Histol Histopathol (2012) 27: 1155-1161
DOI: 10.14670/HH-27.1155

http://www.hh.um.es

Histology and Histopathology
Cellular and Molecular Biology

Review

The role of the CXCR4/CXCL12 axis and its clinical implications in gastric cancer

Hyo Jin Lee and Deog Yeon Jo
Department of Internal Medicine, Cancer Research Institute, and College of Medicine, Chungnam National University, Daejeon, Korea

Summary. Gastric cancer is the second leading cause of cancer deaths worldwide. Despite the extensive body of research on gastric cancer, the prognosis of patients with advanced gastric cancer remains poor, and therapy for advanced gastric cancer relies largely on cytotoxic chemotherapy. Therefore, identifying the distinct molecular pathways underlying disease progression and treatment resistance may lead to novel therapeutic approaches, as well as improve the quality of life and survival of patients. The chemokine CXCL12 and its receptor CXCR4 are now known to play an important role in cancer development and progression. Here, we review the expression and function of CXCR4 and CXCL12, as well as their clinical relevance in gastric cancer. We also cover the current molecular mechanism, specifically the cell-signaling pathway, by which gastric cancer progresses through the CXCR4/CXCL12 axis, and discuss the potential of that axis as a therapeutic target in the treatment of gastric cancer.

Key words: CXCR4, CXCL12, Gastric cancer, Chemokine

Introduction

Gastric cancer is the second leading cause of cancer deaths worldwide, with an estimated 990,000 new cases and 738,000 cancer deaths in 2008 (Brenner et al., 2009; Jemal et al., 2010). Despite extensive diagnostic and therapeutic investigations of gastric cancer, the prognosis of patients with advanced gastric cancer remains poor, and little improvement in survival has been accomplished (Zheng et al., 2004). Over the past years there have been many new developments in our understanding of the molecular biology of gastric cancer. Multiple genetic abnormalities are involved in the development and progression of gastric cancer (Ebert et al., 2002; Zheng et al., 2004; Panani, 2008). Among the molecular aberrations implicated in multi-step gastric tumorigenesis, alteration of c-erbB2 (Oda et al., 1990; Shun et al., 1997), c-met (Kuniyasu et al., 1993), c-myc (Han et al., 1999), K-sam (Hattori et al., 1990), and mutations of TP53 (Liu et al., 2001), APC (Nakatsuru et al., 1992), K-ras (Lee et al., 1995) and E-cadherin (More et al., 2007) have been reported so far. In particular, a recent study reported that targeted therapy against c-erbB2 in combination with conventional chemotherapy improved the survival of patients undergoing treatment for advanced gastric cancer (Bang et al., 2010). However, therapy for advanced gastric cancer relies largely on the response to cytotoxic chemotherapy. Therefore, identifying the distinct molecular pathways underlying disease progression and resistance to treatment in gastric cancer may lead to novel therapeutic approaches and improve the quality of life and survival of patients.

Chemokines are a superfamily of small peptide molecules that are involved in a number of physiological processes. In humans, this superfamily includes more than 46 ligands and 18 chemokine receptors (Zlotnik and Yoshie, 2000; Zlotnik et al., 2006). Under normal physiological conditions chemokines play a role in both proinflammatory and non-inflammatory cell homing. Chemokines mediate the migration of leukocytes to inflammatory sites and also play important roles in the regulation of hematopoietic stem cells, angiogenesis, and the extracellular matrix. The evolving field of chemokine research has led to a greater understanding of their roles in diverse areas, including cancer development and progression (Naiyer et al., 1999; Jo et al., 2000; Slettenaar and Wilson, 2006; Gangadhar et al., 2010).

The chemokine CXCL12, also known as stromal

Offprint requests to: Prof. Deog Yeon Jo, Department of Internal Medicine, Chungnam National University Hospital, 640 Daesa-dong, Jung-gu, Daejeon, Korea. e-mail: ggufwhd@naver.com

cell-derived factor 1α (SDF-1α), is a 68-amino-acid CXC chemokine that activates the receptor CXCR4. Detectable in serum, CXCL12 gradients attract circulating CXCR4-expressing cells to target tissues, where integrin-dependent intracellular adhesion and/or engraftment is facilitated by CXCR4 signaling. The consequence of the adhesive process involved in CXCL12-dependent chemotaxis is illustrated physiologically by the dependence of embryo implantation on CXCR4, and pathologically by the implication of this signaling pathway in neoplastic tissue invasion (Shen et al., 2001; Dominguez et al., 2003; Epstein, 2004; Hwang et al., 2006). CXCR4 is a 352-amino acid seven-span transmembrane G-protein coupled receptor that binds the ligand CXCL12. The expression of CXCR4 on malignant epithelial cells and on several hematopoietic malignant cells implies that the CXCL12/CXCR4 pathway influences cancer biology and plays an important role in the metastatic process of CXCR4-expressing cancer cells to target tissues that express CXCL12. Several CXCR4-expressing cancers metastasize to the bones and lymph nodes in a CXCR4-dependent manner, where bone marrow in particular can provide a favorable environment for cancer cells (Fredriksson et al., 2003; Meads et al., 2008; Teicher and Fricker, 2010). In addition, CXCR4 can modulate cancer cell proliferation, migration, and survival, and can promote tumor vascularization (Hwang et al., 2003; Burger and Kipps, 2006; Lee et al., 2009). This review focuses on the role of CXCL12 and its cognate receptor CXCR4 in gastric cancer, including its clinical implications as they pertain to cancer development and progression.

