



Clinical significance of CXCL13/CXCR5 axis in human cancers

Dawei Zhu^{1,2,3}, Wenfeng Ye^{1,2,3}, Jingting Jiang^{1,2,3}

¹Department of Tumor Biological Treatment, ²Jiangsu Engineering Research Center for Tumor Immunotherapy, ³Institute of Cell Therapy, the Third Affiliated Hospital of Soochow University, Changzhou 213003, China

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Correspondence to: Jingting Jiang, MD, PhD. Department of Tumor Biological Treatment, the Third Affiliated Hospital, Soochow University, Changzhou 213003, China. Email: jiangjingting@suda.edu.cn.

Abstract: As a family of small cytokines, chemokines were well known to contribute to the migration of cells, especially the inflammatory cells such as chemotactic granulocytes, monocytes and macrophages, and their functions are mediated by the corresponding receptors. Both chemokines and their receptors not only play an important role in the physiopathological process of inflammation and anaphylaxis, but also are involved in tumor growth and metastasis. For example, numerous studies have shown that chemokines can regulate the infiltration of leukocytes in tumor tissues, the tumor-associated angiogenesis, and the host-specific immune responses against tumors. Moreover, chemokines could also contribute to the regulation of cancer cell proliferation and motility through autocrine or paracrine processes. In the present review, we summarized the clinical significance and the function of CXCL13/CXCR5 axis in human cancers.

Keywords: Chemokine; CXCL13; CXCR5; cancer progression

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Chemokines and their receptors are important molecules mediating leukocyte migration and infiltration. Abnormal expressions of tumor-associated chemotactic factors in tumor tissues are significantly related to cancer progression, lymphocyte infiltration and specific anti-tumor immune responses. Recently, many studies have shown that the chemokine CXCL13 and its receptor CXCR5 were abnormally expressed in cancer tissues and contributed essentially to cancer progression (1). In the present review, we summarized the expression pattern and clinical significance of CXCL13/CXCR5 axis in human cancers.

Chemokines and their receptors

As small molecule peptides with a molecular weight of 8–10 kD, chemokines can specifically activate and recruit white blood cells (2,3). The amino acid composition of

chemokines has a specific cysteine (Cys) motif. According to the characteristics of the conservative arrangement of Cys motifs, the chemokines can be mainly categorized into four subgroups (CXC, CC, C and CX3C) (4,5). Up to date, most of the chemokines belong to the CC and CXC subgroups, while only two C molecules and one CX3C molecule have been reported. Chemokine receptors are a group of G protein-coupled trans-membranous receptors that mediate the ability of chemokines and contain seven transmembrane domains (6). Chemokine receptors could be found in various immune cells, endothelial cells and neuronal cells, and each receptor has a retention region that binds to the corresponding chemokine ligand (7). The chemokines can participate in the physio-pathological process of infectious and metamorphic diseases, and chemokines as well as their receptors can also promote angiogenesis, tumor cell proliferation, survival and proliferation, involving in the process of organ-specific metastasis of malignant tumors.

Table 1 CXCL13/CXCR5 axis in human cancers

Tumor type	Expression pattern and clinical significance	Function and mechanism	References
Gastric cancer	CXCR5 expression could be found in gastric cancer and adjacent tissues; higher CXCR5 expression correlated with poorer prognosis	CD40 could up-regulate CXCR5 expression and promote the aggregation of MDSCs	(14,15)
Breast cancer	CXCL13 and CXCR5 expression in cancer tissues correlated with tumor invasion and epithelial to mesenchymal transition	Loss of p53 increased the expression and the functional activity of CXCR5	(16-19)
Intestinal cancer	CXCR5 expression significantly correlated with lymph node metastasis, TNM stage and neural invasion; CXCL13 expression significantly correlated with TNM stage, cancer cell differentiation, and neural invasion	Promoted tumor cell growth via the PI3K/AKT signaling pathway	(20-22)
Lung cancer	Higher CXCL13 expression in cancer tissues and increased serum CXCL13 level in lung cancer patients compared with healthy controls	CXCR5-CXCL13 interaction could promote the migration of lung cancer cells	(23,24)
Prostate cancer	Higher CXCR5 expression in cancer tissues compared with normal tissues and correlated with Gleason score of the patients	PKC ξ cooperated with PTEN loss for prostate Tumorigenesis via CXCL13/CXCR5 axis	(25-27)
Lymphoma	Serum CXCL13 expression and high-level CXCL13 in patients were significantly correlated with poor prognosis	Circulating CXCR5 ⁺ CD4 ⁺ T cells could assist the survival and proliferation of primary DLBCL cells through IL-10 pathway	(28,29)

