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

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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.
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\[^{5-8}\]. Molecular alterations in gastric carcinogenesis have been identified in **Her-2/neu** (\(c-erbB2\))\[^{9-11}\], **c-Met**\[^{12,13}\], semaphorin-5A\[^{14}\], **BCL2-like-12** (\(BCL2L12\))\[^{15}\], **c-MET**\[^{16}\], and **K-sam**\[^{17}\], while molecular markers 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\[^{27,28}\]. 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\[^{29}\]. 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 \(\beta\)-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\(^{-}\))\[^{33,34}\].

Chemokines are produced by many cell types, including leukocytes, endothelial cells, fibroblasts, epithelial cells, and tumor cells\[^{35,36}\]. 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 (\(\alpha\), \(\beta\) and \(\gamma\) 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\[^{39,40}\].

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\[^{41,42}\]. 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\[^{43}\]. For example, ELR\(^{+}\) CXC chemokines such as **CXCL8** can enhance tumor growth by inducing angiogenesis and the chemotraction of neutrophilic granulocytes. Neutrophils then further facilitate angiogenesis, tumor growth, and metastasis by releasing matrix-degrading enzymes [such as matrix-metalloproteinase (MMP)-9] and angiogenic tumor-promoting factors such as vascular endothelial growth factor (VEGF)\[^{44,45}\]. In contrast, ELR CXC chemokines such as interferon-\(\gamma\) 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 [5,74]. Furthermore, in contrast to the anti-tumoral activities of the CXCR3-binding ELR CXC chemokines, these chemokines also promote the metastasis of CXC3-positive tumor cells to lymph nodes and distant sites [57,58]. 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 [45-50]. The differential expression of CXCR4 in gastric cancer is also identified by gene expression profiling [51-53]. In addition, pre-operative circulating CXCL4 mRNA levels in the plasma of patients with gastric cancer are elevated compared with normal controls, but then decrease after surgery [48]. 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 [47,49-51]. 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 [57,58]. CXCR4 expression is also associated with aggressive tumor behavior, such as poor differentiation, tumor invasion and metastasis [45,48,50-53,55,56-60], and it could therefore be an independent prognostic marker for the overall survival of patients with gastric cancer [57]. 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 [51,52], 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. 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 [80]. 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]. 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 [5,74,75].

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 [57,76]. Zhuang et al. 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. 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. 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 [5,79]. 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 [50,52]. CXCL12-activated CXCR4 progressively upregulated the expression
of MMP-2 and MMP-7 in gastric cancer cells\cite{5,64}, while CXCR4 expression was also correlated with the expression of MMP-7 and MMP-9 in gastric cancer tissue\cite{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\cite{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\cite{52,52}. 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)\cite{5,47,64,74,95}. 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\cite{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\cite{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\cite{5,47,64,74}.

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]\cite{5,47,92}. 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\cite{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\cite{5,77}, 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\cite{5,46}.

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\cite{5,58}. 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\cite{98,100}. In gastric cancer, Lee et al\cite{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\cite{102,104-107}. The gastric cancer cell lines AGS and KATO III secreted CXCL8 following infection with H. pylori, which is associated with gastric carcinogenesis\cite{103,104}. The up-regulation of CXCL8 was demonstrated in gastric cancer cell lines by gene expression profiling, and in gastric cancer tissue by immunostaining\cite{105,106,107,100,109}. In addition, the serum levels of circulating CXCL8 were higher in gastric cancer patients than healthy controls\cite{111}. The expression of CXCL8 was associated with increased venous and lymphatic invasion, and increased depth of invasion in gastric cancer\cite{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\cite{104,109}. Consistent with these observations, CXCL8 was identified as a strong angiogenic factor in lung, ovarian, and prostate cancer\cite{112,114}. Direct evidence for the role of CXCL8 in the angiogenesis and tumorigenesis of gastric cancer was first provided by Kitadai et al\cite{112} 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. Ju et al. 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. 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. Wang et al. reported an increased incidence of this allele in H. pylori-infected Korean populations. The gastric mucosal concentration of MMP-9 and angiopeptin (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. revealed an interaction between CXCL8 251 polymorphism, particularly with carriers of the A allele, and stn1 cagA 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, suggesting that tumor-derived CXCL8 exerts biological effects on the tumor cells in an autocrine or paracrine manner. Wang et al. 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. 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. 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.