CXCR4 and CXCL12 in gastric cancer

Similar to a variety of other cancer types, such as breast cancer, lung cancer, hepatocellular carcinoma, and thyroid cancer (Muller et al., 2001; Hwang et al., 2003; Kim et al., 2008; Otsuka et al., 2011), many studies have demonstrated that CXCR4 is differentially expressed in adenocarcinoma of the stomach at the mRNA and protein levels, as well as in the cell membrane *in vitro* and *in vivo* (Kwak et al., 2005; Li et al., 2005; Yasumoto et al., 2006; Pituch-Noworolska et al., 2007; Lee et al., 2009; Zhao et al., 2010), although there was no difference in CXCR4 mRNA expression in gastric cancer as compared with non-cancerous tissues (Mitra et al., 1999). The differential expression of CXCR4 in gastric cancer cells was also demonstrated by gene expression profiling (Sun et al., 2006). In addition, circulating CXCR4 mRNA levels in the plasma of gastric cancer patients prior to surgery was upregulated compared to those of healthy subjects, and then decreased after surgery (Xu et al., 2009). Overexpression of CXCR4 in gastric cancer cells was correlated with the development of malignant ascites and peritoneal carcinomatosis, which is induced by dissemination of cancer cells into the peritoneal cavity. Peritoneal dissemination is frequently encountered and an important cause of death in gastric cancer patients (Yasumoto et al., 2006; Hashimoto et al., 2008; Ding et al., 2008; Zieker et al., 2008; Hannelien et al., 2012). In addition, high levels of CXCL12 were found in peritoneal mesothelial cells, indicating that CXCR4-expressing gastric cancer cells are preferentially attracted to the peritoneum, where its ligand CXCL12 is abundantly produced (Yasumoto et al., 2006). Many studies have also demonstrated that strong expression of CXCR4 is associated with aggressive tumor behavior, such as deep tumor invasion, lymph node metastasis, liver metastasis, and poor differentiation (Tsuboi et al., 2008; Arigami et al., 2009; Iwasa et al., 2009; Lee et al., 2009; Ying et al., 2012; Zhao et al., 2011), although

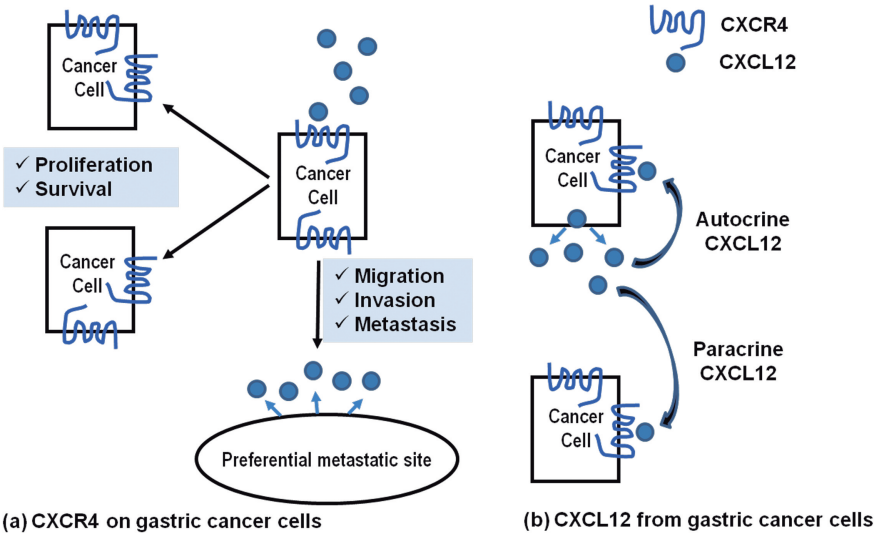

Fig. 1. Schematic illustration of the possible role of the CXCR4 chemokine receptor and its ligand, CXCL12, in gastric cancer progression. **a.** CXCR4 expressed on cancer cells. **b.** CXCL12 derived from cancer cells.

