C-C motif chemokine receptors in gastric cancer (Review)

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Abstract. Gastric cancer is the fifth most common cancer and the third leading cause of cancer-associated mortality worldwide. Despite recent advances in molecular and clinical research, patients with gastric cancer at an advanced stage have a dismal prognosis and poor survival rates, and systemic treatment relies predominantly on traditional cytotoxic chemotherapy. To improve patients' quality of life and survival, an improved understanding of the complex molecular mechanisms involved in gastric cancer progression and treatment resistance, and of its clinical application in the development of novel targeted therapies, is urgently required. Chemokines are a group of small chemotactic cytokines that interact with seven-transmembrane G-protein-coupled receptors, and this interaction serves a crucial role in various physiological processes, including organ development and the host immune response, to recruit cells to specific sites in the body. There is also accumulating evidence that chemokines and chemokine receptors (CCRs) contribute to tumor development and progression, as well as metastasis. However, research regarding the functional roles of chemokines and their receptors in cancer is dynamic and context-dependent, and much remains to be elucidated, although various aspects have been explored extensively. In gastric cancer, C-C motif CCRs are involved in the biological behavior of tumor cells, including the processes of growth, invasion and survival, as well as the epithelial-mesenchymal transition. In the present review, attention is given to the clinical relevance of C-C motif CCRs in the development, progression, and metastasis of gastric cancer, particularly CCR7 and CCR5, which have been investigated extensively, as well as their potential therapeutic implications.

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1. Introduction

Gastric cancer is the fifth most common cancer, and the third leading cause of cancer mortality worldwide (1-3). Despite a steady decline in incidence, gastric cancer causes more than 723,000 mortalities annually (3,4). The systemic treatment options for gastric cancer are limited, and patients have a poor oncologic outcome: Patients with stage 4 cancer show a 5-year overall survival rate of 4.0% (5). The initiation and progression of gastric cancer is a complex multistep process involving genetic and epigenetic aberrations (6,7). An understanding of the molecular pathogenesis of gastric tumorigenesis has resulted in the development of novel treatment options. Trastuzumab (Herceptin®), a monoclonal antibody against human epidermal growth factor receptor 2 (HER-2; also termed ERBB2), has led to an improvement in progression-free survival and overall survival compared with chemotherapy alone in patients with advanced gastric cancer overexpressing HER-2 in their tumor cells (8,9). Another agent with positive results is ramucirumab (CYRAMZA®), an antibody targeting vascular endothelial growth factor receptor-2 (10). That treatment represented the first biological therapy administered as a single drug to have elicited a survival benefit in patients with advanced gastric or gastro-esophageal junction adenocarcinoma that has progressed on first-line chemotherapy (11). Despite these advances in the treatment of gastric cancer, the median survival rate of patients with advanced gastric cancer remains unsatisfactory. An improved understanding of the molecular pathways underlying the development, progression and treatment resistance of gastric cancer would therefore yield novel therapeutic opportunities, resulting in an improved quality of life and the prolonged survival of patients.

Chemokines are a group of small chemotactic cytokines that interact with seven-transmembrane G-protein-coupled receptors, and this interaction is involved in organ development, host immune responses and other physiological

