World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i7.1681

World J Gastroenterol 2014 February 21; 20(7): 1681-1693
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (8): Gastric cancer

CXC chemokines and chemokine receptors in gastric cancer: From basic findings towards therapeutic targeting

Hyo Jin Lee, Ik-Chan Song, Hwan-Jung Yun, Deog-Yeon Jo, Samyong Kim

Hyo Jin Lee, Hwan-Jung Yun, Deog-Yeon Jo, Samyong Kim, Division of Hematology/Oncology, Department of Internal Medicine, School of Medicine Chungnam National University and Chungnam National University Hospital, Daejeon 301-721, South Korea
Hyo Jin Lee, Hwan-Jung Yun, Deog-Yeon Jo, Samyong Kim, Cancer Research Institute, Chungnam National University, Daejeon 301-721, South Korea
Ik-Chan Song, Division of Hematology/Oncology, Department of Internal Medicine, Chungnam National University Hospital, Daejeon 301-721, South Korea
Author contributions: Lee HJ, Song IC, Yun HJ, Jo DY and Kim S conceived the study and coordinated literature data; Lee HJ and Jo DY drafted, reviewed and approved the manuscript.
Supported by Basic Science Research Program through the National Research of Korea (NRF) funded by the Ministry of Education, Science and Technology, NRF-2009-0076540, NRF-2009-0067256
Correspondence to: Deog-Yeon Jo, MD, PhD, Division of Hematology/Oncology, Department of Internal Medicine, School of Medicine Chungnam National University and Chungnam National University Hospital, 640 Daesa-dong, Jung-gu, Daejeon 301-721, South Korea. ggufwhd@naver.com
Telephone: +82-42-2807162 Fax: +82-42-2575753
Received: August 23, 2013 Revised: October 1, 2013
Accepted: November 12, 2013
Published online: February 21, 2014

Abstract

Gastric cancer is the fourth most common cancer, and the second-highest cause of cancer-related deaths worldwide. Despite extensive research to identify novel diagnostic and therapeutic agents, patients with advanced gastric cancer suffer from a poor quality of life and poor prognosis, and treatment is dependent mainly on conventional cytotoxic chemotherapy. To improve the quality of life and survival of gastric cancer patients, a better understanding of the underlying molecular pathologies, and their application towards the development of novel targeted therapies, is urgently needed. Chemokines are a group of small proteins associated with cytoskeletal rearrangements, the directional migration of several cell types during development and physiology, and the host immune response *via* interactions with G-protein coupled receptors. There is also growing evidence to suggest that chemokines not only play a role in the immune system, but are also involved in the development and progression of tumors. In gastric cancer, CXC chemokines and chemokine receptors regulate the trafficking of cells in and out of the tumor microenvironment. CXC chemokines and their receptors can also directly influence tumorigenesis by modulating tumor transformation, survival, growth, invasion and metastasis, as well as indirectly by regulating angiogenesis, and tumor-leukocyte interactions. In this review, we will focus on the roles of CXC chemokines and their receptors in the development, progression, and metastasis of gastric tumors, and discuss their therapeutic potential for gastric cancer.

Key words: Chemokine; Chemokine receptor; Gastric neoplasm; Therapeutic target

Core tip: Chemokines were traditionally believed to regulate the directional migration of leukocytes to inflammatory sites. However, it is now clear that chemokines and chemokine receptors also regulate the processes underlying the development and progression of malignant disease. In gastric cancer, CXC chemokines and their receptors directly influence tumorigenesis by modulating tumor transformation, survival, growth, invasion, and metastasis, as well as indirectly by regulating angiogenesis and interactions between tumor and microenvironment. Aim of this review is to discuss the involvement of CXC chemokines and their receptors in the development, progression, and metastasis of gastric cancer and their therapeutic potential.

Lee HJ, Song IC, Yun HJ, Jo DY, Kim S. CXC chemokines and chemokine receptors in gastric cancer: From basic findings towards therapeutic targeting. *World J Gastroenterol* 2014; 20(7): 1681-1693 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i7/1681.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i7.1681

INTRODUCTION

Gastric cancer is the fourth most common cancer and the second-highest cause of cancer-related deaths worldwide although the incidence is decreasing in many developed countries. Approximately 8% of newly diagnosed malignant tumors are gastric cancer, and over 700000 people die from gastric cancer annually[1-3]. Despite intensive research into novel diagnostic and therapeutic interventions, the prognosis of patients with advanced gastric cancer remains poor, and little improvement in survival has been achieved[4]. In recent years, many new advances have enhanced our understanding of the molecular mechanisms and alterations that lead to initiation and progression of gastric cancer, including multiple genetic and molecular alterations and mutations[4-8]. Molecular alterations in gastric carcinogenesis have been identified in *Her-2/neu* (*c-erbB2*)[9-11], *c-Myc*[12,13], semaphorin-5A[14], BCL2-like-12 (*BCL2L12*)[15], *c-MET*[16], and *K-sam*[17], while mutations have been reported in *TP53*[18], adenomatous polyposis coli (*APC*)[19], *K-ras*[20], and E-cadherin[21]. Importantly, the ToGA (Trastuzumab for Gastric Cancer) trial recently demonstrated that the addition of trastuzumab, a monoclonal antibody against Her-2/neu, to conventional chemotherapy significantly improved the survival of patients with advanced gastric or gastro-esophageal junction cancer compared with chemotherapy alone[22]. In spite of these advances, the successful treatment of advanced or metastatic gastric cancer depends predominantly on the response of the tumor to conventional cytotoxic chemotherapy. Understanding the distinct molecular pathways behind the progression and treatment resistance of gastric cancer may therefore lead to novel therapeutic opportunities, and improve the quality of life and overall survival of patients.

Chemokines are a group of small (8-14 kDa) proteins that interact with their cell-surface receptors during development, the host immune response, and other physiological processes, to direct cells to specific sites throughout the body[23,24]. The term chemokines was originally introduced in 1992 as an abbreviated form of chemotactic cytokines, shortly after the characterization of the first chemokine, interleukin-8 (IL-8; also known as CXCL8)[25,26]. Subsequently, chemokines were characterized as a large family of heparin-binding proteins that modulate cell trafficking and the targeting of immune cells[25,27,28]. The chemokine system evolved with vertebrates, and approximately 50 human genes encode chemokine ligands, together with more than 20 chemokine receptor genes, which encode seven-transmembrane G protein-coupled receptors[23,29]. Chemokines are categorized into four major groups (CXC, CC, CX3C or C), depending on the position of their cysteine residues near the N-terminus, in which X represents any amino acid. Most chemokines are in the CXC and CC groups[30-32]. With the exception of the "C" subgroup, all chemokines include a common four-cysteine residue motif linked by disulfide bonds at conserved sites: one between the first and the third Cys, and one between the second and the fourth Cys, leading to the formation of a triple-stranded β-sheet structure. CXC chemokines can be further subclassified based on the presence or absence of a glutamic acid-leucine-arginine (ELR) motif situated before the first conserved cysteine residue (ELR^+ or ELR^-)[32-35].

Chemokines are produced by many cell types, including leukocytes, endothelial cells, fibroblasts, epithelial cells, and tumor cells[32,36]. Recent evidence has revealed that, in addition to their role in the immune system, chemokines and their receptors are also involved in tumor initiation and progression[37,38]. Chemokines bind to the extracellular domain of chemokine receptors, which comprises the N-terminus and extracellular loops. Following activation, the intracellular domains (consisting of three loops and the C-terminus) dissociate from G-proteins, which are composed of three distinct subunits (α, β and γ heterotrimers). This results in the formation of the second messengers inositol triphosphate (IP3) and diacylglycerol (DAG), leading to cytoplasmic calcium mobilization, and the activation of multiple downstream signaling cascades, including the phosphatidylinositol 3-kinase (PI3K)/Akt, Ras/mitogen-activated protein kinase (MAPK), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways[23,25].

In cancer, chemokines and their receptors play a crucial role in the trafficking of cells in and out of the tumor microenvironment, modulating the behavior of the tumor. Chemokines induce directional cell migration, particularly of leukocytes, during inflammation. Prolonged inflammation can facilitate carcinogenesis by providing a favorable microenvironment around the tumor for its growth and development[30,37]. Chemokines can influence tumorigenesis indirectly by regulating angiogenesis and tumor-leukocyte interactions, and directly by modulating tumor transformation, survival, growth, invasion, and metastasis. However, the roles of chemokines and their receptors in tumorigenesis are complex, since some family members promote conditions favorable for tumor growth and progression, while others demonstrate anti-tumor activity[30]. For example, ELR^+ CXC chemokines such as CXCL8 can enhance tumor growth by inducing angiogenesis and the chemoattraction of neutrophilic granulocytes. Neutrophils then further facilitate angiogenesis, tumor growth, and metastasis by releasing matrix-degrading enzymes [such as matrix-metalloprotease (MMP)-9] and angiogenic tumor-promoting factors such as vascular endothelial growth factor (VEGF)[30,39-41]. In contrast, ELR^- CXC chemokines such as interferon-γ inducible protein-10 (IP-10; also known as CXCL10) are angiostatic factors, and attract

anti-tumoral lymphocytes by binding to CXCR3. Stromal cell-derived factor-1 (SDF-1; also known as CXCL12) is an exception to this characterization, since it is an ELR$^-$ chemokine that can mediate angiogenesis *via* its cognate receptor CXCR4[30,37,40,42]. Furthermore, in contrast to the anti-tumoral activities of the CXCR3-binding ELR$^-$ CXC chemokines, these chemokines also promote the metastasis of CXCR3-positive tumor cells to lymph nodes and distant sites[37,43,44]. The balance of chemokines and chemokine receptors within the tumor environment is highly complex, and organ-dependent. In this review we will focus on the involvement of CXC chemokines and their receptors in the development, progression, and metastasis of gastric cancer, and their therapeutic potential.

CXC CHEMOKINES AND THEIR RECEPTORS IN GASTRIC CANCER

CXCL12-CXCR4/CXCR7

CXCR4 is differentially expressed in gastric adenocarcinoma at the transcriptional and protein levels, and in the cell membrane[5,45-59]. The differential expression of CXCR4 in gastric cancer is also identified by gene expression profiling[57,60,61]. In addition, pre-operative circulating CXCR4 mRNA levels in the plasma of patients with gastric cancer are elevated compared with normal controls, but then decrease after surgery[62]. Increased CXCR4 expression in gastric cancer cells is associated with peritoneal carcinomatosis, which occurs frequently and is a major cause of mortality in patients with gastric cancer[47,63-65]. In addition, elevated expression of CXCL12 was detected in peritoneal mesothelial cells, suggesting that CXCR4-positive gastric cancer cells are preferentially attracted to the peritoneum, where high levels of its ligand CXCL12 are produced[47,53]. CXCR4 expression is also associated with aggressive tumor behavior, such as poor differentiation, tumor invasion and metastasis[45,50,54,55,58,66-70], and it could therefore be an independent prognostic marker for the overall survival of patients with gastric cancer[71]. Several studies have revealed that gastric cancer cells also show altered expression of CXCL12. However, the data are controversial, since increased expression of CXCL12 was associated with tumor size, invasion, lymph node metastasis, and poor prognosis[51,68,72-75], but the opposite data have also been reported[76]. Up-regulation of the *CXCL12* gene was demonstrated by cDNA microarrays, while the secretion of CXCL12 was also reported in gastric cancer cells[77-79]. In addition, Schimanski *et al*[80] reported that a CXCL12 (SNP rs1801157) polymorphism of GA/AA was correlated with distant metastasis. The circulating levels of CXCL12 in gastric cancer patients are elevated pre-treatment, and higher in metastatic than non-metastatic patients, suggesting that secretion correlates with the presence of distant metastases[81]. However, the precise mechanism by which tumor-derived CXCL12 contributes to tumor progression is unclear.