contrasting results were reported by Kwak et al. (2005). Several reports have demonstrated that gastric cancer cells also differentially express CXCL12, and strong expression of CXCL12 was correlated with the depth of invasion, lymph node metastasis, lymphatic invasion, tumor diameter, and stage with poor prognosis (Ishigami et al., 2007; Iwasa et al., 2009; Lee et al., 2011a; Song et al., 2011). Schimanski et al. (2011) reported that expression of the CXCL12 (SNP rs1801157) polymorphisms GA/AA significantly correlated with distant metastasis as well (Schimanski et al., 2011). In addition, the serum levels of pretreatment circulating CXCL12 in patients with gastric cancer was higher than in controls, and higher in metastatic patients than non-metastatic patients, correlating with the presence of distant metastasis (Woo et al., 2008). However, the precise mechanism by which tumor-derived CXCL12 contributes to tumor progression is unclear. One potential explanation is that CXCL12 is involved in tumorigenesis in an autocrine and/or paracrine manner. The concomitant expression of CXCL12 and its receptor CXCR4 in the same tumor cells has been characterized as an autocrine/paracrine mechanism of cancer cell stimulation, resulting in aggressive behavior (Rempel et al., 2000; Barbieri et al., 2008; Lee et al., 2011a). Subsequently, autocrine/paracrine mitogenic activity of CXCL12 was reported in glioblastoma multiforme and gall bladder cancer (Barbero et al., 2003; Bajetto et al., 2006; Lee et al., 2011b). Barbieri et al. also showed that CXCL12 overexpression induced autocrine/paracrine cell proliferation in pituitary tumor cells (Barbieri et al., 2008). Furthermore, immunohistochemical staining demonstrated that CXCR4 and CXCL12 were more prominent and more intense in tumor cells at the invasion front and in lymphatic vessels, respectively, in gastric cancer. Therefore, patients with elevated expression of CXCR4 and CXCL12 exhibit significantly poorer surgical outcomes (Ishigami et al., 2007; Tsuboi et al., 2008; Lee et al., 2009; Hannelien et al., 2012) (Fig. 1).

CXCR4 signaling and functions in gastric cancer

Docking of CXCL12 to CXCR4 induces a variety of intracellular signaling cascades and effector molecules that regulate cell proliferation, survival, migration, invasion, and homing of cancer cells to bones, lungs, and the peritoneal cavity. The large number of downstream effector molecules controlled by CXCR4 likely account for the multiple effects of this CXCR4/CXCL12 axis in the tumor biology of gastric cancer. The extent to which various molecules induced by CXCR4 relate to specific functions, such as cell proliferation and adhesion, remains to be fully elucidated.

Importantly, most of the signaling pathways and effector molecules described below can also be regulated by stimuli other than CXCL12 and CXCR4. Given that almost all studies of CXCR4 signaling have been performed in cultured cells, the extent to which various molecules are preferentially controlled by CXCR4 in gastric cancer in animal models or humans remains unknown. The exact role of various effectors of CXCR4 in gastric cancer has also not been well established. Illuminating downstream effectors of CXCR4 *in vivo* is important to clarify the molecular mechanisms via which CXCR4 promotes gastric cancer (Luker and Luker, 2006).

CXCL12 and CXCR4 activate the phosphorylation of the protein kinase B/AKT and the mTOR pathway, which subsequently induces the activation of p70S6K (S6K) and eukaryotic initiation factor 4E binding protein 1 (4E-BP1) (Yasumoto et al., 2006; Hashimoto et al., 2008; Dubeykovskaya et al., 2009; Koizumi et al., 2012). Treatment of gastric cancer cells with CXCL12 stimulates AKT kinase activity, which peaks at 2 min after stimulation (Yasumoto et al., 2006; Hashimoto et al., 2008). In addition, this AKT activation preceded the subsequent activation of downstream S6K and 4E-BP1. Following stimulation with CXCL12, peaks of enhanced phosphorylation of S6K and 4E-BP1 were seen at 10 and 5 min, respectively. Furthermore, CXCL12-induced activation of S6K and 4E-BP was inhibited selectively by the mTOR inhibitor rapamycin (Hashimoto et al., 2008). Activated AKT/mTOR signaling phosphorylates a wide variety of intracellular targets, including S6K1 and 4E-BP, which are involved in cell survival and inhibition of apoptosis in various types of cancer cells. Beyond these cell survival functions AKT/mTOR has been implicated in the effects of CXCR4 on cell proliferation and chemotactic migration, which are involved in cell growth and metastatic properties (Yasumoto et al., 2006; Hashimoto et al., 2008).