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processes that direct cells to specific sites in the body (12,13). Approximately 50 human genes encode chemokine ligands, and >20 chemokine receptor (CCR) genes have been identified since the term 'chemokine' was originally introduced in 1992 as an abbreviated form of chemotactic cytokine (1,14). Chemokines are classified into four major groups, namely, CXC, CC, CX3C and C, based on the position of the first two cysteine residues adjacent to the N-terminus, in which 'C' represents cysteine and 'X' represents a different amino acid (13,15,16). Chemokines and their receptors are either constitutively expressed or are induced by inflammatory cytokines, growth factors, and other external stimuli in numerous cell types, including leukocytes, endothelial cells, fibroblasts, epithelial cells, and cancer cells (1,17,18). There is accumulating evidence that chemokines and CCRs contribute to tumor development and progression, as well as metastasis, in addition to their role in the immune system (19,20). CCRs act as allosteric molecular relays: The chemokine bound to the extracellular domain of the receptor modifies the tertiary structure of the receptor, resulting in activation of heterotrimeric G-proteins via the intracellular domain. Upon receptor binding, downstream signaling is activated, resulting in the production of the second messengers, inositol trisphosphate and diacylglycerol, with subsequent calcium mobilization and activation of extracellular signal-regulated kinases (ERKs) 1 and 2, p38 mitogen-activated protein kinase, phospholipase-Cβ, phosphatidylinositol 3-kinase (PI3K), Ras, the Rho family of GTPases, p21-activated kinases, and nuclear factor-κB (NF-κB) (1,21).

In cancer, the role of chemokines and their receptors in tumorigenesis is complex and multifaceted, and involves leukocytes, stromal cells, and the cancer cells themselves. In most situations, the majority of chemokines exhibit powerful pro-malignancy effects; however, under certain conditions, chemokines induce the recruitment of leukocytes with anti-tumor activities to exert tumor-suppressive effects (22). For example, the glutamic acid-leucine-arginine (ELR)-expressing CXC chemokine, CXCL8, promotes tumor growth by inducing angiogenesis and chemoattraction of neutrophilic granulocytes. Neutrophils subsequently further promote tumor growth and progression by producing matrix-degrading and angiogenesis-enhancing factors, such as matrix-metalloproteinase-9 and vascular endothelial growth factor, respectively (23-26). In contrast, non-ELR expressing, CXCR3-binding chemokines, such as interferon-γ inducible protein-10, are angiostatic proteins, and recruit anti-tumoral lymphocytes (1). Therefore, research into the functional roles of chemokines and their receptors in cancer is dynamic and context-dependent, and much remains to be elucidated, although various aspects have been investigated extensively. In the present review, the roles of C-C motif CCRs in the development, progression, and metastasis of gastric cancer are discussed, focusing particularly on CCR7 and CCR5, which have been investigated extensively, as well as their potential therapeutic implications.

2. C-C motif CCR7

Among the C-C motif CCRs, the role of CCR7 in gastric cancer has been investigated most extensively. Numerous studies have shown that CCR7 is differentially expressed in tumor cells in gastric cancer at the mRNA and protein levels, as well as in the cell membrane *in vitro* and *in vivo* (27-37). In addition, CCR7 was detected in tumor-infiltrating lymphocytes and dendritic cells in gastric cancer, as well as in mononuclear cells in *Helicobacter pylori* gastritis (35,38). Schmausser *et al* (35) investigated expression of CCR7 during gastric tumorigenesis. As assessed by immunohistochemistry, CCR7 was expressed in gastric epithelial cells in non-inflamed mucosa, *H. pylori* gastritis, intestinal metaplasia and dysplasia, as well as in gastric cancer. The expression of CCR7 in *H. pylori* gastritis, which is associated with gastric carcinogenesis, was markedly higher compared with that in non-infected mucosa, and the intensity of CCR7 expression in precancerous lesions and gastric cancer was similar to that in the gastric epithelium of *H. pylori* gastritis. In addition, *H. pylori* upregulated CCR7 in CCR7-expressing gastric cancer cell lines, whereas no difference in CCR7 upregulation was identified between the *cag*+ and *cag*- *H. pylori* strains (35,39,40). Wang *et al* (32) demonstrated that CCR7 protein expression was significantly higher in gastric cancer compared with peritumoral tissues, and that high levels of CCR7 expression could be induced by loss of Dicer-1 and decreased levels of let-7a microRNA (miRNA) in gastric cancer. In that study, transfection of let-7a miRNA into gastric cancer cells markedly inhibited the expression of functional CCR7, suggesting that miRNA is involved in the regulation of CCR7 expression (32). The expression of CCR7 in gastric cancer was associated with aggressive tumor biology, including the processes of tumor invasion, lymph node metastasis, lymphatic invasion, venous invasion and an advanced stage of cancer (27-29,31,33), and this may be an important prognostic marker for survival in patients with gastric cancer (28,29,31), although contradictory data have also been reported (30).