Chemokine CXCL13 and its receptor CXCR5

CXCR5, also known as Burkitt's lymphoma receptor 1 (BLR-1), is a member of the chemokine CXC receptor family, which is mainly distributed in peripheral mature B cells as well as in a small number of CD4⁺ or CD8⁺ T cells and the skin-derived migratory dendritic cells (8). CXCR5 has seven transmembrane domains, and it couples with GTP2 protein to form a transmembrane receptor. CXCR5 is an important molecule that enables B lymphocytes to home to lymph node follicles and to promote lymphoid follicular formation and lymph node development. CXCL13, also known as B cell chemokine 1 (BLC1), is a ligand of CXCR5 and a member of chemokine CXC family. The coding gene of CXCL13 is located in 4q21. Generally, CXCL13 is secreted by stromal cells in the B cell region of the secondary lymphoid tissue and expressed on the membrane of the follicular dendritic cell. CXCL13 can recruit B cells and directly regulate the maturation and development of B cells *in vivo*, and can participate in the transmission of immune system signals (9,10). CXCL13/CXCR5 axis contributes to the homing process of circulating naive B lymphocytes to lymph nodes, promotes the construction and the development of secondary lymphoid tissue, and facilitates the B cells to differentiate into functional B Cells. Recent studies have also shown that CXCL13 and its receptor CXCR5 not only are involved in maintaining the homeostasis of tissue environment, but also

participate in the occurrence and treatment of autoimmune diseases as well as the repair of trauma (11-13). Moreover, many studies also showed that the CXCL13/CXCR5 axis played a fundamental role in regulating tumor occurrence and development, and herein we reviewed these studies and summarized in *Table 1*.

Studies on CXCL13/CXCR5 axis in human cancers

CXCL13/CXCR5 and gastric cancer

Sun *et al.* (15) have shown that CXCR5 is highly expressed in human gastric cancer cell lines BGC-823, SGC-7901 and HGC-27. The tissue microarray and immunohistochemistry have also shown that CXCR5 is highly expressed in human gastric cancer tissues, and its expression level is significantly correlated to tumor size and overall survival rate of the patients, therefore the examination of CXCR5 may have a great importance in the prognostic prediction of gastric cancer. Ding *et al.* (14) also confirmed that CXCL13/CXCR5 axis played an important role in the migration of CD40⁺ MDSCs to gastric cancer tissues, indicating that the expression of CD40 can up-regulate the CXCR5 expression and promote the migration and recruitment of MDSCs to cancer tissues. Wei *et al.* (30) also showed that higher CXCL13 expression level was associated with larger tumor size and poorer prognoses of gastric cancer patients, and could serve as a predictive biomarker of response to

postoperative adjuvant chemotherapy in these patients.

CXCL13/CXCR5 and breast cancer

Chen *et al.* (16) have demonstrated that there is a significant correlation between the CXCL13 expression level and unfavorable clinical features in patients with breast cancer. Moreover, higher CXCL13 expression could also be found in breast cancer tissues, and is significantly related to the status of lymph node metastasis, estrogen receptor status and other prognostic factors (6,31). Razis *et al.* (17) also examined the expression of CXCL13/CXCR5 in early-stage breast cancer, and the results showed that the higher CXCR5 expression as well as CXCL13 in breast cancer tissues are significantly correlated with the lower estrogen levels, poor grade and axillary lymph node metastases. Biswas *et al.* (18) demonstrated that the co-expression of CXCL13 and CXCR5 is significantly correlated to the status of lymph node metastasis in breast cancer patients. And in breast cancer cell lines, the over-expression of CXCL13 could promote the epithelial-mesenchymal transition (32). Mitkin *et al.* (19) have found that the expression of p53 in breast cancer cell line MCF-7 is negatively correlated with CXCR5 expression level. Furthermore, the mechanic studies have shown that CXCR5 over-expression can lead to the survival of abnormal cells in breast cancer when the function of p53 is missing.