CXCL12 may regulate tumorigenesis in an autocrine and/or paracrine manner. The concomitant expression of CXCL12 and its receptor CXCR4 in tumor cells can lead to the autocrine/paracrine stimulation of cancer cells, resulting in aggressive tumor behavior[5,73,82,83]. Subsequently, autocrine/paracrine mitogenic effects of CXCL12 were reported in glioblastoma multiforme, gall bladder cancer, and pituitary tumors[83-86]. Furthermore, immunohistochemical analysis demonstrated that the staining of CXCR4 and CXCL12 in gastric cancer was more prominent and intense in tumor cells at the invasion front and in lymphatic vessels, respectively. Patients with elevated expression of CXCR4 and CXCL12 therefore exhibit significantly poorer surgical outcomes[5,37,45,66,72].

Another possible mechanism by which CXCL12 contributes to tumor progression is by inducing a favorable tumor microenvironment by attracting endothelial cells or recruiting immune suppressive cells to the tumor site, resulting in angiogenesis and immune evasion, respectively[75,86]. Zhuang *et al*[87] recently demonstrated that CD8$^+$ T cells secrete IL-17, which induces gastric cancer cells to produce CXCL12. CXCL12 then recruits myeloid-derived suppressor cells (MDSCs) into the tumor microenvironment in a CXCR4-dependent manner, where MDSCs promote the progression of gastric cancer. In addition, Ingold *et al*[51] reported that the expression of CXCL12 in tumor cells and CXCR4 in the microvessels surrounding the tumor is associated with increased local tumor growth and a more advanced tumor stage, suggesting an important role of the CXCL12-CXCR4 axis in tumor neo-angiogenesis in gastric cancer.

Lastly Shibata *et al*[88] used CXCL12 transgenic mouse models to demonstrate that overexpression of CXCL12 contributed to the early stages of gastric carcinogenesis by recruiting CXCR4-positive mesenchymal stem cells and stimulating the expansion of myofibroblasts in the gastric stem cell niche, leading to increased numbers of epithelial progenitors.

CXCR4 mediates several biological processes in cancer cells such as directional migration, invasion and adhesion, all of which are associated with the aggressive behavior of tumors. The ligation of CXCL12 to CXCR4 activates actin polymerization to induce cell motility[5,89]. In gastric cancer cells, CXCL12 stimulation induced the formation of lamellipodia and filopodia. Within lamellipodia, the condensation of F-actin at the leading edge suggested that stimulation of the cells with CXCL12 resulted in the reorganization of F-actin. In addition, compounds targeting the PI3K/mammalian target of rapamycin (mTOR) pathway inhibited CXCL12/CXCR4-mediated cell migration by preventing F-actin reorganization and lamellipodia formation, and by reducing the expression of GTPases, particularly RhoA[74]. CXCR4 also activates members of the Src family of protein tyrosine kinases, thereby inducing the activation of focal adhesion complexes such as related adhesion focal tyrosine kinase/Pyk2, focal adhesion kinase, Crk and paxillin. CXCR4 also facilitates the adhesion of tumor cells to components of the extracellular matrix *via* integrins[5,90-92]. CXCL12-activated CXCR4 progressively upregulated the expression

of MMP-2 and MMP-7 in gastric cancer cells[5,64], while CXCR4 expression was also correlated with the expression of MMP-7 and MMP-9 in gastric cancer tissue[58]. MMP-7 activates MMP-2 and MMP-9, and plays a central role in the degradation of the extracellular matrix, including type Ⅳ collagen. In addition, MMP-7 expression is related to the transformation of cancer cells, suggesting a possible mechanism by which CXCL12 stimulates the invasion, metastasis, and aggressive behavior of gastric cancer[5,58,93,94].

The binding of CXCL12 to CXCR4 activates a number of intracellular signaling cascades and effector molecules that regulate the proliferation, migration, invasion, and metastasis of cancer cells. The large number of downstream effectors modulated by CXCR4 likely account for the varying effects of the CXCL12-CXCR4 axis in the biology of gastric cancer. However, the roles of the various effectors induced by CXCR4 on the individual gastric cancer processes-such as cell proliferation and adhesion-remains unclear. Nevertheless, identifying downstream effectors of CXCR4 *in vivo* is important to clarify the molecular mechanisms by which CXCR4 promotes gastric cancer[5,92]. CXCL12 interacts with and activates CXCR4, which in turn activates the p110β isoform PI3K, leading to the generation of phosphatidylinositol (3,4,5)-triphosphate, and the phosphorylation of the protein kinase B/Akt and mTOR pathways. Activated mTOR subsequently induces the activation of p70S6K (S6K), and eukaryotic initiation factor 4E binding protein 1 (4E-BP1)[5,47,64,74,95,96]. The treatment of gastric cancer cells with CXCL12 stimulates Akt kinase activity, which leads to the activation of its downstream targets S6K and 4E-BP1. In addition, CXCL12-induced activation of S6K and 4E-BP can be inhibited selectively using the mTOR inhibitor rapamycin[5,47,64,74]. Activated Akt/mTOR signaling leads to the phosphorylation of a variety of intracellular targets (including S6K1 and 4E-BP) that are involved in increased survival and decreased apoptosis in a variety of cancer cells. Akt and mTOR have also been implicated in the effects of CXCR4 on cell proliferation and chemotactic migration, which play a role in cell growth and metastasis[5,47,64]. Accordingly, inhibiting the Akt/mTOR pathway blocked migration and reduced the proliferation of gastric cancer cells. Interestingly, gastric cancer cells expressing high levels of CXCL12 were more sensitive to rapamycin-mediated inhibition of migration and proliferation compared with cells expressing low levels of CXCL12. The correlation between *CXCL12* gene expression profiles and the anti-proliferative activities of rapamycin were confirmed in NCI-60 cells[74].

The MAPK pathway is also modulated by CXCR4. In response to CXCL12, CXCR4 activates mitogen-activated protein kinase kinase, the upstream activator of the p42/44 MAPK [also known as extracellular receptor kinase (ERK)-1/2][5,92]. In gastric cancer cells, treatment with CXCL12 rapidly induced the phosphorylation of MAPK, which could be blocked by AMD3100, a small molecule that specifically inhibits the CXCR4 receptor[5,45,47,95]. Collectively, these data suggest that the activation of MAPK is another mechanism by which CXCR4 may promote the progression of gastric cancer.

The JAK/STAT pathway is involved in the migration and invasion of cancer cells[5,97], and is a third potential pathway by which CXCR4 regulates the growth and progression of gastric cancer. After treatment with CXCL12, JAK kinases associate with CXCR4, leading to the activation of members of the STAT family of transcription factors. In a study using a single gastric cancer cell line, it was reported that CXCR4 signaling is independent of the JAK/STAT pathway. However, the role of this pathway in the biological actions of CXCR4 in gastric cancer remains unclear due to insufficient data[5,45].

Recently, CXCR7 was identified as a novel receptor for CXCL12, which has complicated our understanding of the role of the CXCL12-CXCR4 axis in regulating cancer development and progression[86]. CXCR7 is highly expressed on the surface of malignant cells compared with cells in normal adult tissues. It binds CXCL12 with a high affinity, and exerts various biological effects depending on cell type, either by activating intracellular signaling pathways, or *via* its role as a scavenger-type receptor. Importantly, CXCR7 was implicated in cancer cell growth, survival, and metastasis in various cancers, including breast and lung cancer[98-100]. In gastric cancer, Lee *et al*[101] demonstrated that CXCR7 was differentially expressed in gastric cancer tissues, and that elevated expression of both CXCR7 and CXCL12 in tumor cells correlated with aggressive tumor behavior and poor prognosis. This suggests that additional studies should be carried out to elucidate the role of the CXCL12-CXCR7 axis in gastric carcinogenesis.

CXCL8-CXCR1/CXCR2

Several reports have suggested that gastric cancer cells produce CXCL8 both *in vitro* and *in vivo*[102-107]. The gastric cancer cell lines AGS and KATO Ⅲ secreted CXCL8 following infection with *H. pylori*, which is associated with gastric carcinogenesis[103,108]. The up regulation of CXCL8 was demonstrated in gastric cancer cell lines by gene expression profiling, and in gastric cancer tissue by immunostaining[78,104,109,110]. In addition, the serum levels of circulating CXCL8 were higher in gastric cancer patients than healthy controls[111]. The expression of CXCL8 was associated with increased venous and lymphatic invasion, and increased depth of invasion in gastric cancer[106]. Elevated mRNA and protein expression of CXCL8 is also significantly correlated with tumor vascularization, suggesting that it may play a role in gastric cancer[104,109]. Consistent with these observations, CXCL8 was identified as a strong angiogenic factor in lung, ovarian, and prostate cancer[112-114]. Direct evidence for the role of CXCL8 in the angiogenesis and tumorigenesis of gastric cancer was first provided by Kitadai *et al*[115] who used CXCL8-stably transfected gastric cancer cells to demonstrate angiogenic activity *in vitro*. In addition, the orthotopic implantation of CXCL8-transfected gastric cancer cells into nude mice

in vivo led to the development of rapidly growing and highly vascularized tumors.

CXCL8 also plays a role in the migration, invasion, and adhesion of gastric cancer[116,117]. Ju *et al*[116] treated the human gastric cancer cell line SCG-7901 with recombinant CXCL8, and observed enhanced adhesion to endothelial cells and extracellular matrix components, and increased migration and invasion, possibly by regulating the expression of MMP-9, intracellular adhesion molecule (ICAM)-1, and E-cadherin. Similarly, Kuai *et al*[117] demonstrated that constitutive expression of CXCL8 in MKN45 cells facilitated cell adhesion, migration, and invasion, all of which were inhibited by silencing CXCL8 expression in KATO Ⅲ cells. In addition, they demonstrated that overexpression of CXCL8 increased the expression of the adhesion molecules ICAM-1, vascular cell adhesion molecule-1 and CD44, as well as the activities of activated nuclear factor (NF)-κB and Akt. Finally, CXCL8 decreased the sensitivity of gastric cancer cells to the cytotoxic effects of the chemotherapy agent oxaliplatin.

Polymorphisms of the CXCL8 251 allele have also been linked to gastric cancer risk[118-124]. Wang *et al*[122] demonstrated that the AA genotype at the CXCL8 251 allele was a risk factor for gastric cancer, particularly in Asian populations. Consistent with this, Song *et al*[124] reported an increased incidence of this allele in *H. pylori*-infected Korean populations. The gastric mucosal concentration of MMP-9 and angiopoietin (Ang)-1 were correlated with disease progression in patients with the CXCL8 251 AA allele, suggesting that this genotype may be associated with angiogenesis in gastric carcinogenesis. Finally, Vinagre *et al*[123] revealed an interaction between CXCL8 251 polymorphism, particularly with carriers of the A allele, and *s1m1 cag*A positive *H. pylori* infection. Taken together, these data suggest that polymorphisms of CXCL8 251 allele play an important role in the development of gastric cancer.

