenvironment of tumor-surrounding regions, as chemokine were confirmed to be involved in metastatic cancer cell homing. The local chemokine in the tumor milieu may recruits macrophages and leukocytes that can be able to induce the release of matrix metalloproteases (MMPs) encouraging tumor cell survival, invasion and growth, thereby improving the cytokine-rich microenvironment [7]. According to studies, Chemokine has demonstrated a major role in tumor growth as it can activate MAPK/ERK signaling pathway and it also promotes cell proliferation. This class of chemokine (CXCL12) is involved in several cancers especially in ovarian cancer [18]. The biological characteristics of individual eotaxin receptors are yet not been investigated in the ovarian cancer cell. However, CCL11 was reported to have responsibilities in ovarian carcinoma cell such as chemotactic and proliferation was likely to be initiated by CCR2,35 receptors that could cause proliferation and migration/invasion [19]. According to Granot., *et al*. CCL2 plays a major role in early stage of tumor development in which its function is by acting as anti-tumor [20]. Table 1, shows the expressional characteristics of chemokine in the ovarian cancer treatment.

Chemokine Receptor	Expression mechanism	Function	Reference
CXCR1	Endothelial cell	It helps in endothelial survival, proliferation and angiogenesis	(Agarwal Tressel., *et al*. 2010)
CXCR2	Endothelial cell	It controls the endothelial survival, proliferation and angiogenesis.	(Agarwal, Tressel., *et al*. 2010)
CXC4 antagonist	Monocytic MDSCs	It controls the migration of tumour-isolated MDSCs effectively in the ovarian cancer environment	(Obermajer Muthuswamy., *et al*. 2011)
CXCL12	Epithelial cell	High level of CXCL12 represents a negative prognostic factor of ovarian cancer patients.	(Obermajer Muthuswamy., *et al*. 2011)
$CXCL_{12}/CXCR_4$	Signaling	It stimulates tumour growth and migration/ invasion of ovarian cancer	(Levina Nolen., *et al*. 2009)
$CCLL_{11}$	Epithelial cell	It plays a major role in stimulating proliferation and migration/invasion in both ovarian carcinoma cell lines	(Levina Nolen., *et al.* 2009)
$CXCL9/CXCL_{10}$	Endothelial cell	It inhibits endothelial cell migration and cell migration	(Rainczuk Rao., *et al.* 2012)
CCL_2	Epithelial cells	It promotes and suppress tumourigenicity	(Wojnarowicz Gambaro., *et al*. 2012)
CX_3CL1	Epithelial cell	It occurs in malignant ascites with higher level of expression in the CD326+	(Gaudin Nasreddine., *et al*. 2011)

Table 1: *Shows the expressional characteristics of chemokine in the ovarian cancer treatment.*

The significant of Chemokine and cytokines in the epithelial ovarian cancer

The inflammation of the female peritoneum associated with ovarian micrometastases and stromal invasion has been subjected to elevate expression of interleukin-8 (IL-8). Interleukin 8 is known as a chemokine produced by macrophages and cell types like smooth muscle cells, endothelial cells and epithelial cells. The up-regulation of a tumor regulates IL-6, IL-8 and IL-1 β is related to the inflammatory networking, angiogenesis, promotion of tumorigenesis and metastasis in cancers such as pancreas, prostate and breast cancer. Schauer., *et al*. reported that several stromal-activating chemokines known as IL-6, IL-8 and growth-regulated oncogene α (GRO- α) are elevated in transformed and neoplastic ovarian surface epithelial cells [3]. Chemokine functions very well in the immune system and it was confirmed that it has the ability to mediate leukocyte migration. Moreover, chemokine and cognate receptors play a very vital role in tumor initiation and progression such as attraction of leukocytes, angiogenesis, induction of cells migration and homing in metastatic sites. Researchers first explained that angiogenesis chemokine, CXCL/IL-8 can bind to CXCR1 and CXCR2. It is secreted by several normal and tumor cells that are exposed to pro-inflammatory cytokines such as IL- and TNF- α. The CXCR2 were proved to be associated with multiple signaling pathways involved in tumorigenesis, proliferation, angiogenesis and metastasizes in many malignancies such as pancreatic, lungs, melanoma, gastric and ovarian cancer. The overexpression of CXCR2 causes the aggressive phenotype of melanoma cells which can induce proliferation, migration and tumor growth in mice [11]. Chemokine promotes angiogenesis by interaction with epithelial cells because in EOC, the tumor-derived vascular endothelial growth factor which promotes angiogenesis. Chemokine may be mediated by transcriptional activity and post-translation regulation. It was believed that certain chemokine may promote an inflammatory microenvironment for tumor initiation, growth, angiogenesis, progression and metastasis while others may suppress tumor proliferation by promoting antitumor immunity [21].