CXCL13/CXCR5 and colorectal cancer

Xing *et al.* (22) demonstrated that the CXCR5⁺CD8⁺ T cells are significantly increased in colorectal cancer tissues compared with the adjacent normal tissues, but the effector function of these CXCR5⁺CD8⁺ T cells is not as good as CXCR5⁻CD8⁺ T cells. When the CXCR5⁺CD8⁺ T cells are stimulated by PMA and ionomycin, the effector function of CXCR5⁺CD8⁺ T cells is significantly enhanced, indicating that CXCR5⁺CD8⁺ T cells are an important subpopulation of CD8⁺ T cells infiltrating in the colon cancer tissues, and have the potential of anti-tumor immunity. Qi *et al.* (20) detected 144 paraffin-embedded samples of advanced colorectal cancer by using immunohistochemistry, and they have found that the expression of CXCL13 in advanced colorectal cancer tissues is significantly different from that of the normal tissues. They also confirmed that the increased protein expression levels of CXCL13 and CXCR5 are significantly correlated with the status of lymph node metastasis, distant metastasis, tumor stage and recurrence.

Zhu *et al.* (21) have shown that CXCL13 could promote growth, migration and invasion of colon cancer cells. CXCL13/CXCR5 axis may also promote the growth of cancer cells through the PI3K/AKT signal pathway, suggesting that CXCL13 is a potential biological marker for the detection and therapeutic treatment of colon cancer.

CXCL13/CXCR5 and lung cancer

Wang *et al.* found that CXCL13 is over-expressed in 62% of smokers and 45% of non-smokers in lung cancer patients (23). Mouse experiments also confirmed that the key carcinogen benzopyrene could induce the CXCL13 expression in lung epithelial cells, indicating that the important role of CXCL13/CXCR5 in PAH-induced lung cancer (23). Singh *et al.* (24) found that CXCR5 expression in lung cancer tissues (both squamous cell carcinoma and adenocarcinoma tissues) is significantly higher than that in adjacent normal tissues, they also showed that nuclear and membrane CXCR5 expression were higher in adenocarcinoma tissues in contrast to squamous cell carcinoma tissues. Moreover, serum CXCL13 levels in lung cancer patients were significantly higher than that in healthy controls (24). Thus all these data suggest that the CXCL13/CXCR5 axis can affect the progression of lung cancer, and both CXCL13 and CXCR5 can be used as biomarkers for lung cancer.

CXCL13/CXCR5 and prostate cancer

Singh *et al.* (27) reported that CXCR5 expression in prostate cancer tissues was significantly higher than that in normal tissues, and the increased intensity of CXCR5 staining significantly correlated with Gleason score of the patients. Moreover, CXCR5 expression level in prostate cancer cell lines was higher than that in normal prostatic epithelial cells, and when the prostate cancer cells treated by using CXCL13, the expression levels of collagenase-1 or matrix metalloproteinase-1 (MMP-1), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10) and stromelysin-3 (MMP-11) were significantly increased (27). El-Haibi *et al.* (33) reported that CXCL13 could promote the invasion of prostate cancer cell via Akt and ERK1/2 activation and suggested a new role for DOCK2 in proliferation of hormone-refractory CXCR5-positive prostate cancer cells. Moreover, the over-expression of protein kinase C epsilon and PTEN loss could individually and synergistically up-regulate the production of the