CXCR1 and CXCR2 are the receptors for CXCL8, and both are expressed on the surface of gastric cancer cells[107,109,125-127], suggesting that tumor-derived CXCL8 exerts biological effects on the tumor cells in an autocrine or paracrine manner. Wang *et al*[125] reported that increased CXCR1 expression was associated with advanced stage, and was an independent risk factor for a higher nodal stage. They also demonstrated that CXCR1/2 expression was higher in gastric cancer compared with corresponding non-neoplastic tissue, and was correlated with increased invasion, metastasis, and microvessel density, as well as increased levels of phospho-Akt, phospho-ERK, cyclin D1, epidermal growth factor receptor (EGFR), Bcl-2, MMP-9 and MMP-2. This suggests that CXCR1/2 signaling plays a crucial role in the progression of gastric cancer, possibly *via* the phosphorylation of ERK and Akt[126]. Elevated expression of CXCR1 was also detected in most, and CXCR2 in only a few, tumor-infiltrating neutrophils, suggesting that tumor-secreted CXCL8 recruits neutrophils to the tumor microenvironment *via* CXCR1[109]. This is consistent with previous observations that the over-expression of CXCL8 by tumor cells attracts a large number of CXCL8 receptor-expressing leukocytes to the tumor site by chemotaxis, and that these leukocytes then secrete growth factors to further facilitate the growth and progression of tumors[128,129].

CXCL1-CXCR2

CXCL1 and its receptor CXCR2 are differentially expressed in gastric cancer[109,130-132]. Gastric cancer cells produce CXCL1, and its gene expression was detected both *in vitro* and in gastric cancer mouse models *in vivo*[103,105,133-135]. In addition, the expression of CXCL1 mRNA and protein was higher in gastric cancer tissue compared with non-cancerous gastric tissues[130,131,136]. Further studies analyzed gene expression profiles, and revealed the upregulation of circulating CXCL1 levels in patients with gastric cancer compared with healthy controls[78,130,131,137]. In addition, the expression of CXCR2, the CXCL1 receptor, was increased significantly in tumor tissue compared with non-cancerous adjacent tissue. The immunostaining of consecutive sections revealed that CXCL1 and CXCR2 were predominantly co-expressed in tumor epithelial cells, with a significant correlation between the staining scores of CXCL1 and CXCR2 in gastric cancer tissue[131]. Increased expression of both proteins was also associated with tumor progression, and more advanced stages of gastric cancer[131,132], while elevated CXCL1 expression was an independent prognostic factor for patient survival[131]. However, the role of CXCL1 in gastric cancer remains controversial. Some studies revealed that increased circulating levels of CXCL1 correlated with aggressive tumor behavior, such as lymph node metastasis and higher tumor stage[131,137]. In contrast, Junnila *et al*[130] reported that increased levels of CXCL1 mRNA transcripts in gastric cancer tissue were associated with increased survival, although protein levels of CXCL1 were not measured.

CXCL1 and CXCR2 play important regulatory roles in the migration, invasion and metastasis of tumor cells, in a variety of cancers, such as melanoma, colon and breast cancer[138-140]. In gastric cancer, CXCL1-overexpressing cells showed increased migratory and invasive potential, whereas depletion of CXCL1 or CXCR2 significantly decreased the migration and invasion of the same cells[131]. CXCL1-overexpressing cells also expressed significantly higher levels of MMP-2 and MMP-9 activity than control cells, and upregulation of Ras and STAT3[131], suggesting a potential mechanism by which CXCL1-CXCR2 contributes to the progression of gastric cancer.

Additional CXC chemokines and chemokine receptors

CXCL5 is expressed in gastric cancer, and is correlated with nodal and overall stage[141,142]. Elevated serum CXCL5 expression is also observed in late-stage gastric cancer patients compared with those with benign tumors, suggesting that CXCL5 may play a role in the progression of gastric cancer[142]. In addition, *CXCL5* gene ex-

pression was up regulated in the gastric mucosa of the *A4gnt*$^{-/-}$ gastric cancer mouse model compared with wild-type mice, which was confirmed by quantitative reverse transcription-polymerase chain reaction[134]. However, the role of the chemokine CXCL5 in gastric carcinogenesis is still unclear, and additional *in vitro* and *in vivo* studies are needed to characterize its effects.

Recently Yanagi *et al*[78] used a cDNA microarray to carry out a comparative analysis on the differential expression of chemokines and chemokine receptors in gastric cancer cell lines. They showed that CXCL7 and CXCL14 were upregulated (along with CXCL1, CXCL8 and CXCL12), suggesting that these chemokines play a role in the progression of gastric cancer.

CXCL9, CXCL10 and CXCL11 have also been linked to gastric cancer, and are constitutively expressed in gastric cancer cell lines such as AGS, KATO Ⅲ and NCI. In addition, their secretion was strongly induced by treatment with a combination of interferon-γ and tumor necrosis factor-α[143]. Jung *et al*[137] used genome-wide gene expression databases to show that the *CXCL9* and *CXCL10* genes were overexpressed more than twofold in gastric cancer compared to normal tissues. Consistent with this, Rajkumar *et al*[144] demonstrated that the plasma levels of CXCL9 and CXCL10 were decreased significantly in gastric cancer patients after surgery. Additional studies revealed that a small portion of gastric cancer cells expressed both CXCL9 and CXCL10, and that their expression co-localized with cytokeratin[145]. In the same study, cells in lymphocyte-rich gastric cancers were more frequently positive for CXCL9 and CXCL10 than were conventional gastric cancer cells.

The chemokine CXCL16 and its receptor CXCR6 are up regulated in multiple cancer tissues and cell lines compared with normal samples and cells. In addition, both CXCL16 and CXCR6 levels increase as tumor malignancy increases. The CXCL16 exists both in a soluble form and a transmembrane form. Soluble CXCL16 promotes cell proliferation and migration while transmembranous CXCL16 suppresses proliferation[146]. For example, Darash-Yahana *et al*[147] showed that CXCL16-CXCR6 expression level was closely related to high malignant degree in prostate cancer. Soluble CXCL16 facilitated the migration of CXCR6-expressing cancer cells and promoted the proliferation *in vitro*. Hojo *et al*[148] demonstrated that CXCL16 expression was up regulated in colorectal tumor tissue compared with normal mucosa, and suggested that the transmembranous expression of CXCL16 by tumor cells enhanced the recruitment of tumor-infiltrating lymphocytes, thereby improving prognosis. In gastric cancer, Xing *et al*[149] recently reported that eight gastric cancer cell lines and the gastric epithelial cell line GES-1 differentially expressed CXCL16 and CXCR6 mRNA. They demonstrated that CXCL16 mRNA expression was elevated in cancer tissue compared with adjacent mucosa, while CXCR6 was expressed in the opposite manner. Nuclear CXCL16 expression inversely correlated with the invasion depth of the tumor, lymphatic invasion, and stage, suggesting that CXCL16 and its receptor CXCR6 may play a role in gastric tumorigenesis.

THERAPEUTIC TARGETING OF CHEMOKINES AND THEIR RECEPTORS IN GASTRIC CANCER

CXCL12-CXCR4/CXCR7 axis

The CXCL12-CXCR4/CXCR7 axis is a potential novel therapeutic target for the treatment of cancer, and so multiple agents that modulate this pathway are being developed for use in malignant tumors. Examples include the anti-CXCR4 drug AMD3100 (also known as plerixafor, or Mozobil), the CXCL12 analog CTCE-9908 (Chemokine Therapeutics), the anti-CXCL12 aptamer Nox-A12 (Noxxon), and the CXCR7-specific inhibitor CCX2066 (ChemoCentryx). Additional strategies to inhibit CXCL12 signaling, including chalcone 4 (C7870) or RNA interference, could also be assessed for the treatment of solid tumors[150].

In gastric cancer, several preclinical studies have demonstrated that blocking the CXCL12-CXCR4 axis showed anti-tumor activity *in vitro* and *in vivo*. CXCL12-induced migration, cell proliferation, and cell survival were significantly blocked by treatment with a neutralizing anti-CXCR4 antibody or AMD3100, a specific CXCR4 antagonist[45,47,50,63]. AMD3100 also significantly reduced tumor growth, inhibited the formation of malignant ascitic fluid, and increased survival in nude mice inoculated with NUGC-4 cells compared with control. Importantly, none of the mice showed signs of drug-associated toxicity[47,151,152]. In addition, Xie *et al*[153] demonstrated that elevated CXCR4 mRNA levels in gastric cancer tissues were significantly correlated with docetaxel sensitivity, and that AMD3100 enhanced docetaxel cytotoxicity *in vitro*. Additional studies reported that plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone), an analogue of vitamin K3, inhibited CXCL12-induced migration and invasion of gastric cancer cells by down-regulating the expression of functional CXCR4 at the transcriptional level[154]. Plumbagin suppressed the binding of NF-κB to the CXCR4 promoter, suggesting that it inhibits CXCR4 expression by suppressing NF-κB-mediated CXCR4 transcription. Taken together, these data suggest CXCR4 antagonists to be attractive therapeutic candidates, necessitating a better understanding of the CXCL12-CXCR4 axis in gastric tumorigenesis.

Recent studies suggested that fluorescent magnetic nanoparticle-labeled mesenchymal stem cells (MSCs) could target *in vivo* mouse gastric cancer cells *via* the CXCL12-CXCR4 axis to inhibit tumor growth during hyperthermic therapy[79]. In this study, gastric cancer cells produced CXCL12, which attracted CXCR4-expressing MSCs to gastric tumor sites. These data suggest that gastric tumor-expressed CXCL12 could be targeted during treatments, such as hyperthermia combined with fluorescent magnetic nanoparticle-labeled MSCs, to attract CXCR4-expressing MSCs.

CXCL8-CXCR1/CXCR2 axis

The chemokine CXCL8 and its receptors CXCR1/2 are potential therapeutic targets in a variety of solid tumors such as malignant melanoma, colon, breast, and bladder cancer. As such, several antagonists of CXCL8-CXCR1/CXCR2-mediated signaling are in development, including neutralizing antibodies and small-molecule antagonists[140,155-158]. In melanoma, neutralizing antibodies to CXCR1 and CXCR2 inhibited cell proliferation and invasive potential, while knock down of CXCR1 or CXCR2 using small interfering RNA inhibited melanoma tumor growth and invasion *in vitro* and *in vivo*[156,159]. Varney *et al*[160] reported that orally active small molecular antagonists against CXCR2 and CXCR1 (such as SCH-527123 and SCH-479833) inhibited liver metastasis by decreasing neovascularization and enhancing malignant cell apoptosis in colon cancer. Consistent with this, Ning *et al*[155] demonstrated that treatment with SCH-527123 alone or in combination with oxaliplatin synergistically inhibited proliferation and angiogenesis, and enhanced chemosensitivity in colorectal cancer cells and xenograft models. However, little data in gastric cancer have explored the potential of the CXCL8-CXCR1/CXCR2 axis as therapeutic targets until recently. Ju *et al*[107] reported that Xiaotan Sanjie Decoction, a traditional Chinese herbal medicine, inhibited tumor growth by decreasing the expression of CXCL8, CXCR1, and CXCR2 in gastric cancer xenograft models, suggesting that inhibiting this axis may be one of mechanisms by which the herb inhibits tumor growth and prevents recurrence. However, with the recent advances in understanding the role of CXCL8 and its receptors in the development and progression of gastric cancer, additional studies are needed to maximize the therapeutic potential of this axis for the treatment of gastric cancer.