CCR7 is involved in various biological processes, including the migration, invasion, survival and metastasis of multiple cell types, including cancer cells (13,41,42). The interaction between CCR7 and its ligand, CCL21, induces actin polymerization and pseudopodia formation (43). However, the mechanism by which CCR7 contributes to tumor progression has yet to be fully elucidated. In gastric cancer, CCL21 stimulation induced calcium mobilization and induced a transient increase in intracellular F-actin levels in CCR7-expressing gastric cancer cells, indicating that the morphological changes required for efficient metastasis were induced by the interaction between CCR7 and its ligand (31). In addition, signaling via CCR7 induced chemotactic and invasive responses in CCR7-positive gastric cancer cells, suggesting that functional CCR7 in gastric cancer cells may exert an important role in migration and invasion of gastric cancer. Recently, two groups demonstrated that CCR7 is involved in the epithelial-mesenchymal transition in gastric cancer (44,45). Zhang *et al* (44) reported that CCR7 induced the epithelial-mesenchymal transition by upregulating Snail, and that Snail signaling was regulated by the ERK and PI3K pathways instead of the Rho pathway, resulting in G_1/S cell cycle progression, migration and invasion of gastric tumor cells. Ma *et al* (45) investigated a CCR7-associated mechanism involved in gastric cancer progression, which was predicted on the basis of a bioinformatics analysis and verified in gastric cancer cells and primary tumor tissues. Those authors

demonstrated that CCR7 contributed to transforming growth factor β1 (TGF-β1)-induced epithelial-mesenchymal transition via crosstalk with the NF-κB signaling pathway, facilitating lymph node metastasis and tumor progression.

3. C-C motif CCR5

CCR5 and its ligand CCL5 [also termed regulated on activation, normal T cell expressed and secreted (RANTES)] are among the best-studied chemokines. These chemokines exert their major role in inflammatory processes, wherein they induce chemoattraction of various types of leukocytes to sites of infection and injury (22,46). Subsequently, it was revealed that certain strains of human immunodeficiency virus (HIV) utilize CCR5 as a co-receptor for cellular entry (22,47). Several studies have reported tumor-promoting functions of CCR5/CCL5, particularly in breast cancer (22,48-51), whereas, in certain cases, the CCR5/CCL5 system has been revealed to exert anti-tumoral functions (52,53). In breast cancer, for example, several groups demonstrated that the expression levels of CCR5 and CCL5 were higher in metastatic lymph nodes compared with primary tumors, and a high level of intratumoral CCL5 expression was correlated with advanced-stage disease (54-58). In addition, strong pro-malignancy effects associated with a high expression of CCR5/CCL5 in breast cancer was demonstrated (48). In terms of the role of CCR5/CCL5 in gastric cancer, several studies have demonstrated that gastric cancer cells express CCR5 and its ligand *in vitro* and *in vivo* (59-62). CCR5 expression, detected in the cell membrane, differs among gastric cell lines, including MKN45, MKN74, and KATO III, at the RNA and protein levels (60,61). The differential expression of CCR5 was confirmed by immunostaining of human gastric cancer tissue, and CCR5 expression was associated with lymph node metastasis and a worse prognosis in patients with gastric cancer (59,62). Furthermore, CCR5 expression was shown to be an independent indicator of a poor prognosis in gastric cancer (62). In addition, Gawron *et al* (63) reported that a CCR5 haplotype containing the common alleles, IVS1+151 G>T (rs2734686) and IVS2+80 C>T (rs1800024), and the minor allele, IVS1+246 A>G (rs1799987), was moderately associated with an increased risk of gastric cancer. It was reported that CCL5/RANTES is produced by gastric cancer cells, and higher serum concentrations of RANTES are associated with more advanced stages of gastric cancer (62). The expression level of RANTES in malignant lymph nodes was higher compared with that in normal lymph nodes in patients with gastric cancer (59). However, the mechanism governing how the CCR5/CCL5 axis contributes to gastric cancer progression has yet to be properly elucidated. Recently, Ding *et al* (64) reported that CCL5 secreted by tumor-associated macrophages may promote the proliferation, invasion and metastasis of gastric cancer cells. In that study, CCL5 and CD68, which are surface markers of tumor-associated macrophages, were highly expressed in gastric cancer tissue; furthermore, their expression levels were positively correlated with each other. In addition, CCL5 and CD68 expression was significantly associated with the depth of invasion, lymph node metastasis, staging and tumor differentiation. The serum level of CCL5 was also elevated in patients with gastric cancer