The potentiality of cytokine used for the diagnostic and prognostic marker in ovarian cancer and determining the immune response profile where differentiation and proliferation result in response to the production of certain cytokines that is capable of contributing to the induction of apoptosis and tumor regression control. The development of cancer may indicate the failure of the immune response known as tumor escape mechanism. Moreover, tumor cells undergo various mechanisms that enable them to overcome immunodetection and destruction, and this makes the immune response ineffective. Epithelial ovarian cancer appears to be associated with inflammation and growth, differentiation, and signaling of these tumors appears to be regulated by cytokines. The growth and progression of ovarian cancer carcinoma may be due to local cytokine-induced immunosuppression which allows tumor development as an escape mechanism [22]. Cytokine has low molecular weight (< 80 kDa) peptide cell regulatory factors that produce variety range of effect on different cell population. Reports have shown that some cytokines can directly or indirectly inhibit tumor growth and it has been used in cancer therapy. The inappropriate cytokine activity has resulted in the pathogenesis effects in infectious, autoimmune disease, inflammatory and it has shown that there is evidence of rising rate of cytokine production by a tumor which contributes to the pathophysiology of cancer. Interleukin-6 as an example has been revealed to be an autocrine growth factor in myeloma and overproduction of IL-6 causes the systemic symptoms and the immunological abnormalities in Castleman's disease. The production of several cytokines by human ovarian cancer cell lines and fresh tumor biopsy material provides that TNF mRNA and protein is expressed by ovarian tumor cells in biopsies from patients with epithelial ovarian cancer. Moreover, the damage that occurs during ovulation could lead to the local release of cytokines called TNF and TGF- β by host macrophage and it contributes to the healing fibrotic response. This cytokine has the ability to induce metalloproteinase production by tumor cells, which increases the invasive potentials [23].

Chemokine as a targeting therapy for ovarian cancer treatment

The recent development of CXC chemokine signaling has played a very vital role in the reduction of morbidity and mortality associated with epithelial ovarian cancer. This involves the stimulation of Th17 cells via the use of vaccines or immunotherapy to stimulate 1L17 resulting in elevated CXCL9 and CXCL10 levels. The use of CXC chemokine inhibitors and antagonists for a variety of different cancers such as epithelial ovarian cancer has confirmed to the most promising strategy for new treatment [24]. CXCL1 was found to induce EOC cell proliferation and this occurs through CXCR2 activation, and we, however, found that CXCL1 has a potential therapeutic target for epithelial ovarian cancer. CXCL1 popularly known as melanoma growth stimulating activity or Gro- α is a member of the CXC chemokine family that binds to and activates the G-Protein-coupled receptor (GPCR). The phosphatidylinositol 3-kinase (PI3-K) signaling pathway is activated in EOC and several components are increased in cell survival and proliferation [25]. The effects of signaling pathways of CCL25/CCR9 in