CONCLUSION

Advanced gastric cancer patients, particularly those with peritoneal seeding, have a very poor quality of life, and poor prognosis. To improve quality of life and survival in these patients, a better understanding of the underlying molecular pathogenesis of gastric carcinogenesis, and its application for the development of novel targeted therapies, are urgently needed. Chemokines, also known as chemotactic cytokines, were traditionally believed to regulate the directional migration of leukocytes to inflammatory sites. However, it is now clear that chemokines and their receptors also regulate the processes underlying the development and progression of malignant diseases, including tumor growth, survival, angiogenesis, invasion, and metastasis. CXC chemokines and their receptors are widely expressed in gastrointestinal tumors, including gastric cancer, and are associated with prognosis. CXCL12 and its receptor CXCR4 play a crucial role in aspects of gastric carcinogenesis including cell proliferation, migration, invasion, peritoneal seeding, and resistance to treatment. In addition, there is accumulating evidence to suggest that modulating CXCL12-CXCR4 signaling could be an important therapeutic strategy, either alone or in combination with conventional treatment modalities. CXCL8-CXCR1/2 and CXCL1-CXCR2 are differentially expressed in gastric cancer, and are involved in its progression. This suggests that they may also be future therapeutic candidates. About CXCL16-CXCR6, both CXCL16 and its receptor CXCR6 are aberrantly expressed in gastric cancer suggesting their involvement in gastric carcinogenesis. However, the role and significance of CXCL16-CXCR6 in gastric cancer remain uncertain due to insufficient data. Overall, the role of the various chemokines and chemokine receptors in the development and progression of gastric cancer is complex. In addition, little is known of the roles of other CXC chemokines and chemokine receptors in gastric cancer. More extensive studies are therefore needed to elucidate the roles of the complex chemokine and chemokine receptor network in gastric tumorigenesis, which may result in therapeutic applications for patients with gastric cancer.

REFERENCES

1 **Thiel A**, Ristimäki A. Gastric cancer: basic aspects. *Helicobacter* 2012; **17** Suppl 1: 26-29 [PMID: 22958152 DOI: 10.1111/j.1523-5378.2012.00979.x]

2 **Pisani P**, Parkin DM, Bray F, Ferlay J. Estimates of the worldwide mortality from 25 cancers in 1990. *Int J Cancer* 1999; **83**: 18-29 [PMID: 10449602]

3 **Lee HJ**, Cho do Y, Park JC, Bae SB, Lee KT, Cho IS, Han CS, Park SY, Yun HJ, Kim S. Phase II trial of biweekly paclitaxel plus infusional 5-fluorouracil and leucovorin in patients with advanced or recurrent inoperable gastric cancer. *Cancer Chemother Pharmacol* 2009; **63**: 427-432 [PMID: 18415100 DOI: 10.1007/s00280-008-0752-4]

4 **Zheng L**, Wang L, Ajani J, Xie K. Molecular basis of gastric cancer development and progression. *Gastric Cancer* 2004; **7**: 61-77 [PMID: 15224192 DOI: 10.1007/s10120-004-0277-4]

5 **Lee HJ**, Jo DY. The role of the CXCR4/CXCL12 axis and its clinical implications in gastric cancer. *Histol Histopathol* 2012; **27**: 1155-1161 [PMID: 22806902]

6 **Ebert MP**, Fei G, Kahmann S, Müller O, Yu J, Sung JJ, Malfertheiner P. Increased beta-catenin mRNA levels and mutational alterations of the APC and beta-catenin gene are present in intestinal-type gastric cancer. *Carcinogenesis* 2002; **23**: 87-91 [PMID: 11756228]

7 **Panani AD**. Cytogenetic and molecular aspects of gastric cancer: clinical implications. *Cancer Lett* 2008; **266**: 99-115 [PMID: 18381231 DOI: 10.1016/j.canlet.2008.02.053]

8 **Resende C**, Ristimäki A, Machado JC. Genetic and epigenetic alteration in gastric carcinogenesis. *Helicobacter* 2010; **15** Suppl 1: 34-39 [PMID: 21054651 DOI: 10.1111/j.1523-5378.2010.00782.x]

9 **Oda N**, Tsujino T, Tsuda T, Yoshida K, Nakayama H, Yasui W, Tahara E. DNA ploidy pattern and amplification of ERBB and ERBB2 genes in human gastric carcinomas. *Virchows Arch B Cell Pathol Incl Mol Pathol* 1990; **58**: 273-277 [PMID: 1970690]

10 **Ross JS**, McKenna BJ. The HER-2/neu oncogene in tumors of the gastrointestinal tract. *Cancer Invest* 2001; **19**: 554-568 [PMID: 11458821]

11 **Shun CT**, Wu MS, Lin JT, Chen SY, Wang HP, Lee WJ, Wang TH, Chuang SM. Relationship of p53 and c-erbB-2 expression to histopathological features, Helicobacter pylori infection and prognosis in gastric cancer. *Hepatogastroenterology* 1997; **44**: 604-609 [PMID: 9164544]

12 **Han S**, Kim HY, Park K, Cho HJ, Lee MS, Kim HJ, Kim YD. c-Myc expression is related with cell proliferation and associated with poor clinical outcome in human gastric cancer. *J Korean Med Sci* 1999; **14**: 526-530 [PMID: 10576148]
13 **Kozma L**, Kiss I, Hajdú J, Szentkereszty Z, Szakáll S, Ember I. C-myc amplification and cluster analysis in human gastric carcinoma. *Anticancer Res* 2001; **21**: 707-710 [PMID: 11299830]
14 **Pan G**, Lv H, Ren H, Wang Y, Liu Y, Jiang H, Wen J. Elevated expression of semaphorin 5A in human gastric cancer and its implication in carcinogenesis. *Life Sci* 2010; **86**: 139-144 [PMID: 20026339 DOI: 10.1016/j.lfs.2009.12.004]
15 **Florou D**, Papadopoulos IN, Scorilas A. Molecular analysis and prognostic impact of the novel apoptotic gene BCL2L12 in gastric cancer. *Biochem Biophys Res Commun* 2010; **391**: 214-218 [PMID: 19903463 DOI: 10.1016/j.bbrc.2009.11.034]
16 **Kuniyasu H**, Yasui W, Yokozaki H, Kitadai Y, Tahara E. Aberrant expression of c-met mRNA in human gastric carcinomas. *Int J Cancer* 1993; **55**: 72-75 [PMID: 8344755]
17 **Hattori Y**, Odagiri H, Nakatani H, Miyagawa K, Naito K, Sakamoto H, Katoh O, Yoshida T, Sugimura T, Terada M. K-sam, an amplified gene in stomach cancer, is a member of the heparin-binding growth factor receptor genes. *Proc Natl Acad Sci USA* 1990; **87**: 5983-5987 [PMID: 2377625]
18 **Liu XP**, Tsushimi K, Tsushimi M, Oga A, Kawauchi S, Furuya T, Sasaki K. Expression of p53 protein as a prognostic indicator of reduced survival time in diffuse-type gastric carcinoma. *Pathol Int* 2001; **51**: 440-444 [PMID: 11422805]
19 **Nakatsuru S**, Yanagisawa A, Ichii S, Tahara E, Kato Y, Nakamura Y, Horii A. Somatic mutation of the APC gene in gastric cancer: frequent mutations in very well differentiated adenocarcinoma and signet-ring cell carcinoma. *Hum Mol Genet* 1992; **1**: 559-563 [PMID: 1338691]
20 **Lee KH**, Lee JS, Suh C, Kim SW, Kim SB, Lee JH, Lee MS, Park MY, Sun HS, Kim SH. Clinicopathologic significance of the K-ras gene codon 12 point mutation in stomach cancer. An analysis of 140 cases. *Cancer* 1995; **75**: 2794-2801 [PMID: 7773929]
21 **More H**, Humar B, Weber W, Ward R, Christian A, Lintott C, Graziano F, Ruzzo AM, Acosta E, Boman B, Harlan M, Ferreira P, Seruca R, Suriano G, Guilford P. Identification of seven novel germline mutations in the human E-cadherin (CDH1) gene. *Hum Mutat* 2007; **28**: 203 [PMID: 17221870 DOI: 10.1002/humu.9473]
22 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [PMID: 20728210 DOI: 10.1016/s0140-6736(10)61121-x]
23 **Balkwill FR**. The chemokine system and cancer. *J Pathol* 2012; **226**: 148-157 [PMID: 21989643 DOI: 10.1002/path.3029]
24 **Koizumi K**, Hojo S, Akashi T, Yasumoto K, Saiki I. Chemokine receptors in cancer metastasis and cancer cell-derived chemokines in host immune response. *Cancer Sci* 2007; **98**: 1652-1658 [PMID: 17894551 DOI: 10.1111/j.1349-7006.2007.00606.x]
25 **Burger JA**. Chemokines and chemokine receptors in chronic lymphocytic leukemia (CLL): from understanding the basics towards therapeutic targeting. *Semin Cancer Biol* 2010; **20**: 424-430 [PMID: 20883788 DOI: 10.1016/j.semcancer.2010.09.005]
26 **Kunkel SL**, Strieter RM, Lindley IJ, Westwick J. Chemokines: new ligands, receptors and activities. *Immunol Today* 1995; **16**: 559-561 [PMID: 8579746 DOI: 10.1016/0167-5699(95)80076-x]
27 **Keeley EC**, Mehrad B, Strieter RM. CXC chemokines in cancer angiogenesis and metastases. *Adv Cancer Res* 2010; **106**: 91-111 [PMID: 20399957 DOI: 10.1016/s0065-230x(10)06003-3]
28 **Charo IF**, Ransohoff RM. The many roles of chemokines and chemokine receptors in inflammation. *N Engl J Med* 2006; **354**: 610-621 [PMID: 16467548 DOI: 10.1056/NEJMra052723]
29 **Vicari AP**, Caux C. Chemokines in cancer. *Cytokine Growth Factor Rev* 2002; **13**: 143-154 [PMID: 11900990]
30 **Vandercappellen J**, Van Damme J, Struyf S. The role of CXC chemokines and their receptors in cancer. *Cancer Lett* 2008; **267**: 226-244 [PMID: 18579287 DOI: 10.1016/j.canlet.2008.04.050]
31 **Zhu Q**, Han X, Peng J, Qin H, Wang Y. The role of CXC chemokines and their receptors in the progression and treatment of tumors. *J Mol Histol* 2012; **43**: 699-713 [PMID: 22752457 DOI: 10.1007/s10735-012-9435-x]
32 **Verbeke H**, Struyf S, Laureys G, Van Damme J. The expression and role of CXC chemokines in colorectal cancer. *Cytokine Growth Factor Rev* 2011; **22**: 345-358 [PMID: 22000992 DOI: 10.1016/j.cytogfr.2011.09.002]
33 **Strieter RM**, Burdick MD, Mestas J, Gomperts B, Keane MP, Belperio JA. Cancer CXC chemokine networks and tumour angiogenesis. *Eur J Cancer* 2006; **42**: 768-778 [PMID: 16510280 DOI: 10.1016/j.ejca.2006.01.006]
34 **Rainczuk A**, Rao J, Gathercole J, Stephens AN. The emerging role of CXC chemokines in epithelial ovarian cancer. *Reproduction* 2012; **144**: 303-317 [PMID: 22771929 DOI: 10.1530/rep-12-0153]
35 **Fernandez EJ**, Lolis E. Structure, function, and inhibition of chemokines. *Annu Rev Pharmacol Toxicol* 2002; **42**: 469-499 [PMID: 11807180 DOI: 10.1146/annurev.pharmtox.42.091901.115838]
36 **Arya M**, Patel HR, Williamson M. Chemokines: key players in cancer. *Curr Med Res Opin* 2003; **19**: 557-564 [PMID: 14594528 DOI: 10.1185/030079903125002216]
37 **Verbeke H**, Geboes K, Van Damme J, Struyf S. The role of CXC chemokines in the transition of chronic inflammation to esophageal and gastric cancer. *Biochim Biophys Acta* 2012; **1825**: 117-129 [PMID: 22079531 DOI: 10.1016/j.bbcan.2011.10.008]
38 **Luster AD**. Chemokines--chemotactic cytokines that mediate inflammation. *N Engl J Med* 1998; **338**: 436-445 [PMID: 9459648 DOI: 10.1056/nejm199802123380706]
39 **Tazzyman S**, Lewis CE, Murdoch C. Neutrophils: key mediators of tumour angiogenesis. *Int J Exp Pathol* 2009; **90**: 222-231 [PMID: 19563607 DOI: 10.1111/j.1365-2613.2009.00641.x]
40 **Strieter RM**, Polverini PJ, Kunkel SL, Arenberg DA, Burdick MD, Kasper J, Dzuiba J, Van Damme J, Walz A, Marriott D. The functional role of the ELR motif in CXC chemokine-mediated angiogenesis. *J Biol Chem* 1995; **270**: 27348-27357 [PMID: 7592998]
41 **Strieter RM**, Burdick MD, Gomperts BN, Belperio JA, Keane MP. CXC chemokines in angiogenesis. *Cytokine Growth Factor Rev* 2005; **16**: 593-609 [PMID: 16046180 DOI: 10.1016/j.cytogfr.2005.04.007]
42 **Strieter RM**, Belperio JA, Phillips RJ, Keane MP. CXC chemokines in angiogenesis of cancer. *Semin Cancer Biol* 2004; **14**: 195-200 [PMID: 15246055 DOI: 10.1016/j.semcancer.2003.10.006]
43 **Zipin-Roitman A**, Meshel T, Sagi-Assif O, Shalmon B, Avivi C, Pfeffer RM, Witz IP, Ben-Baruch A. CXCL10 promotes invasion-related properties in human colorectal carcinoma cells. *Cancer Res* 2007; **67**: 3396-3405 [PMID: 17409450 DOI: 10.1158/0008-5472.can-06-3087]
44 **Kawada K**, Sonoshita M, Sakashita H, Takabayashi A, Yamaoka Y, Manabe T, Inaba K, Minato N, Oshima M, Taketo MM. Pivotal role of CXCR3 in melanoma cell metastasis to lymph nodes. *Cancer Res* 2004; **64**: 4010-4017 [PMID: 15173015 DOI: 10.1158/0008-5472.can-03-1757]
45 **Lee HJ**, Kim SW, Kim HY, Li S, Yun HJ, Song KS, Kim S, Jo DY. Chemokine receptor CXCR4 expression, function, and clinical implications in gastric cancer. *Int J Oncol* 2009; **34**:

473-480 [PMID: 19148483]
46 **Li S**, Huang S, Peng SB. Overexpression of G protein-coupled receptors in cancer cells: involvement in tumor progression. *Int J Oncol* 2005; **27**: 1329-1339 [PMID: 16211229]
47 **Yasumoto K**, Koizumi K, Kawashima A, Saitoh Y, Arita Y, Shinohara K, Minami T, Nakayama T, Sakurai H, Takahashi Y, Yoshie O, Saiki I. Role of the CXCL12/CXCR4 axis in peritoneal carcinomatosis of gastric cancer. *Cancer Res* 2006; **66**: 2181-2187 [PMID: 16489019 DOI: 10.1158/0008-5472.can-05-3393]
48 **Zhao BC**, Zhao B, Han JG, Ma HC, Wang ZJ. Adipose-derived stem cells promote gastric cancer cell growth, migration and invasion through SDF-1/CXCR4 axis. *Hepatogastroenterology* 2010; **57**: 1382-1389 [PMID: 21443090]
49 **Mitra P**, Shibuta K, Mathai J, Shimoda K, Banner BF, Mori M, Barnard GF. CXCR4 mRNA expression in colon, esophageal and gastric cancers and hepatitis C infected liver. *Int J Oncol* 1999; **14**: 917-925 [PMID: 10200342]
50 **Zhao BC**, Wang ZJ, Mao WZ, Ma HC, Han JG, Zhao B, Xu HM. CXCR4/SDF-1 axis is involved in lymph node metastasis of gastric carcinoma. *World J Gastroenterol* 2011; **17**: 2389-2396 [PMID: 21633638 DOI: 10.3748/wjg.v17.i19.2389]
51 **Ingold B**, Simon E, Ungethüm U, Kuban RJ, Müller BM, Lupp A, Neumann U, Ebert MP, Denkert C, Weichert W, Schulz S, Röcken C. Vascular CXCR4 expression - a novel antiangiogenic target in gastric cancer? *PLoS One* 2010; **5**: e10087 [PMID: 20386750 DOI: 10.1371/journal.pone.0010087]
52 **Pituch-Noworolska A**, Drabik G, Szatanek R, Białas M, Kołodziejczyk P, Szczepanik A, Stachura J, Zembala M. Immunophenotype of isolated tumour cells in the blood, bone marrow and lymph nodes of patients with gastric cancer. *Pol J Pathol* 2007; **58**: 93-97 [PMID: 17715675]
53 **Yasumoto K**, Yamada T, Kawashima A, Wang W, Li Q, Donev IS, Tacheuchi S, Mouri H, Yamashita K, Ohtsubo K, Yano S. The EGFR ligands amphiregulin and heparin-binding egf-like growth factor promote peritoneal carcinomatosis in CXCR4-expressing gastric cancer. *Clin Cancer Res* 2011; **17**: 3619-3630 [PMID: 21482691 DOI: 10.1158/1078-0432.ccr-10-2475]
54 **Ying J**, Xu Q, Zhang G, Liu B, Zhu L. The expression of CXCL12 and CXCR4 in gastric cancer and their correlation to lymph node metastasis. *Med Oncol* 2012; **29**: 1716-1722 [PMID: 21630055 DOI: 10.1007/s12032-011-9990-0]
55 **Zhao C**, Ma H, Bu X, Wang W, Zhang N. SFRP5 inhibits gastric epithelial cell migration induced by macrophage-derived Wnt5a. *Carcinogenesis* 2013; **34**: 146-152 [PMID: 23054609 DOI: 10.1093/carcin/bgs309]
56 **Xue Z**, Yan H, Li J, Liang S, Cai X, Chen X, Wu Q, Gao L, Wu K, Nie Y, Fan D. Identification of cancer stem cells in vincristine preconditioned SGC7901 gastric cancer cell line. *J Cell Biochem* 2012; **113**: 302-312 [PMID: 21913215 DOI: 10.1002/jcb.23356]
57 **Graziosi L**, Mencarelli A, Santorelli C, Renga B, Cipriani S, Cavazzoni E, Palladino G, Laufer S, Burnet M, Donini A, Fiorucci S. Mechanistic role of p38 MAPK in gastric cancer dissemination in a rodent model peritoneal metastasis. *Eur J Pharmacol* 2012; **674**: 143-152 [PMID: 22119383 DOI: 10.1016/j.ejphar.2011.11.015]
58 **Fanelli MF**, Chinen LT, Begnami MD, Costa WL, Fregnami JH, Soares FA, Montagnini AL. The influence of transforming growth factor-α, cyclooxygenase-2, matrix metalloproteinase (MMP)-7, MMP-9 and CXCR4 proteins involved in epithelial-mesenchymal transition on overall survival of patients with gastric cancer. *Histopathology* 2012; **61**: 153-161 [PMID: 22582975 DOI: 10.1111/j.1365-2559.2011.04139.x]
59 **Kwak MK**, Hur K, Park DJ, Lee HJ, Lee HS, Kim WH, Lee KU, Choe KJ, Yang HK. Expression of chemokine receptors in human gastric cancer. *Tumour Biol* 2005; **26**: 65-70 [PMID: 15867478 DOI: 10.1159/000085587]
60 **Sun XJ**, Sun KL, Zheng ZH, Fu WN, Hao DM, Xu HM, Li XM. Gene expression patterns in gastric cancer. *Zhonghua Yixue Yichuanxue Zazhi* 2006; **23**: 142-146 [PMID: 16604482]
61 **Graziosi L**, Mencarelli A, Renga B, Santorelli C, Cantarella F, Bugiantella W, Cavazzoni E, Donini A, Fiorucci S. Gene expression changes induced by HIPEC in a murine model of gastric cancer. *In Vivo* 2012; **26**: 39-45 [PMID: 22210714]
62 **Xu W**, Zhou H, Qian H, Bu X, Chen D, Gu H, Zhu W, Yan Y, Mao F. Combination of circulating CXCR4 and Bmi-1 mRNA in plasma: A potential novel tumor marker for gastric cancer. *Mol Med Rep* 2012; **2**: 765-771 [PMID: 21475899 DOI: 10.3892/mmr_00000170]
63 **Ding YL**, Zhang JL, Tang SF, Fu QY, Li ZT. [Effect of chemokine stromal cell derived factor-1 and its receptor CXCR4 on the peritoneal carcinometastasis of gastric cancer]. *Zhonghua Yixue Zazhi* 2008; **88**: 202-205 [PMID: 18361822]
64 **Hashimoto I**, Koizumi K, Tatematsu M, Minami T, Cho S, Takeno N, Nakashima A, Sakurai H, Saito S, Tsukada K, Saiki I. Blocking on the CXCR4/mTOR signalling pathway induces the anti-metastatic properties and autophagic cell death in peritoneal disseminated gastric cancer cells. *Eur J Cancer* 2008; **44**: 1022-1029 [PMID: 18375114 DOI: 10.1016/j.ejca.2008.02.043]
65 **Zieker D**, Königsrainer I, Traub F, Nieselt K, Knapp B, Schillinger C, Stirnkorb C, Fend F, Northoff H, Kupka S, Brücher BL, Königsrainer A. PGK1 a potential marker for peritoneal dissemination in gastric cancer. *Cell Physiol Biochem* 2008; **21**: 429-436 [PMID: 18453750 DOI: 10.1159/000129635]
66 **Tsuboi K**, Kodera Y, Nakanishi H, Ito S, Mochizuki Y, Nakayama G, Koike M, Fujiwara M, Yamamura Y, Nakao A. Expression of CXCL12 and CXCR4 in pT3-stage gastric cancer does not correlate with peritoneal metastasis. *Oncol Rep* 2008; **20**: 1117-1123 [PMID: 18949410]
67 **Arigami T**, Natsugoe S, Uenosono Y, Yanagita S, Arima H, Hirata M, Ishigami S, Aikou T. CCR7 and CXCR4 expression predicts lymph node status including micrometastasis in gastric cancer. *Int J Oncol* 2009; **35**: 19-24 [PMID: 19513547]
68 **Iwasa S**, Yanagawa T, Fan J, Katoh R. Expression of CXCR4 and its ligand SDF-1 in intestinal-type gastric cancer is associated with lymph node and liver metastasis. *Anticancer Res* 2009; **29**: 4751-4758 [PMID: 20032431]
69 **Zhu S**, Hong J, Tripathi MK, Sehdev V, Belkhiri A, El-Rifai W. Regulation of CXCR4-mediated invasion by DARPP-32 in gastric cancer cells. *Mol Cancer Res* 2013; **11**: 86-94 [PMID: 23160836 DOI: 10.1158/1541-7786.mcr-12-0243-t]
70 **Bao W**, Fu HJ, Xie QS, Wang L, Zhang R, Guo ZY, Zhao J, Meng YL, Ren XL, Wang T, Li Q, Jin BQ, Yao LB, Wang RA, Fan DM, Chen SY, Jia LT, Yang AG. HER2 interacts with CD44 to up-regulate CXCR4 via epigenetic silencing of microRNA-139 in gastric cancer cells. *Gastroenterology* 2011; **141**: 2076-2087.e6 [PMID: 21925125 DOI: 10.1053/j.gastro.2011.08.050]
71 **He H**, Wang C, Shen Z, Fang Y, Wang X, Chen W, Liu F, Qin X, Sun Y. Upregulated expression of C-X-C chemokine receptor 4 is an independent prognostic predictor for patients with gastric cancer. *PLoS One* 2013; **8**: e71864 [PMID: 23936528 DOI: 10.1371/journal.pone.0071864]
72 **Ishigami S**, Natsugoe S, Okumura H, Matsumoto M, Nakajo A, Uenosono Y, Arigami T, Uchikado Y, Setoyama T, Arima H, Hokita S, Aikou T. Clinical implication of CXCL12 expression in gastric cancer. *Ann Surg Oncol* 2007; **14**: 3154-3158 [PMID: 17653799 DOI: 10.1245/s10434-007-9521-6]
73 **Lee HJ**, Huang SM, Kim HY, Oh YS, Hwang JY, Liang ZL, Ki Min J, Yun HJ, Sul JY, Kim S, Jo DY, Kim JM. Evaluation of the combined expression of chemokine SDF-1α and its receptor CXCR4 as a prognostic marker for gastric cancer. *Exp Ther Med* 2011; **2**: 499-504 [PMID: 22977531 DOI: 10.3892/etm.2011.228]
74 **Chen G**, Chen SM, Wang X, Ding XF, Ding J, Meng LH. Inhibition of chemokine (CXC motif) ligand 12/chemokine