The mitogen-activated protein (MAP) kinase pathway is another signal transduction pathway

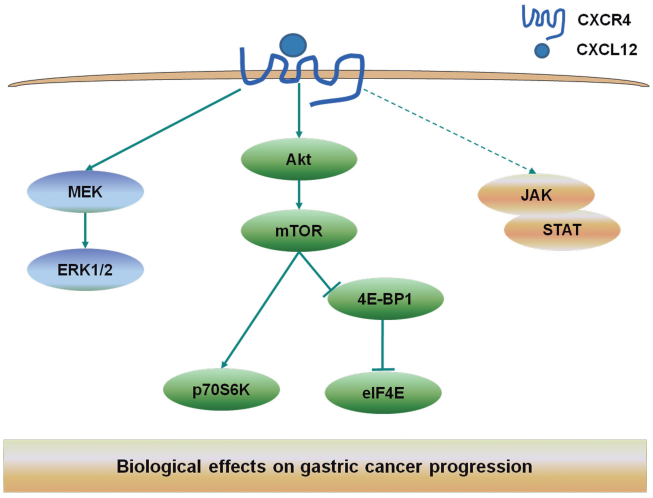

Fig. 2. Schematic illustration of the CXCL12/CXCR4 intracellular signal transduction pathway investigated in gastric cancer cells.

regulated by CXCR4. In response to CXCL12, CXCR4 activates MEK, the upstream activator of the p42/44 MAP kinase (also known as ERK 1/2) (Luker and Luker, 2006). In gastric cancer cells, treatment with CXCL12 rapidly induced phosphorylation of MAP kinase. In addition, increased phosphorylation of MAP kinase was blocked by AMD3100, a small molecule that specifically inhibits the CXCR4 receptor (Yasumoto et al., 2006; Dubeykovskaya et al., 2009; Lee et al., 2009). Collectively, these data suggest that activation of MAP kinase is another pathway via which CXCR4 may promote gastric cancer progression.

The JAK/STAT (Janus kinase/signal transducer and activator of transcription) pathway is a third potential effector of CXCR4 in gastric cancer. After treatment with CXCL12, JAK kinases associate with CXCR4 then activate members of the STAT family of transcription factors. The JAK/STAT pathway is involved in migration and invasion of cancer cells (Soriano et al., 2003). In gastric cancer cells, one study reported that CXCR4 signaling is independent of the JAK/STAT pathway in only one cultured gastric cancer cell line (Lee et al., 2009). However, the significance of the JAK/STAT pathway in the biological effects of CXCR4 in gastric cancer remains uncertain due to insufficient data.

CXCR4 activates several different biological processes such as chemotactic migration, invasion, and adhesion of cancer cells, all of which are characteristics associated with the metastatic behavior of cancer cells. CXCL12 binding to CXCR4 promotes actin polymerization to initiate cell motility. CXCR4 also activates members of the src family of protein tyrosine kinases, thereby inducing phosphorylation and activation of focal adhesion complexes such as RAFTK/Pyk2, focal adhesion kinase, Crk, and paxillin. CXCR4 also promotes adhesion to components of the extracellular matrix through integrins (Fernandis et al., 2004; Hartmann et al., 2005; Luker and Luker, 2006). Activated CXCR4 in response to CXCL12 progressively upregulated the expression of MMP-2 and MMP-7 at 2 hr after stimulation in NUGC 4 gastric cancer cells (Hashimoto et al., 2008). MMP-7 activates MMP-2 and plays a central role in the degradation of the extracellular matrix, including type IV collagen. In addition, MMP-7 expression is associated with the transformation of tumor cells, thereby providing a possible mechanism for invasion and metastasis of cancer cells accompanied by the aggressive behavior of gastric cancer (Yamashita et al., 1998; Shim et al., 2007) (Fig. 2).

CXCR4/CXCL12 axis as a potential therapeutic target in gastric cancer

The CXCR4/CXCL12 axis is now considered a novel and potential target for therapeutics that block interactions between CXCL12 and CXCR4 or which inhibit the activities of downstream signal pathways in the treatment of cancer. To date, multiple antagonists have been designed to target CXCR4, such as bicyclams (AMD3100), T22, TN14003, CTCE-9908 and ALX40-4C, which are analogs and peptides designed to target the amino-terminal region of the chemokine CXCL12 (Sun et al., 2010).

In gastric cancer, several preclinical studies have demonstrated that anti-CXCR4 monoclonal antibodies and specific low molecular weight antagonists for CXCR4 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 (Yasumoto et al., 2006; Ding et al., 2008; Lee et al., 2009). AMD3100 also markedly reduced tumor growth and malignant ascitic fluid formation in nude mice inoculated with NUGC 4 cells (Yasumoto et al., 2006). Additionally, the mice injected with both NUGC4 cells and AMD3100 showed significantly lower tumor numbers and longer survival times as compared with the control group (Ding et al., 2008). Furthermore, tumor volume was significantly reduced in BALB/C (nu/nu) nude mice transplanted with CXCR4-expressing human gastric cancer cell lines when AMD3100 was administered together as compared with the control group, and none of the nude mice showed toxic signs associated with toxicity (Iwanaga et al., 2007). Furthermore, Xie et al. (2010) demonstrated that CXCR4 mRNA levels in gastric cancer tissues were significantly correlated with docetaxel sensitivity and were significantly higher in resistant specimens, and that AMD3100 enhanced the docetaxel cytotoxicity *in vitro* (Xie et al., 2010). Taken together, these data suggest that CXCR4 antagonists might be attractive therapeutic candidates, thus necessitating a better understanding of the CXCR4/CXCL12 axis in gastric cancer tumorigenesis and its further clinical applications.