**CXCL1-CXCR2**

CXCL1 and its receptor CXCR2 are differentially expressed in gastric cancer. Gastric cancer cells produce CXCL1, and its gene expression was detected both in vitro and in gastric cancer mouse models in vivo. In addition, the expression of CXCL1 mRNA and protein was higher in gastric cancer tissue compared with non-cancerous gastric tissues. Further studies analyzed gene expression profiles, and revealed the upregulation of circulating CXCL1 levels in patients with gastric cancer compared with healthy controls. 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. Increased expression of both proteins was also associated with tumor progression, and more advanced stages of gastric cancer, while elevated CXCL1 expression was an independent prognostic factor for patient survival. 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. In contrast, Junila et al. 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. 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. CXCL1-overexpressing cells also expressed significantly higher levels of MMP-2 and MMP-9 activity than control cells, and upregulation of Ras and STAT3 contributed 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. 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. In addition, CXCL5 gene ex-
pression was up regulated in the gastric mucosa of the \textsc{Akat}\textsuperscript{1} gastric cancer mouse model compared with wild-type mice, which was confirmed by quantitative reverse transcription-polymerase chain reaction\textsuperscript{134}. However, the role of the chemokine CXCL5 in gastric carcinogenesis is still unclear, and additional \textit{in vitro} and \textit{in vivo} studies are needed to characterize its effects.

Recently Yanagi \textit{et al}\textsuperscript{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 \textsc{III} and NCI. In addition, their secretion was strongly induced by treatment with a combination of interferon-\textgamma and tumor necrosis factor-\alpha\textsuperscript{143}. Jung \textit{et al}\textsuperscript{139} used genome-wide gene expression databases to show that the CXCL9 and CXCL10 genes were upregulated more than twofold in gastric cancer compared to normal tissues. Consistent with this, Rajkumar \textit{et al}\textsuperscript{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 \textsuperscript{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\textsuperscript{146}. For example, Darash-Yaha\textit{a} \textit{et al}\textsuperscript{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 \textit{in vitro}. Hojo \textit{et al}\textsuperscript{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 \textit{et al}\textsuperscript{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.

\textbf{THERAPEUTIC TARGETING OF CHEMOKINES AND THEIR RECEPTORS IN GASTRIC CANCER}

\textbf{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 (Noxson), and the CXCR7-specific inhibitor CCX2066 (ChemoCentrix). Additional strategies to inhibit CXCL12 signaling, including chalone 4 (C7870) or RNA interference, could also be assessed for the treatment of solid tumors\textsuperscript{150}.

In gastric cancer, several preclinical studies have demonstrated that blocking the CXCL12-CXCR4 axis showed anti-tumor activity \textit{in vitro} and \textit{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\textsuperscript{150,47,50,63}. 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\textsuperscript{47,131,152}. In addition, Xie \textit{et al}\textsuperscript{153} demonstrated that elevated CXCR4 mRNA levels in gastric cancer tissues were significantly correlated with docetaxel sensitivity, and that AMD3100 enhanced docetaxel cytotoxicity \textit{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\textsuperscript{154}. Plumbagin suppressed the binding of NF-\textkappaB to the CXCR4 promoter, suggesting that it inhibits CXCR4 expression by suppressing NF-\textkappaB-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 \textit{in vivo} mouse gastric cancer cells \textsc{via} the CXCL12-CXCR4 axis to inhibit tumor growth during hyperthermic therapy\textsuperscript{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. 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. Varney et al. 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. 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. 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.

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