(CXC motif) receptor 4 axis (CXCL12/CXCR4)-mediated cell migration by targeting mammalian target of rapamycin (mTOR) pathway in human gastric carcinoma cells. *J Biol Chem* 2012; **287**: 12132-12141 [PMID: 22337890 DOI: 10.1074/jbc.M111.302299]

75 **Song IC**, Liang ZL, Lee JC, Huang SM, Kim HY, Oh YS, Yun HJ, Sul JY, Jo DY, Kim S, Kim JM, Lee HJ. Expression of stromal cell-derived factor-1α is an independent risk factor for lymph node metastasis in early gastric cancer. *Oncol Lett* 2011; **2**: 1197-1202 [PMID: 22848288 DOI: 10.3892/ol.2011.389]

76 **Zhi Y**, Chen J, Zhang S, Chang X, Ma J, Dai D. Down-regulation of CXCL12 by DNA hypermethylation and its involvement in gastric cancer metastatic progression. *Dig Dis Sci* 2012; **57**: 650-659 [PMID: 21960286 DOI: 10.1007/s10620-011-1922-5]

77 **Ruan J**, Song H, Li C, Bao C, Fu H, Wang K, Ni J, Cui D. DiR-labeled Embryonic Stem Cells for Targeted Imaging of in vivo Gastric Cancer Cells. *Theranostics* 2012; **2**: 618-628 [PMID: 22768029 DOI: 10.7150/thno.4561]

78 **Yanagie H**, Hisa T, Ono M, Eriguchi M. [Chemokine and chemokine receptor related to cancer metastasis]. *Gan To Kagaku Ryoho* 2010; **37**: 2052-2057 [PMID: 21084802]

79 **Ruan J**, Ji J, Song H, Qian Q, Wang K, Wang C, Cui D. Fluorescent magnetic nanoparticle-labeled mesenchymal stem cells for targeted imaging and hyperthermia therapy of in vivo gastric cancer. *Nanoscale Res Lett* 2012; **7**: 309 [PMID: 22709686 DOI: 10.1186/1556-276x-7-309]

80 **Schimanski CC**, Jordan M, Schlaegel F, Schmidtmann I, Lang H, Galle PR, Moehler M, Gockel I. SNP rs1801157 significantly correlates with distant metastasis in CXCL12 expressing esophagogastric cancer. *Int J Oncol* 2011; **39**: 515-520 [PMID: 21584490 DOI: 10.3892/ijo.2011.1044]

81 **Woo IS**, Hong SH, Byun JH, Kang JH, Jeon HM, Choi MG. Circulating stromal cell derived factor-1alpha (SDF-1alpha) is predictive of distant metastasis in gastric carcinoma. *Cancer Invest* 2008; **26**: 256-261 [PMID: 18317966 DOI: 10.1080/07357900701684057]

82 **Rempel SA**, Dudas S, Ge S, Gutiérrez JA. Identification and localization of the cytokine SDF1 and its receptor, CXC chemokine receptor 4, to regions of necrosis and angiogenesis in human glioblastoma. *Clin Cancer Res* 2000; **6**: 102-111 [PMID: 10656438]

83 **Barbieri F**, Bajetto A, Stumm R, Pattarozzi A, Porcile C, Zona G, Dorcaratto A, Ravetti JL, Minuto F, Spaziante R, Schettini G, Ferone D, Florio T. Overexpression of stromal cell-derived factor 1 and its receptor CXCR4 induces autocrine/paracrine cell proliferation in human pituitary adenomas. *Clin Cancer Res* 2008; **14**: 5022-5032 [PMID: 18698020 DOI: 10.1158/1078-0432.ccr-07-4717]

84 **Barbero S**, Bonavia R, Bajetto A, Porcile C, Pirani P, Ravetti JL, Zona GL, Spaziante R, Florio T, Schettini G. Stromal cell-derived factor 1alpha stimulates human glioblastoma cell growth through the activation of both extracellular signal-regulated kinases 1/2 and Akt. *Cancer Res* 2003; **63**: 1969-1974 [PMID: 12702590]

85 **Bajetto A**, Barbieri F, Dorcaratto A, Barbero S, Daga A, Porcile C, Ravetti JL, Zona G, Spaziante R, Corte G, Schettini G, Florio T. Expression of CXC chemokine receptors 1-5 and their ligands in human glioma tissues: role of CXCR4 and SDF1 in glioma cell proliferation and migration. *Neurochem Int* 2006; **49**: 423-432 [PMID: 16621164 DOI: 10.1016/j.neuint.2006.03.003]

86 **Lee HJ**, Lee K, Lee DG, Bae KH, Kim JS, Liang ZL, Huang SM, Suk Oh Y, Kim HY, Jo DY, Min JK, Kim JM, Lee HJ. Chemokine (C-X-C motif) ligand 12 is associated with gallbladder carcinoma progression and is a novel independent poor prognostic factor. *Clin Cancer Res* 2012; **18**: 3270-3280 [PMID: 22553346 DOI: 10.1158/1078-0432.ccr-11-2417]

87 **Zhuang Y**, Peng LS, Zhao YL, Shi Y, Mao XH, Chen W, Pang KC, Liu XF, Liu T, Zhang JY, Zeng H, Liu KY, Guo G, Tong WD, Shi Y, Tang B, Li N, Yu S, Luo P, Zhang WJ, Lu DS, Yu PW, Zou QM. CD8(+) T cells that produce interleukin-17 regulate myeloid-derived suppressor cells and are associated with survival time of patients with gastric cancer. *Gastroenterology* 2012; **143**: 951-962.e8 [PMID: 22710190 DOI: 10.1053/j.gastro.2012.06.010]

88 **Shibata W**, Ariyama H, Westphalen CB, Worthley DL, Muthupalani S, Asfaha S, Dubeykovskaya Z, Quante M, Fox JG, Wang TC. Stromal cell-derived factor-1 overexpression induces gastric dysplasia through expansion of stromal myofibroblasts and epithelial progenitors. *Gut* 2013; **62**: 192-200 [PMID: 22362916 DOI: 10.1136/gutjnl-2011-301824]

89 **Oh YS**, Kim HY, Song IC, Yun HJ, Jo DY, Kim S, Lee HJ. Hypoxia induces CXCR4 expression and biological activity in gastric cancer cells through activation of hypoxia-inducible factor-1α. *Oncol Rep* 2012; **28**: 2239-2246 [PMID: 23023480 DOI: 10.3892/or.2012.2063]

90 **Fernandis AZ**, Prasad A, Band H, Klösel R, Ganju RK. Regulation of CXCR4-mediated chemotaxis and chemoinvasion of breast cancer cells. *Oncogene* 2004; **23**: 157-167 [PMID: 14712221 DOI: 10.1038/sj.onc.1206910]

91 **Hartmann TN**, Burger JA, Glodek A, Fujii N, Burger M. CXCR4 chemokine receptor and integrin signaling co-operate in mediating adhesion and chemoresistance in small cell lung cancer (SCLC) cells. *Oncogene* 2005; **24**: 4462-4471 [PMID: 15806155 DOI: 10.1038/sj.onc.1208621]

92 **Luker KE**, Luker GD. Functions of CXCL12 and CXCR4 in breast cancer. *Cancer Lett* 2006; **238**: 30-41 [PMID: 16046252 DOI: 10.1016/j.canlet.2005.06.021]

93 **Yamashita K**, Azumano I, Mai M, Okada Y. Expression and tissue localization of matrix metalloproteinase 7 (matrilysin) in human gastric carcinomas. Implications for vessel invasion and metastasis. *Int J Cancer* 1998; **79**: 187-194 [PMID: 9583735]

94 **Shim KN**, Jung SA, Joo YH, Yoo K. Clinical significance of tissue levels of matrix metalloproteinases and tissue inhibitors of metalloproteinases in gastric cancer. *J Gastroenterol* 2007; **42**: 120-128 [PMID: 17351800 DOI: 10.1007/s00535-006-1975-y]

95 **Dubeykovskaya Z**, Dubeykovskiy A, Solal-Cohen J, Wang TC. Secreted trefoil factor 2 activates the CXCR4 receptor in epithelial and lymphocytic cancer cell lines. *J Biol Chem* 2009; **284**: 3650-3662 [PMID: 19064997 DOI: 10.1074/jbc.M804935200]

96 **Koizumi K**, Kato S, Sakurai H, Hashimoto I, Yasumoto K, Saiki I. Therapeutics target of CXCR4 and its downstream in peritoneal carcinomatosis of gastric cancer. *Front Biosci* (Schol Ed) 2012; **4**: 269-276 [PMID: 22202059]

97 **Soriano SF**, Serrano A, Hernanz-Falcón P, Martín de Ana A, Monterrubio M, Martínez C, Rodríguez-Frade JM, Mellado M. Chemokines integrate JAK/STAT and G-protein pathways during chemotaxis and calcium flux responses. *Eur J Immunol* 2003; **33**: 1328-1333 [PMID: 12731058 DOI: 10.1002/eji.200323897]

98 **Maksym RB**, Tarnowski M, Grymula K, Tarnowska J, Wysoczynski M, Liu R, Czerny B, Ratajczak J, Kucia M, Ratajczak MZ. The role of stromal-derived factor-1--CXCR7 axis in development and cancer. *Eur J Pharmacol* 2009; **625**: 31-40 [PMID: 19835865 DOI: 10.1016/j.ejphar.2009.04.071]

99 **Burns JM**, Summers BC, Wang Y, Melikian A, Berahovich R, Miao Z, Penfold ME, Sunshine MJ, Littman DR, Kuo CJ, Wei K, McMaster BE, Wright K, Howard MC, Schall TJ. A novel chemokine receptor for SDF-1 and I-TAC involved in cell survival, cell adhesion, and tumor development. *J Exp Med* 2006; **203**: 2201-2213 [PMID: 16940167 DOI: 10.1084/jem.20052144]

100 **Miao Z**, Luker KE, Summers BC, Berahovich R, Bhojani MS, Rehemtulla A, Kleer CG, Essner JJ, Nasevicius A, Luker GD, Howard MC, Schall TJ. CXCR7 (RDC1) promotes breast and lung tumor growth in vivo and is expressed

on tumor-associated vasculature. *Proc Natl Acad Sci USA* 2007; **104**: 15735-15740 [PMID: 17898181 DOI: 10.1073/pnas.0610444104]