compared with healthy volunteers. Co-culture of AGS gastric cancer cells with THP-1-derived macrophages enhanced the proliferation, migration and clone-forming ability of the gastric cancer cells, and upregulated CCR5/CCL5 and phosphorylated signal transducer and activator of transcription 3 (p-Stat3) (64), suggesting that Stat3 activation and induction of the CCR5/CCL5 axis could serve a crucial role in gastric tumorigenesis. Okita *et al* (65) suggested that gastric cancer cells acquire invasive features by co-operating with peripheral blood mononuclear cells, in which CCL5 exerts an important role. Collectively, these data suggest that CCR5/CCL5 serves a role in gastric tumorigenesis.

4. Therapeutic implications of C-C motif CCRs in gastric cancer

The CCR7 signaling axis is involved in the oncogenic cascade in various cancer types, and is considered to be potentially a novel therapeutic target (66-71). For example, Cuesta-Mateos *et al* (68) reported that an anti-CCR7 monoclonal antibody effectively eradicated chronic lymphocytic leukemia cells via complement-dependent cytotoxicity, while sparing subsets of T cells in patients with high-risk cytogenetics and/or refractoriness to the drug, fludarabine. Additionally, the activity of this monoclonal antibody was greater compared with that of alemtuzumab, a monoclonal antibody that had shown the highest efficacy in this patient group. This *in vitro* activity was confirmed in patients refractory to both fludarabine and alemtuzumab (68). Recently, Boyle *et al* (70) reported further evidence that loss of CCR7 activity either through deletion or pharmacological inhibition markedly decreased the functional pools of stem-like cells in mouse primary tumors, suggesting a mechanism for the tumor-promoting role of this CCR, and suggesting a novel therapeutic intervention targeting cancer stem cells.

In gastric cancer, preclinical data have demonstrated that blocking CCR7 signaling induces antitumor activity *in vitro* and *in vivo*. Zhang *et al* (44) demonstrated that CCR7 contributed to the epithelial-mesenchymal transition via Snail upregulation in gastric cancer, and that blocking the CCR7-Snail axis decreased CCL19-induced cell migration, invasion and proliferation. This suggested CCR7 signaling to be a potential therapeutic target in gastric cancer. In addition, the CCR7 axis mediated the TGF-β1-induced epithelial-mesenchymal transition via crosstalk with NF-κB signaling, and blocking the CCR7 axis using a CCR7-neutralizing antibody inhibited the effects of TGF-β1 (45). Recently, Ruan *et al* (72) suggested that fluorescent, magnetic nanoparticle-labeled mesenchymal stem cells (MSCs) were able to target gastric cancer cells *in vivo* via the CCR7/CCL19 axis to inhibit tumor growth during hyperthermia therapy. In that study, gastric cancer cells produced CCL19, which recruited CCR7-expressing MSCs to gastric tumor sites. These data suggested that gastric tumors expressing CCL19 may be targeted during the treatment of hyperthermia via the combination of CCL19 with fluorescent, magnetic nanoparticle-labeled MSCs to attract CCR7-expressing MSCs (72).