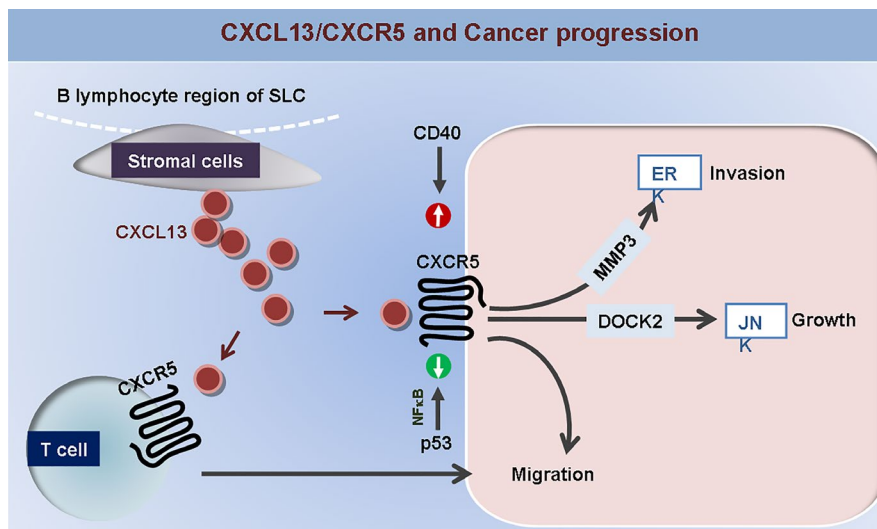


Figure 1 Graphic description of CXCL13/CXCR5 axis in cancer progression.

chemokine CXCL13 in prostate cancer via NF- κ B pathway, and the disruption of CXCL13/CXCR5 axis in prostate cancer cells could significantly impaired the migratory and tumorigenic properties (26).

CXCL13/CXCR5 and lymphoma

Cha *et al.* (29) investigated the pathogenesis of diffuse large B-cell lymphoma, and found that the peripheral CXCR5⁺CD4⁺ T cells could promote tumor cell proliferation by inhibiting lymphoma cell apoptosis. Moreover, CXCR5⁺CD4⁺T cells could promote the tumorigenesis via reducing cytokine IL-12 and enhancing IL-10 secretion, indicating that CXCR5 signaling plays an important role in tumor development in this malignancy (29). Kim *et al.* (28) examined the serum level of CXCL13 in patients with extranodal NK/T-cell lymphoma and analyzed its correlation with the Glasgow Prognostic Score as well as its prognostic significance, and the increased serum CXCL13 level of the patients is significantly correlated with the poorer PFS and higher GPS, larger tumor burden and poorer prognosis. Therefore, the serum CXCL13 level can be used as the prognostic indicator and a potential therapeutic target for these patients.

CXCL13/CXCR5 and other tumors

Sambandam *et al.* (34) reported that the c-Myc activation through CXCL13/CXCR5 axis signal pathway could

stimulate the expression of RANKL in stromal or preosteoblast cells, which implicated that CXCL13 could serve as a potential therapeutic target to prevent invasion of bone/osteolysis in oral squamous cell carcinoma. Duan *et al.* (35) have conducted a 5-year follow-up of patients with hepatocellular carcinoma and found that the serum level of CXCL13 was significantly increased in cancer patients compared with healthy controls, and the immunohistochemical staining results also showed that the percentage of CXCR5⁺ or CXCL13⁺ cells in poorly differentiated patients was significantly higher than that in well-differentiated patients, and thus CXCL13 could be served as a potential biomarker for the recurrence in patients with liver cancer after hepatectomy. Del Grosso *et al.* (36) found that the malignant neuroblastoma cells could express CXCR5 and the Schwann blast cells could express CXCL13, and the CXCL13 produced by stromal cells may contribute to the generation of an environment in which the malignant neuroblasts were retained.

Outlook

Numerous studies confirmed that the abnormal expression of CXCL13/CXCR5 could be found in human cancer tissues, and CXCL13/CXCR5 axis plays an important role in the regulation of cancer cell proliferation, migration and metastasis (Figure 1), and thus contributes to the cancer progression and the prognostic prediction of cancer patients. In future, the validation of CXCR5 and CXCL13

as useful biomarkers for cancer diagnosis and prevention, and the potential value of clinical application of CXCL13/CXCR5 axis blockade as an effective therapy against human cancers still merit further investigation.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2018.11.26>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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