101 **Lee HJ**, Lee KS, Ryu H, Song IC, Huang SM, Yun HJ, Kim J, Jo DY, Kim S. The combined expression of CXCR7 and its ligand CXCL12 is a marker for unfavorable prognosis in gastric cancer. *Ann Oncol* 2012; **23** suppl 9: 541-541 Available from: URL: http://annonc.oxfordjournals.org/content/23/suppl_9/ix541.full?sid=956a7a70-63a0-4e96-80d1-7d8982754c6c

102 **Miyazaki H**, Takabe K, Yeudall WA. Chemokines, chemokine receptors and the gastrointestinal system. *World J Gastroenterol* 2013; **19**: 2847-2863 [PMID: 23704819 DOI: 10.3748/wjg.v19.i19.2847]

103 **Sieveking D**, Mitchell HM, Day AS. Gastric epithelial cell CXC chemokine secretion following Helicobacter pylori infection in vitro. *J Gastroenterol Hepatol* 2004; **19**: 982-987 [PMID: 15304113 DOI: 10.1111/j.1440-1746.2004.03413.x]

104 **Kitadai Y**, Haruma K, Sumii K, Yamamoto S, Ue T, Yokozaki H, Yasui W, Ohmoto Y, Kajiyama G, Fidler IJ, Tahara E. Expression of interleukin-8 correlates with vascularity in human gastric carcinomas. *Am J Pathol* 1998; **152**: 93-100 [PMID: 9422527]

105 **Torti D**, Sassi F, Galimi F, Gastaldi S, Perera T, Comoglio PM, Trusolino L, Bertotti A. A preclinical algorithm of soluble surrogate biomarkers that correlate with therapeutic inhibition of the MET oncogene in gastric tumors. *Int J Cancer* 2012; **130**: 1357-1366 [PMID: 21500189 DOI: 10.1002/ijc.26137]

106 **Kido S**, Kitadai Y, Hattori N, Haruma K, Kido T, Ohta M, Tanaka S, Yoshihara M, Sumii K, Ohmoto Y, Chayama K. Interleukin 8 and vascular endothelial growth factor -- prognostic factors in human gastric carcinomas? *Eur J Cancer* 2001; **37**: 1482-1487 [PMID: 11506954]

107 **Ju DW**, Wei PK, Lin HM, Sun DZ, Yu S, Xiu LJ. Effects of Xiaotan Sanjie Decoction on expressions of interleukin-8 and its receptors in gastric tumor xenografts and gastric tissue adjacent to the tumor in mice. *Zhongxi Yijiehe Xuebao* 2010; **8**: 74-79 [PMID: 20082763]

108 **Sakitani K**, Hirata Y, Hayakawa Y, Serizawa T, Nakata W, Takahashi R, Kinoshita H, Sakamoto K, Nakagawa H, Akanuma M, Yoshida H, Maeda S, Koike K. Role of interleukin-32 in Helicobacter pylori-induced gastric inflammation. *Infect Immun* 2012; **80**: 3795-3803 [PMID: 22890997 DOI: 10.1128/iai.00637-12]

109 **Eck M**, Schmausser B, Scheller K, Brändlein S, Müller-Hermelink HK. Pleiotropic effects of CXC chemokines in gastric carcinoma: differences in CXCL8 and CXCL1 expression between diffuse and intestinal types of gastric carcinoma. *Clin Exp Immunol* 2003; **134**: 508-515 [PMID: 14632759]

110 **Allison CC**, Ferrand J, McLeod L, Hassan M, Kaparakis-Liaskos M, Grubman A, Bhathal PS, Dev A, Sievert W, Jenkins BJ, Ferrero RL. Nucleotide oligomerization domain 1 enhances IFN-γ signaling in gastric epithelial cells during Helicobacter pylori infection and exacerbates disease severity. *J Immunol* 2013; **190**: 3706-3715 [PMID: 23460743 DOI: 10.4049/jimmunol.1200591]

111 **Macrì A**, Versaci A, Loddo S, Scuderi G, Travagliante M, Trimarchi G, Teti D, Famulari C. Serum levels of interleukin 1beta, interleukin 8 and tumour necrosis factor alpha as markers of gastric cancer. *Biomarkers* 2006; **11**: 184-193 [PMID: 16766394 DOI: 10.1080/13547500600565677]

112 **Smith DR**, Polverini PJ, Kunkel SL, Orringer MB, Whyte RI, Burdick MD, Wilke CA, Strieter RM. Inhibition of interleukin 8 attenuates angiogenesis in bronchogenic carcinoma. *J Exp Med* 1994; **179**: 1409-1415 [PMID: 7513008]

113 **Yoneda J**, Kuniyasu H, Crispens MA, Price JE, Bucana CD, Fidler IJ. Expression of angiogenesis-related genes and progression of human ovarian carcinomas in nude mice. *J Natl Cancer Inst* 1998; **90**: 447-454 [PMID: 9521169]

114 **Inoue K**, Slaton JW, Eve BY, Kim SJ, Perrotte P, Balbay MD, Yano S, Bar-Eli M, Radinsky R, Pettaway CA, Dinney CP. Interleukin 8 expression regulates tumorigenicity and metastases in androgen-independent prostate cancer. *Clin Cancer Res* 2000; **6**: 2104-2119 [PMID: 10815938]

115 **Kitadai Y**, Takahashi Y, Haruma K, Naka K, Sumii K, Yokozaki H, Yasui W, Mukaida N, Ohmoto Y, Kajiyama G, Fidler IJ, Tahara E. Transfection of interleukin-8 increases angiogenesis and tumorigenesis of human gastric carcinoma cells in nude mice. *Br J Cancer* 1999; **81**: 647-653 [PMID: 10574250 DOI: 10.1038/sj.bjc.6690742]

116 **Ju D**, Sun D, Xiu L, Meng X, Zhang C, Wei P. Interleukin-8 is associated with adhesion, migration and invasion in human gastric cancer SCG-7901 cells. *Med Oncol* 2012; **29**: 91-99 [PMID: 21191670 DOI: 10.1007/s12032-010-9780-0]

117 **Kuai WX**, Wang Q, Yang XZ, Zhao Y, Yu R, Tang XJ. Interleukin-8 associates with adhesion, migration, invasion and chemosensitivity of human gastric cancer cells. *World J Gastroenterol* 2012; **18**: 979-985 [PMID: 22408359 DOI: 10.3748/wjg.v18.i9.979]

118 **Taguchi A**, Ohmiya N, Shirai K, Mabuchi N, Itoh A, Hirooka Y, Niwa Y, Goto H. Interleukin-8 promoter polymorphism increases the risk of atrophic gastritis and gastric cancer in Japan. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 2487-2493 [PMID: 16284368 DOI: 10.1158/1055-9965.epi-05-0326]

119 **Ye BD**, Kim SG, Park JH, Kim JS, Jung HC, Song IS. The interleukin-8-251 A allele is associated with increased risk of noncardia gastric adenocarcinoma in Helicobacter pylori-infected Koreans. *J Clin Gastroenterol* 2009; **43**: 233-239 [PMID: 18542040 DOI: 10.1097/MCG.0b013e3181646701]

120 **Ohyauchi M**, Imatani A, Yonechi M, Asano N, Miura A, Iijima K, Koike T, Sekine H, Ohara S, Shimosegawa T. The polymorphism interleukin 8 -251 A/T influences the susceptibility of Helicobacter pylori related gastric diseases in the Japanese population. *Gut* 2005; **54**: 330-335 [PMID: 15710978 DOI: 10.1136/gut.2003.033050]

121 **Lu W**, Pan K, Zhang L, Lin D, Miao X, You W. Genetic polymorphisms of interleukin (IL)-1B, IL-1RN, IL-8, IL-10 and tumor necrosis factor {alpha} and risk of gastric cancer in a Chinese population. *Carcinogenesis* 2005; **26**: 631-636 [PMID: 15579481 DOI: 10.1093/carcin/bgh349]

122 **Wang J**, Pan HF, Hu YT, Zhu Y, He Q. Polymorphism of IL-8 in 251 allele and gastric cancer susceptibility: a meta-analysis. *Dig Dis Sci* 2010; **55**: 1818-1823 [PMID: 19777350 DOI: 10.1007/s10620-009-0978-y]

123 **Vinagre RM**, Corvelo TC, Arnaud VC, Leite AC, Barile KA, Martins LC. Determination of strains of Helicobacter pylori and of polymorphism in the interleukin-8 gene in patients with stomach cancer. *Arq Gastroenterol* 2011; **48**: 46-51 [PMID: 21537542]

124 **Song JH**, Kim SG, Jung SA, Lee MK, Jung HC, Song IS. The interleukin-8-251 AA genotype is associated with angiogenesis in gastric carcinogenesis in Helicobacter pylori-infected Koreans. *Cytokine* 2010; **51**: 158-165 [PMID: 20621718 DOI: 10.1016/j.cyto.2010.05.001]

125 **Wang JP**, Hu WM, Wang KS, Luo BH, Wu C, Chen ZH, Luo GQ, Liu YW, Liu QL, Yu J, Li JH, Wen JF. Upregulation of C-X-C chemokine receptor type 1 expression is associated with late-stage gastric adenocarcinoma. *Exp Ther Med* 2012; **4**: 55-60 [PMID: 23060922 DOI: 10.3892/etm.2012.568]

126 **Wang JP**, Hu WM, Wang KS, Yu J, Luo BH, Wu C, Chen ZH, Luo GQ, Liu YW, Liu QL, Xiao Y, Zhou HY, Yang XJ, Jiang HY, Li JH, Wen JF. Expression of C-X-C chemokine receptor types 1/2 in patients with gastric carcinoma: Clinicopathological correlations and significance. *Oncol Lett* 2013; **5**: 574-582 [PMID: 23420470 DOI: 10.3892/ol.2012.1043]

127 **Kitadai Y**, Haruma K, Mukaida N, Ohmoto Y, Matsutani N, Yasui W, Yamamoto S, Sumii K, Kajiyama G, Fidler IJ, Tahara E. Regulation of disease-progression genes in human gastric carcinoma cells by interleukin 8. *Clin Cancer Res* 2000;