Conclusions

Patients with advanced gastric cancer, particularly peritoneal dissemination, show very poor prognoses. To improve quality of life and survival in gastric cancer, novel targeted therapies are needed. The CXCR4/CXCL12 axis plays an important role in gastric cancer development and progression, such as cell proliferation, migration, survival, peritoneal dissemination, and treatment resistance. In addition, some studies have shown anti-tumor activities using CXCR4 antagonists or neutralizing antibodies *in vitro* and *in vivo*. This pathway, therefore, could be an attractive candidate for the treatment of gastric cancer. However, extensive research is still required to clarify the biological function of the CXCR4/CXCL12 axis in gastric cancer progression and to translate its therapeutic potential into clinical applications.

Acknowledgements. This study was supported in part by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (NRF-2009-0076540, NRF-2009-0067256).

References

Arigami T., Natsugoe S., Uenosono Y., Yanagita S., Arima H., Hirata M., Ishigami S. and Aikou T. (2009). CCR7 and CXCR4 expression predicts lymph node status including micrometastasis in gastric cancer. Int. J. Oncol. 35, 19-24.

Bajetto A., Barbieri F., Dorcaratto A., Barbero S., Daga A., Porcile C., Ravetti J.L., Zona G., Spaziante R., Corte G., Schettini G. and Florio T. (2006). 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. 49, 423-432.

Bang Y.J., Van Cutsem E., Feyereislova A., Chung H.C., Shen L., Sawaki A., Lordick F., Ohtsu A., Omuro Y., Satoh T., Aprile G., Kulikov E., Hill J., Lehle M., Ruschoff J. and Kang Y.K. (2010). 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 376, 687-697.

Barbero S., Bonavia R., Bajetto A., Porcile C., Pirani P., Ravetti J.L., Zona G.L., Spaziante R., Florio T. and Schettini G. (2003). 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. 63, 1969-1974.

Barbieri F., Bajetto A., Stumm R., Pattarozzi A., Porcile C., Zona G., Dorcaratto A., Ravetti J.L., Minuto F., Spaziante R., Schettini G., Ferone D. and Florio T. (2008). Overexpression of stromal cell-derived factor 1 and its receptor CXCR4 induces autocrine/paracrine cell proliferation in human pituitary adenomas. Clin. Cancer Res. 14, 5022-5032.

Brenner H., Rothenbacher D. and Arndt V. (2009). Epidemiology of stomach cancer. Methods Mol. Biol. 472, 467-477.

Burger J.A. and Kipps T.J. (2006). CXCR4: a key receptor in the crosstalk between tumor cells and their microenvironment. Blood 107, 1761-1767.

Ding Y.L., Zhang J.L., Tang S.F., Fu Q.Y. and Li Z.T. (2008). [Effect of chemokine stromal cell derived factor-1 and its receptor CXCR4 on the peritoneal carcinometastasis of gastric cancer]. Zhonghua Yi Xue Za Zhi 88, 202-205.

Dominguez F., Galan A., Martin J.J., Remohi J., Pellicer A. and Simon C. (2003). Hormonal and embryonic regulation of chemokine receptors CXCR1, CXCR4, CCR5 and CCR2B in the human endometrium and the human blastocyst. Mol. Hum. Reprod. 9, 189-198.

Dubeykovskaya Z., Dubeykovskiy A., Solal-Cohen J. and Wang T.C. (2009). Secreted trefoil factor 2 activates the CXCR4 receptor in epithelial and lymphocytic cancer cell lines. J. Biol. Chem. 284, 3650-3662.

Ebert M.P., Fei G., Kahmann S., Muller O., Yu J., Sung J.J. and Malfertheiner P. (2002). Increased beta-catenin mRNA levels and mutational alterations of the APC and beta-catenin gene are present in intestinal-type gastric cancer. Carcinogenesis 23, 87-91.

Epstein R.J. (2004). The CXCL12-CXCR4 chemotactic pathway as a target of adjuvant breast cancer therapies. Nat. Rev. Cancer 4, 901-909.

Fernandis A.Z., Prasad A., Band H., Klosel R. and Ganju R.K. (2004). Regulation of CXCR4-mediated chemotaxis and chemoinvasion of breast cancer cells. Oncogene 23, 157-167.

Fredriksson R., Lagerstrom M.C., Lundin L.G. and Schioth H.B. (2003). The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. Mol. Pharmacol. 63, 1256-1272.

Gangadhar T., Nandi S. and Salgia R. (2010). The role of chemokine receptor CXCR4 in lung cancer. Cancer Biol. Ther. 9, 409-416.

Han S., Kim H.Y., Park K., Cho H.J., Lee M.S., Kim H.J. and Kim Y.D. (1999). c-Myc expression is related with cell proliferation and associated with poor clinical outcome in human gastric cancer. J. Korean Med. Sci. 14, 526-530.