cancer chemoresistance and tumor metastasis through P13K/AKT (chemoresistance) and MMPs (tumor metastasis) in ovarian cancer have been reported. Several studies have been done and were able to develop a chemokine receptor-specific monoclonal antibodies as a potential targeted therapy based on the vital roles of chemokine and their receptor such as CXCR5, CCR7, CCR4 and CXCR4 in cancer. CCR9-based targeted therapy involves an immunotoxin-CCL25 combination that has a small molecular weight and a high specificity and was reported that its chemotactic ability to target cells makes it useful in the targeted therapy of CCR9+ malignant cancers with good prospects for application [26]. Chemokine stromal cell-derived factor-1 generally known as CXCL12 and its receptors CXCR4 are the major key players that determine tumor initiation, metastasis and initiation in ovarian carcinomas. It is confirmed that blocking the CXCR4/CXCL12 pathways will serve as a potential therapy for patients with ovarian cancer. Nevertheless, the role of CXCR4/CXCL12 axis in regulating ovarian cancer progression was investigated and the result shows that the chemokine receptor CXCR4 protein and mRNA were overexpressed in human epithelial ovarian cancer cell lines and they were closely correlated with poor outcomes [27]. CXCL12-CXCLR4 signaling promotes multiple steps in proliferation and dissemination of ovarian cancer and this predicts that targeted inhibition of this pathway will limit tumor progression. Ray., *et al*. also investigated CXCL12-CXCLR4 signaling in ovarian cancer using Gaussia luciferase complementation imaging reporter system to detect the CXCL12 binding to CXCR4 in the ovarian cancer cell and he provides that the complementation imaging could detect CXCL12 binding to CXCR4 and quantify specific inhibition of ligand-receptor interaction. Chemokine CXCL12 and its receptor CXCR4 is strongly becoming the promising therapeutic target in ovarian cancer. CXCL12-CXCLR4 signaling has revealed to regulate metastasis of over 20 different cancers. The expression of CXCR4 in ovarian cancer and levels of CXCL12 in ascites both increase progressively with higher stages of disease suggesting that CXCL12- CXCLR4 signaling may contribute to tumor growth and dissemination [28].

Conclusion

Chemokine receptor is one of the families of the GPCRs that are closely linked to tumor metastasis. Chemokine initiates the motility and survival of cancer cells in the vicinity and milieu of a tumor as a result of the release of paracrine and autocrine into the microenvironment of tumor-surrounding regions. It was confirmed that chemokine is involved in metastatic cancer cell homing. The CXCR2 were proved to be associated with multiple signaling pathways involved in tumorigenesis, proliferation, angiogenesis and metastasis in many malignancies such as pancreatic, lungs, melanoma, gastric and ovarian cancer. Our studies showed that some cytokines can directly or indirectly inhibit tumor growth and it has been used in cancer therapy. However, inappropriate cytokine activity has resulted in the pathogenesis effects of infectious, autoimmune disease, inflammatory and there is evidence of rising rate of cytokine production by a tumor which contributes to the pathophysiology of cancer. This review agreed with the report that demonstrated the use of CXC chemokine inhibitors and antagonists for a variety of different cancers (epithelial ovarian cancer) as the most promising strategy for new treatment.

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DA contributed in designing and writing of the manuscript and HO participated in coordinating and editing of the manuscript while GR and UE participated in designing and coordinating the manuscripts. All authors in this review have read and agreed with the contents of the final manuscript.

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All authors declare no conflict of interest.

Bibliography

1. Hayes MP and DL Roman. "Regulator of G Protein Signaling 17 as a Negative Modulator of GPCR Signaling in Multiple Human Cancers". *The AAPS Journal* 18.3 (2016): 550-559.

2. Berek JS and RC Bast Jr. Epithelial ovarian cancer (2003).

3. Schauer IG., *et al*. "Cancer-associated fibroblasts and their putative role in potentiating the initiation and development of epithelial ovarian cancer". *Neoplasia* 13.5 (2011): 393-405.

4. Zhang Q., *et al*. "The role of endocrine G protein-coupled receptors in ovarian cancer progression". *Frontiers in Endocrinology* 8 (2017): 66.

5. Cianfrocca R., *et al*. "Nuclear β-arrestin1 is a critical cofactor of hypoxia-inducible factor-1α signaling in endothelin-1-induced ovarian tumor progression". *Oncotarget* 7.14 (2016): 17790-17804.

6. Zhang L and G Shi. "Gq-Coupled Receptors in Autoimmunity". *Journal of Immunology Research* (2016).

7. Bar-Shavit R., *et al*. "G protein-coupled receptors in cancer". *International Journal of Molecular Sciences* 17.8 (2016): E1320.