6: 2735-2740 [PMID: 10914718]
128 **Ewington L**, Taylor A, Sriraksa R, Horimoto Y, Lam EW, El-Bahrawy MA. The expression of interleukin-8 and interleukin-8 receptors in endometrial carcinoma. *Cytokine* 2012; **59**: 417-422 [PMID: 22626766 DOI: 10.1016/j.cyto.2012.04.036]
129 **Waugh DJ**, Wilson C. The interleukin-8 pathway in cancer. *Clin Cancer Res* 2008; **14**: 6735-6741 [PMID: 18980965 DOI: 10.1158/1078-0432.ccr-07-4843]
130 **Junnila S**, Kokkola A, Mizuguchi T, Hirata K, Karjalainen-Lindsberg ML, Puolakkainen P, Monni O. Gene expression analysis identifies over-expression of CXCL1, SPARC, SPP1, and SULF1 in gastric cancer. *Genes Chromosomes Cancer* 2010; **49**: 28-39 [PMID: 19780053 DOI: 10.1002/gcc.20715]
131 **Cheng WL**, Wang CS, Huang YH, Tsai MM, Liang Y, Lin KH. Overexpression of CXCL1 and its receptor CXCR2 promote tumor invasion in gastric cancer. *Ann Oncol* 2011; **22**: 2267-2276 [PMID: 21343381 DOI: 10.1093/annonc/mdq739]
132 **Xu J**, Zhang C, He Y, Wu H, Wang Z, Song W, Li W, He W, Cai S, Zhan W. Lymphatic endothelial cell-secreted CXCL1 stimulates lymphangiogenesis and metastasis of gastric cancer. *Int J Cancer* 2012; **130**: 787-797 [PMID: 21387301 DOI: 10.1002/ijc.26035]
133 **Kuzuhara T**, Suganuma M, Kurusu M, Fujiki H. Helicobacter pylori-secreting protein Tipalpha is a potent inducer of chemokine gene expressions in stomach cancer cells. *J Cancer Res Clin Oncol* 2007; **133**: 287-296 [PMID: 17393199 DOI: 10.1007/s00432-006-0169-6]
134 **Karasawa F**, Shiota A, Goso Y, Kobayashi M, Sato Y, Masumoto J, Fujiwara M, Yokosawa S, Muraki T, Miyagawa S, Ueda M, Fukuda MN, Fukuda M, Ishihara K, Nakayama J. Essential role of gastric gland mucin in preventing gastric cancer in mice. *J Clin Invest* 2012; **122**: 923-934 [PMID: 22307328 DOI: 10.1172/jci59087]
135 **Sheh A**, Ge Z, Parry NM, Muthupalani S, Rager JE, Raczynski AR, Mobley MW, McCabe AF, Fry RC, Wang TC, Fox JG. 17β-estradiol and tamoxifen prevent gastric cancer by modulating leukocyte recruitment and oncogenic pathways in Helicobacter pylori-infected INS-GAS male mice. *Cancer Prev Res* (Phila) 2011; **4**: 1426-1435 [PMID: 21680705 DOI: 10.1158/1940-6207.capr-11-0219]
136 **Tang W**, Morgan DR, Meyers MO, Dominguez RL, Martinez E, Kakudo K, Kuan PF, Banet N, Muallem H, Woodward K, Speck O, Gulley ML. Epstein-barr virus infected gastric adenocarcinoma expresses latent and lytic viral transcripts and has a distinct human gene expression profile. *Infect Agent Cancer* 2012; **7**: 21 [PMID: 22929309 DOI: 10.1186/1750-9378-7-21]
137 **Jung JJ**, Noh S, Jeung HC, Jung M, Kim TS, Noh SH, Roh JK, Chung HC, Rha SY. Chemokine growth-regulated oncogene 1 as a putative biomarker for gastric cancer progression. *Cancer Sci* 2010; **101**: 2200-2206 [PMID: 20731665 DOI: 10.1111/j.1349-7006.2010.01666.x]
138 **Sharma B**, Nawandar DM, Nannuru KC, Varney ML, Singh RK. Targeting CXCR2 enhances chemotherapeutic response, inhibits mammary tumor growth, angiogenesis, and lung metastasis. *Mol Cancer Ther* 2013; **12**: 799-808 [PMID: 23468530 DOI: 10.1158/1535-7163.mct-12-0529]
139 **Yamamoto M**, Kikuchi H, Ohta M, Kawabata T, Hiramatsu Y, Kondo K, Baba M, Kamiya K, Tanaka T, Kitagawa M, Konno H. TSU68 prevents liver metastasis of colon cancer xenografts by modulating the premetastatic niche. *Cancer Res* 2008; **68**: 9754-9762 [PMID: 19047154 DOI: 10.1158/0008-5472.can-08-1748]
140 **Singh S**, Sadanandam A, Nannuru KC, Varney ML, Mayer-Ezell R, Bond R, Singh RK. Small-molecule antagonists for CXCR2 and CXCR1 inhibit human melanoma growth by decreasing tumor cell proliferation, survival, and angiogenesis. *Clin Cancer Res* 2009; **15**: 2380-2386 [PMID: 19293256 DOI: 10.1158/1078-0432.ccr-08-2387]
141 **Okayama H**, Kumamoto K, Saitou K, Hayase S, Kofunato Y, Sato Y, Miyamoto K, Nakamura I, Ohki S, Sekikawa K, Takenoshita S. CD44v6, MMP-7 and nuclear Cdx2 are significant biomarkers for prediction of lymph node metastasis in primary gastric cancer. *Oncol Rep* 2009; **22**: 745-755 [PMID: 19724852]
142 **Park JY**, Park KH, Bang S, Kim MH, Lee JE, Gang J, Koh SS, Song SY. CXCL5 overexpression is associated with late stage gastric cancer. *J Cancer Res Clin Oncol* 2007; **133**: 835-840 [PMID: 17479287 DOI: 10.1007/s00432-007-0225-x]
143 **Kraft M**, Riedel S, Maaser C, Kucharzik T, Steinbuechel A, Domschke W, Luegering N. IFN-gamma synergizes with TNF-alpha but not with viable H. pylori in up-regulating CXC chemokine secretion in gastric epithelial cells. *Clin Exp Immunol* 2001; **126**: 474-481 [PMID: 11737065]
144 **Rajkumar T**, Vijayalakshmi N, Gopal G, Sabitha K, Shirley S, Raja UM, Ramakrishnan SA. Identification and validation of genes involved in gastric tumorigenesis. *Cancer Cell Int* 2010; **10**: 45 [PMID: 21092330 DOI: 10.1186/1475-2867-10-45]
145 **Ohtani H**, Jin Z, Takegawa S, Nakayama T, Yoshie O. Abundant expression of CXCL9 (MIG) by stromal cells that include dendritic cells and accumulation of CXCR3+ T cells in lymphocyte-rich gastric carcinoma. *J Pathol* 2009; **217**: 21-31 [PMID: 18980207 DOI: 10.1002/path.2448]
146 **Deng L**, Chen N, Li Y, Zheng H, Lei Q. CXCR6/CXCL16 functions as a regulator in metastasis and progression of cancer. *Biochim Biophys Acta* 2010; **1806**: 42-49 [PMID: 20122997 DOI: 10.1016/j.bbcan.2010.01.004]
147 **Darash-Yahana M**, Gillespie JW, Hewitt SM, Chen YY, Maeda S, Stein I, Singh SP, Bedolla RB, Peled A, Troyer DA, Pikarsky E, Karin M, Farber JM. The chemokine CXCL16 and its receptor, CXCR6, as markers and promoters of inflammation-associated cancers. *PLoS One* 2009; **4**: e6695 [PMID: 19690611 DOI: 10.1371/journal.pone.0006695]
148 **Hojo S**, Koizumi K, Tsuneyama K, Arita Y, Cui Z, Shinohara K, Minami T, Hashimoto I, Nakayama T, Sakurai H, Takano Y, Yoshie O, Tsukada K, Saiki I. High-level expression of chemokine CXCL16 by tumor cells correlates with a good prognosis and increased tumor-infiltrating lymphocytes in colorectal cancer. *Cancer Res* 2007; **67**: 4725-4731 [PMID: 17510400 DOI: 10.1158/0008-5472.can-06-3424]
149 **Xing YN**, Xu XY, Nie XC, Yang X, Yu M, Xu HM, Liu YP, Takano Y, Zheng HC. Role and clinicopathologic significance of CXC chemokine ligand 16 and chemokine (C-X-C motif) receptor 6 expression in gastric carcinomas. *Hum Pathol* 2012; **43**: 2299-2307 [PMID: 22863086 DOI: 10.1016/j.humpath.2011.08.027]
150 **Duda DG**, Kozin SV, Kirkpatrick ND, Xu L, Fukumura D, Jain RK. CXCL12 (SDF1alpha)-CXCR4/CXCR7 pathway inhibition: an emerging sensitizer for anticancer therapies? *Clin Cancer Res* 2011; **17**: 2074-2080 [PMID: 21349998 DOI: 10.1158/1078-0432.ccr-10-2636]
151 **Iwanaga T**, Iwasaki Y, Ohashi M, Nunobe S, Iwagami S. [Establishment of a CXCR4-expressing gastric cancer cell line in nude mice and the effect of AMD 3100 on tumor regression]. *Gan To Kagaku Ryoho* 2007; **34**: 1917-1919 [PMID: 18219852]
152 **Iwanaga T**, Iwasaki Y, Ohashi M, Ohinata R, Takahashi K, Yamaguchi T, Matsumoto H, Nakano D. [Inhibitory effect of CXCR4 blockers on a CXCR4-expressing gastric cancer cell line in nude mice]. *Gan To Kagaku Ryoho* 2012; **39**: 1788-1790 [PMID: 23267887]
153 **Xie L**, Wei J, Qian X, Chen G, Yu L, Ding Y, Liu B. CXCR4, a potential predictive marker for docetaxel sensitivity in gastric cancer. *Anticancer Res* 2010; **30**: 2209-2216 [PMID: 20651371]
154 **Manu KA**, Shanmugam MK, Rajendran P, Li F, Ramachandran L, Hay HS, Kannaiyan R, Swamy SN, Vali S, Kapoor S, Ramesh B, Bist P, Koay ES, Lim LH, Ahn KS, Kumar AP, Sethi G. Plumbagin inhibits invasion and migration of breast and gastric cancer cells by downregulating the expression of chemokine receptor CXCR4. *Mol Cancer* 2011; **10**: 107 [PMID:

21880153 DOI: 10.1186/1476-4598-10-107]
155 **Ning Y**, Labonte MJ, Zhang W, Bohanes PO, Gerger A, Yang D, Benhaim L, Paez D, Rosenberg DO, Nagulapalli Venkata KC, Louie SG, Petasis NA, Ladner RD, Lenz HJ. The CXCR2 antagonist, SCH-527123, shows antitumor activity and sensitizes cells to oxaliplatin in preclinical colon cancer models. *Mol Cancer Ther* 2012; **11**: 1353-1364 [PMID: 22391039 DOI: 10.1158/1535-7163.mct-11-0915]
156 **Varney ML**, Li A, Dave BJ, Bucana CD, Johansson SL, Singh RK. Expression of CXCR1 and CXCR2 receptors in malignant melanoma with different metastatic potential and their role in interleukin-8 (CXCL-8)-mediated modulation of metastatic phenotype. *Clin Exp Metastasis* 2003; **20**: 723-731 [PMID: 14713106]
157 **Singh JK**, Farnie G, Bundred NJ, Simões BM, Shergill A, Landberg G, Howell SJ, Clarke RB. Targeting CXCR1/2 significantly reduces breast cancer stem cell activity and increases the efficacy of inhibiting HER2 via HER2-dependent and -independent mechanisms. *Clin Cancer Res* 2013; **19**: 643-656 [PMID: 23149820 DOI: 10.1158/1078-0432.ccr-12-1063]
158 **Mian BM**, Dinney CP, Bermejo CE, Sweeney P, Tellez C, Yang XD, Gudas JM, McConkey DJ, Bar-Eli M. Fully human anti-interleukin 8 antibody inhibits tumor growth in orthotopic bladder cancer xenografts via down-regulation of matrix metalloproteases and nuclear factor-kappaB. *Clin Cancer Res* 2003; **9**: 3167-3175 [PMID: 12912969]
159 **Singh S**, Sadanandam A, Varney ML, Nannuru KC, Singh RK. Small interfering RNA-mediated CXCR1 or CXCR2 knock-down inhibits melanoma tumor growth and invasion. *Int J Cancer* 2010; **126**: 328-336 [PMID: 19585580 DOI: 10.1002/ijc.24714]
160 **Varney ML**, Singh S, Li A, Mayer-Ezell R, Bond R, Singh RK. Small molecule antagonists for CXCR2 and CXCR1 inhibit human colon cancer liver metastases. *Cancer Lett* 2011; **300**: 180-188 [PMID: 21035946 DOI: 10.1016/j.canlet.2010.10.004]

P- Reviewer: Yun S **S- Editor**: Wen LL **L- Editor**: A
E- Editor: Wu HL

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327