Hannelien V., Karel G., Jo V.D. and Sofie S. (2012). The role of CXC chemokines in the transition of chronic inflammation to esophageal and gastric cancer. Biochim. Biophys. Acta 1825, 117-129.

Hartmann T.N., Burger J.A., Glodek A., Fujii N. and Burger M. (2005). CXCR4 chemokine receptor and integrin signaling co-operate in mediating adhesion and chemoresistance in small cell lung cancer (SCLC) cells. Oncogene 24, 4462-4471.

Hashimoto I., Koizumi K., Tatematsu M., Minami T., Cho S., Takeno N., Nakashima A., Sakurai H., Saito S., Tsukada K. and Saiki I. (2008). 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 44, 1022-1029.

Hattori Y., Odagiri H., Nakatani H., Miyagawa K., Naito K., Sakamoto H., Katoh O., Yoshida T., Sugimura T. and Terada M. (1990). K-sam, an amplified gene in stomach cancer, is a member of the heparin-binding growth factor receptor genes. Proc. Natl. Acad. Sci. USA 87, 5983-5987.

Hwang J.H., Hwang J.H., Chung H.K., Kim D.W., Hwang E.S., Suh J.M., Kim H., You K.H., Kwon O.Y., Ro H.K., Jo D.Y. and Shong M. (2003). CXC chemokine receptor 4 expression and function in human anaplastic thyroid cancer cells. J. Clin. Endocrinol. Metab. 88, 408-416.

Hwang J.H., Kim S.W., Park S.E., Yun H.J., Lee Y., Kim S. and Jo D.Y. (2006). Overexpression of stromal cell-derived factor-1 enhances endothelium-supported transmigration, maintenance, and proliferation of hematopoietic progenitor cells. Stem Cells Dev. 15, 260-268.

Ishigami S., Natsugoe S., Okumura H., Matsumoto M., Nakajo A., Uenosono Y., Arigami T., Uchikado Y., Setoyama T., Arima H., Hokita S. and Aikou T. (2007). Clinical implication of CXCL12 expression in gastric cancer. Ann. Surg. Oncol. 14, 3154-3158.

Iwanaga T., Iwasaki Y., Ohashi M., Nunobe S. and Iwagami S. (2007). 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 34, 1917-1919. (in japanese).

Iwasa S., Yanagawa T., Fan J. and Katoh R. (2009). Expression of CXCR4 and its ligand SDF-1 in intestinal-type gastric cancer is associated with lymph node and liver metastasis. Anticancer Res. 29, 4751-4758.

Jemal A., Center M.M., DeSantis C. and Ward E.M. (2010). Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol. Biomarkers Prev. 19, 1893-1907.

Jo D.Y., Rafii S., Hamada T. and Moore M.A. (2000). Chemotaxis of primitive hematopoietic cells in response to stromal cell-derived

factor-1. J. Clin. Invest. 105, 101-111.

Kim S.W., Kim H.Y., Song I.C., Jin S.A., Lee H.J., Yun H.J., Kim S. and Jo D.Y. (2008). Cytoplasmic trapping of CXCR4 in hepatocellular carcinoma cell lines. Cancer Res. Treat. 40, 53-61.

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

Kuniyasu H., Yasui W., Yokozaki H., Kitadai Y. and Tahara E. (1993). Aberrant expression of c-met mRNA in human gastric carcinomas. Int. J. Cancer 55, 72-75.

Kwak M.K., Hur K., Park D.J., Lee H.J., Lee H.S., Kim W.H., Lee K.U., Choe K.J. and Yang H.K. (2005). Expression of chemokine receptors in human gastric cancer. Tumour Biol. 26, 65-70.

Lee K.H., Lee J.S., Suh C., Kim S.W., Kim S.B., Lee J.H., Lee M.S., Park M.Y., Sun H.S. and Kim S.H. (1995). Clinicopathologic significance of the K-ras gene codon 12 point mutation in stomach cancer. An analysis of 140 cases. Cancer 75, 2794-2801.

Lee H.J., Kim S.W., Kim H.Y., Li S., Yun H.J., Song K.S., Kim S. and Jo D.Y. (2009). Chemokine receptor CXCR4 expression, function, and clinical implications in gastric cancer. Int. J. Oncol. 34, 473-480.

Lee H.J., Huang S.M., Kim H.Y., Oh Y.S., Hwang J.Y., Liang Z.L., Min J.K., Yun H.J., Sul J.Y., Kim S., Jo D.Y. and Kim J.M. (2011a). Evaluation of the combined expression of chemokine SDF-1 alpha and its receptor CXCR4 as a prognostic marker for gastric cancer. Exp. Therapeutic Med. 2, 499-504.