The CCR5 signaling axis is a potential therapeutic target in a variety of malignancies, including breast, colorectal carcinoma, and uterine cervical cancer (22,73-76). As such,

a number of therapeutic strategies have been developed to inhibit CCR5, including small molecules that inhibit CCR5, peptide antagonists, glycosaminoglycan (GAG) mimetics, and antibodies against CCR5, which have been clinically evaluated in humans (15,22,77). The small molecules, maraviroc and vicriviroc, reduced the invasive abilities of breast cancer cells *in vitro*. Of the two compounds, maraviroc was shown to decrease pulmonary metastasis by basal breast cancer cells *in vivo*, and to reduce the tumor burden and prolong the survival of mice with hepatocellular carcinoma (74,78). Similarly, another small-molecule CCR5 inhibitor, TAK-779, was identified to reduce infiltration of regulatory T cells (Tregs) and to reduce tumor size in a pancreatic cancer model *in vivo* (79). The second group of CCR5 inhibitors comprises peptides, including Met-CCL5 (also termed Met-RANTES). Met-CCL5 was revealed to inhibit cell migration *in vitro* and to reduce tumor volume *in vivo* (22,80). The third group of inhibitors comprises GAG mimetics, which serve as 'decoys' of chemokines and bind to their receptors. Of these compounds, OTR4120 and OTR4131 inhibited CCL5-dependent migration and invasion of hepatoma cells *in vitro* (81). Consistent with this, in gastric cancer, Mencarelli *et al* (61) reported that inhibition of CCR5 signaling reduced gastric cancer cell migration and adhesion to explanted murine peritoneum *in vitro*. Furthermore, administration of maraviroc between days 3-10 following MKN45 cell inoculation in severe combined immunodeficient mice reduced the extent of peritoneal disease and increased the survival rate. Maraviroc treatment also reduced tumor burden in a xenograft model. In that study, CCR5 antagonism was shown to modulate the expression of genes responsible for tumor growth, including interleukin-10 receptor B, hepatocyte growth factor receptor (MET), the homolog of the atypical cadherin gene (FAT1), Nm23-H1, and lymphotoxin β-receptor (61). Recently, Lin *et al* (60) reported that saponin DT-13 demonstrated antitumor activity in gastric cancer by modulating CCR5 signaling. DT-13 inhibited the growth of BGC-823 and HGC-27 cells in a dose-dependent manner, and significantly decreased gastric cancer cell migration by downregulating CCR5, as indicated by the protein and gene expression levels (60).

5. Conclusion

Patients with gastric cancer at advanced stages of the disease have a dismal prognosis and a poor quality of life. An improved understanding of the complex molecular mechanisms involved in gastric cancer development, progression and metastasis is required for early diagnosis and to improve the patients' quality of life and survival by developing novel targeted therapies. Chemokines and their receptors are traditionally considered to modulate directional migration of leukocytes to specific sites, and to be involved in host immune modulation and other physiological processes. However, this system is also considered to participate in the initiation, progression and metastasis of malignant diseases via cell proliferation, migration, invasion, survival, and angiogenesis. C-C motif CCRs are widely expressed in various cell types, including leukocytes, endothelial cells, fibroblasts, epithelial cells, and cancer cells, and they contribute to the tumorigenesis of several types of cancer. CCR7 exerts an important role in

gastric tumorigenesis, including cell migration, invasion and the epithelial-mesenchymal transition. In addition, accumulating data suggest that CCR7 signaling may be a potential therapeutic target in gastric cancer. CCR5 and its ligand are differentially expressed in gastric cancer, and their expression is associated with aggressive tumor behavior and a poor prognosis. Additionally, targeting CCR5 could be an attractive strategy for the treatment of gastric cancer. Further research is therefore required to determine the roles of the complex CCR systems in gastric tumorigenesis to facilitate the development of clinical and therapeutic applications.

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