8. Muralidhar GG and MV Barbolina. "Chemokine receptors in epithelial ovarian cancer". *International Journal of Molecular Sciences* 15.1 (2013): 361-376.

9. Li J., *et al*. "Ovarian cancer G protein coupled receptor 1 suppresses cell migration of MCF7 breast cancer cells via a Gα 12/13-Rho-Rac1 pathway". *Journal of Molecular Signaling* 8.1 (2013): 6.

10. Preston CC., *et al*. "Immunity and immune suppression in human ovarian cancer". *Immunotherapy* 3.4 (2011): 539-556.

11. Lappano R and M Maggiolini. "GPCRs and cancer". *Acta Pharmacologica Sinica* 33.3 (2012): 351-362.

12. Cardona SM., *et al*. "The fine balance of chemokines during disease: trafficking, inflammation, and homeostasis". *Chemokines: Methods and Protocols* 1013 (2013): 1-16.

13. Schauer IG., *et al*. "Interleukin-1β promotes ovarian tumorigenesis through a p53/NF-κB-mediated inflammatory response in stromal fibroblasts". *Neoplasia* 15.4 (2013): 409IN14-420IN18.

14. Keeley EC., *et al*. "Chemokines as mediators of tumor angiogenesis and neovascularization". *Experimental Cell Research* 317.5 (2011): 685-690.

15. Scotton CJ., *et al*. "Multiple actions of the chemokine CXCL12 on epithelial tumor cells in human ovarian cancer". *Cancer Research* 62.20 (2002): 5930-5938.

16. Agarwal A., *et al*. "Identification of a metalloprotease-chemokine signaling system in the ovarian cancer microenvironment: implications for antiangiogenic therapy". *Cancer Research* 70.14 (2010): 5880-5890.

17. Barbieri F., *et al*. "Role of chemokine network in the development and progression of ovarian cancer: a potential novel pharmacological target". *Journal of Oncology* (2010).

18. Sarvaiya PJ., *et al*. "Chemokines in tumor progression and metastasis". *Oncotarget* 4.12 (2013): 2171.

19. Levina V., *et al*. "Role of eotaxin-1 signaling in ovarian cancer". *Clinical Cancer Research* 15.8 (2009): 2647-2656.

20. Wojnarowicz P., *et al*. "Overexpressing the CCL2 chemokine in an epithelial ovarian cancer cell line results in latency of in vivo tumourigenicity". *Oncogenesis* 1.9 (2012): e27.

21. Zhu Q., *et al*. "The expression of Duffy antigen receptor for chemokines by epithelial ovarian cancer decreases growth potential". *Oncology Letters* 13.6 (2017): 4302-4306.

22. Jammal MP., *et al*. "Cytokines and Prognostic Factors in Epithelial Ovarian Cancer". *Clinical Medicine Insights Oncology* 10 (2016): 71-76.

23. Malik S and F Balkwill. "Epithelial ovarian cancer: a cytokine propelled disease?" *British Journal of Cancer* 64.4 (1991): 617-620.

24. Rainczuk A., *et al*. "The emerging role of CXC chemokines in epithelial ovarian cancer". *Reproduction* 144.3 (2012): 303-317.

25. Bolitho C., *et al*. "The chemokine CXCL1 induces proliferation in epithelial ovarian cancer cells by transactivation of the epidermal growth factor receptor". *Endocrine-Related Cancer* 17.4 (2010): 929-940.

26. Tu Z., *et al*. "CCR9 in cancer: oncogenic role and therapeutic targeting". *Journal of Hematology and Oncology* 9.1 (2016): 10.

27. Mao T., *et al*. "Targeting the CXCR4/CXCL12 axis in treating epithelial ovarian cancer". *Gene Therapy* 24.10 (2017): 621-629.

28. Ray P., *et al*. "Noninvasive imaging reveals inhibition of ovarian cancer by targeting CXCL12-CXCR4". *Neoplasia* 13.12 (2011): 1152-1161.

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