Lee H.J., Oh Y.S., Liang Z.L., Kim H.Y., Yun H.J., Kim S., Jo D.Y., Min J.K. and Kim J.M. (2011b). Stromal Cell-derived Factor-1 Alpha is a Novel Independent Poor Prognostic Factor in Gallbladder Carcinoma. Eur. J. Cancer 47, S445-S446.

Li S., Huang S. and Peng S.B. (2005). Overexpression of G protein-coupled receptors in cancer cells: involvement in tumor progression. Int. J. Oncol. 27, 1329-1339.

Liu X.P., Tsushimi K., Tsushimi M., Oga A., Kawauchi S., Furuya T. and Sasaki K. (2001). Expression of p53 protein as a prognostic indicator of reduced survival time in diffuse-type gastric carcinoma. Pathol. Int .51, 440-444.

Luker K.E. and Luker G.D. (2006). Functions of CXCL12 and CXCR4 in breast cancer. Cancer Lett. 238, 30-41.

Meads M.B., Hazlehurst L.A. and Dalton W.S. (2008). The bone marrow microenvironment as a tumor sanctuary and contributor to drug resistance. Clin Cancer Res. 14, 2519-2526.

Mitra P., Shibuta K., Mathai J., Shimoda K., Banner B.F., Mori M. and Barnard G.F. (1999). CXCR4 mRNA expression in colon, esophageal and gastric cancers and hepatitis C infected liver. Int. J. Oncol. 14, 917-925.

More H., Humar B., Weber W., Ward R., Christian A., Lintott C., Graziano F., Ruzzo A.M., Acosta E., Boman B., Harlan M., Ferreira P., Seruca R., Suriano G. and Guilford P. (2007). Identification of seven novel germline mutations in the human E-cadherin (CDH1) gene. Hum. Mutat. 28, 203.

Muller A., Homey B., Soto H., Ge N., Catron D., Buchanan M.E., McClanahan T., Murphy E., Yuan W., Wagner S.N., Barrera J.L., Mohar A., Verastegui E. and Zlotnik A. (2001). Involvement of chemokine receptors in breast cancer metastasis. Nature 410, 50-56.

Naiyer A.J., Jo D.Y., Ahn J., Mohle R., Peichev M., Lam G., Silverstein R.L., Moore M.A. and Rafii S. (1999). Stromal derived factor-1-induced chemokinesis of cord blood CD34(+) cells (long-term culture-initiating cells) through endothelial cells is mediated by E-selectin. Blood 94, 4011-4019.

Nakatsuru S., Yanagisawa A., Ichii S., Tahara E., Kato Y., Nakamura Y. and Horii A. (1992). Somatic mutation of the APC gene in gastric cancer: frequent mutations in very well differentiated adenocarcinoma and signet-ring cell carcinoma. Hum Mol Genet 1, 559-563.

Oda N., Tsujino T., Tsuda T., Yoshida K., Nakayama H., Yasui W. and Tahara E. (1990). DNA ploidy pattern and amplification of ERBB and ERBB2 genes in human gastric carcinomas. Virchows Arch. 58, 273-277.

Otsuka S., Klimowicz A.C., Kopciuk K., Petrillo S.K., Konno M., Hao D., Muzik H., Stolte E., Boland W., Morris D., Magliocco A.M. and Bebb D.G. (2011). CXCR4 overexpression is associated with poor outcome in females diagnosed with stage IV non-small cell lung cancer. J. Thorac. Oncol. 6, 1169-1178.

Panani A.D. (2008). Cytogenetic and molecular aspects of gastric cancer: clinical implications. Cancer Lett. 266, 99-115.

Pituch-Noworolska A., Drabik G., Szatanek R., Bialas M., Kolodziejczyk P., Szczepanik A., Stachura J. and Zembala M. (2007). Immunophenotype of isolated tumour cells in the blood, bone marrow and lymph nodes of patients with gastric cancer. Pol. J. Pathol. 58, 93-97.

Rempel S.A., Dudas S., Ge S. and Gutierrez J.A. (2000). 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. 6, 102-111.

Schimanski C.C., Jordan M., Schlaegel F., Schmidtmann I., Lang H., Galle P.R., Moehler M. and Gockel I. (2011). SNP rs1801157 significantly correlates with distant metastasis in CXCL12 expressing esophagogastric cancer. Int. J. Oncol. 39, 515-520.

Shen W., Bendall L.J., Gottlieb D.J. and Bradstock K.F. (2001). The chemokine receptor CXCR4 enhances integrin-mediated in vitro adhesion and facilitates engraftment of leukemic precursor-B cells in the bone marrow. Exp. Hematol. 29, 1439-1447.

Shim K.N., Jung S.A., Joo Y.H. and Yoo K. (2007). Clinical significance of tissue levels of matrix metalloproteinases and tissue inhibitors of metalloproteinases in gastric cancer. J. Gastroenterol. 42, 120-128.

Shun C.T., Wu M.S., Lin J.T., Chen S.Y., Wang H.P., Lee W.J., Wang T.H. and Chuang S.M. (1997). Relationship of p53 and c-erbB-2 expression to histopathological features, Helicobacter pylori infection and prognosis in gastric cancer. Hepatogastroenterology 44, 604-609.

Slettenaar V.I. and Wilson J.L. (2006). The chemokine network: a target in cancer biology? Adv. Drug Deliv. Rev. 58, 962-974.

Song I.C., Liang Z.L., Lee J.C., Huang S.M., Kim H.Y., Oh Y.S., Yun H.J., Sul J.Y., Joi D.Y., Kim S., Kim J.M. and Lee H.J. (2011). Expression of stromal cell-derived factor-1 alpha is an independent risk factor for lymph node metastasis in early gastric cancer. Oncol. Lett. 2, 1197-1202.

Soriano S.F., Serrano A., Hernanz-Falcon P., Martin de Ana A., Monterrubio M., Martinez C., Rodriguez-Frade J.M. and Mellado M. (2003). Chemokines integrate JAK/STAT and G-protein pathways during chemotaxis and calcium flux responses. Eur. J. Immunol .33, 1328-1333.

Sun X.J., Sun K.L., Zheng Z.H., Fu W.N., Hao D.M., Xu H.M. and Li X.M. (2006). Gene expression patterns in gastric cancer. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 23, 142-146.

Sun X., Cheng G., Hao M., Zheng J., Zhou X., Zhang J., Taichman R.S.,

Pienta K.J. and Wang J. (2010). CXCL12 / CXCR4 / CXCR7 chemokine axis and cancer progression. Cancer Metast. Rev. 29, 709-722.

Teicher B.A. and Fricker S.P. (2010). CXCL12 (SDF-1)/CXCR4 pathway in cancer. Clin Cancer Res. 16, 2927-2931.

Tsuboi K., Kodera Y., Nakanishi H., Ito S., Mochizuki Y., Nakayama G., Koike M., Fujiwara M., Yamamura Y. and Nakao A. (2008). Expression of CXCL12 and CXCR4 in pT3-stage gastric cancer does not correlate with peritoneal metastasis. Oncol. Rep. 20, 1117-1123.

Woo I.S., Hong S.H., Byun J.H., Kang J.H., Jeon H.M. and Choi M.G. (2008). Circulating stromal cell derived factor-1alpha (SDF-1alpha) is predictive of distant metastasis in gastric carcinoma. Cancer Invest. 26, 256-261.

Xie L., Wei J., Qian X., Chen G., Yu L., Ding Y. and Liu B. (2010). CXCR4, a potential predictive marker for docetaxel sensitivity in gastric cancer. Anticancer Res. 30, 2209-2216.

Xu W., Zhou H., Qian H., Bu X., Chen D., Gu H., Zhu W., Yan Y. and Mao F. (2009). Combination of circulating CXCR4 and Bmi-1 mRNA in plasma: A potential novel tumor marker for gastric cancer. Mol. Med. Rep. 2, 765-771.

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

Yasumoto K., Koizumi K., Kawashima A., Saitoh Y., Arita Y., Shinohara K., Minami T., Nakayama T., Sakurai H., Takahashi Y., Yoshie O. and Saiki I. (2006). Role of the CXCL12/CXCR4 axis in peritoneal carcinomatosis of gastric cancer. Cancer Res. 66, 2181-2187.

Ying J., Xu Q., Zhang G., Liu B. and Zhu L. (2012). The expression of CXCL12 and CXCR4 in gastric cancer and their correlation to lymph node metastasis. Med. Oncol. (in press).

Zhao B.C., Zhao B., Han J.G., Ma H.C. and Wang Z.J. (2010). Adipose-derived stem cells promote gastric cancer cell growth, migration and invasion through SDF-1/CXCR4 axis. Hepatogastroenterology 57, 1382-1389.

Zhao B.C., Wang Z.J., Mao W.Z., Ma H.C., Han J.G., Zhao B. and Xu H.M. (2011). CXCR4/SDF-1 axis is involved in lymph node metastasis of gastric carcinoma. World J. Gastroenterol. 17, 2389-2396.

Zheng L., Wang L., Ajani J. and Xie K. (2004). Molecular basis of gastric cancer development and progression. Gastric Cancer 7, 61-77.

Zieker D., Konigsrainer I., Traub F., Nieselt K., Knapp B., Schillinger C., Stirnkorb C., Fend F., Northoff H., Kupka S., Brucher B.L. and Konigsrainer A. (2008). PGK1 a potential marker for peritoneal dissemination in gastric cancer. Cell Physiol. Biochem. 21, 429-436.

Zlotnik A. and Yoshie O. (2000). Chemokines: a new classification system and their role in immunity. Immunity 12, 121-127.

Zlotnik A., Yoshie O. and Nomiyama H. (2006). The chemokine and chemokine receptor superfamilies and their molecular evolution. Genome Biol. 7, 243.

Accepted April 26, 2012