Regulative role of the CXCL13-CXCR5 axis in the tumor microenvironment

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Abstract
Chemokines are best known for their abilities of recruiting immune cells and forming lymphoid tissue. Through interactions between chemokines and their receptors, various immune cell subsets are recruited into the tumor microenvironment which is the primary location for tumor cells interacting with responding host cells. In recent decades, a large volume of studies have revealed chemokines’ role in the tumor microenvironment in regulating tumor growth, invasion, and/or metastasis as well as tumor immune response; however, their molecular mechanisms are not well understood. Recently, increasing evidence has reported the importance of the CXCL13-CXCR5 axis in the tumor microenvironment of various human malignancies. Thus, in this review, we will focus on the CXCL13-CXCR5 axis and elaborate on the expression patterns, regulating and corresponding regulatory mechanisms as well as clinical values in a wide range of human cancers.

Key words: chemokine; CXCL13; CXCR5; tumor; microenvironment

Introduction
Chemokines are a family of small chemotactic cytokines (8–10 kDa), which are classified into four subgroups (CXC, CC, CX3C, and C chemokines) based on their N-terminal cysteines.1 Chemokines can be expressed by tumor cells and other cells in the tumor microenvironment. Chemokines are essential coordinators of cell-cell adhesion and interactions. They play a main role in chemo-attraction and leukocyte recruitment regulation in diverse immunological responses by binding to their corresponding G-protein coupled receptors on target cells.1–5 By expressing and releasing a

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series of different chemokines, host cells and tumors cells in the tumor microenvironment can recruit and activate different types of immune cell and pathways to regulate anti-tumor and pro-tumor responses.6,7 Recently, the expression patterns and regulative roles of most chemokines in various human tumor micro-environments have been summarized.8,9 In particular, CXC-chemokine ligands and their corresponding receptors have been proven to play an important role in angiogenesis, neoplastic transformation, as well as cancer cell migration, invasion, and metastasis.10 However, these reviews completely ignored CXCL13, one of the most important members of the CXC-chemokine family. CXCL13 is a chemotactic protein for B cells, and its receptor, CXCR5, is expressed by a specific subset of T cells.12 CXCL13 is usually expressed by stromal cells and follicular DC (FDC) in B cell follicles.13 It is also expressed in lymphoid organs, such as in lymph nodes and the spleen.13 Studies have proven that CXCL13 can also be secreted by tumor cells, myofibroblasts, CXCL13-producing CD4+ follicular helper T cells, bone marrow endothelial cells, and osteoblasts.9,12–14 Also, CXCL13 can sustain an active immune response by inducing an influx of immune cells to lymph organs and activating B cells to produce immunoglobulins.15 To date, a large number of studies have reported that CXCL13 and CXCR5 might also play important roles in regulating tumor growth, progression, and metastasis in the tumor micro-environment.16–21 Figure 1 shows the pathway of the CXCL13-CXCR5 axis in promoting tumor immunity and regulating tumor cell growth, invasion, and migration. In this review, we will discuss the regulative role of CXCL13-CXCR5 axis in the tumor microenvironment.

Role of the CXCL13-CXCR5 axis in breast cancer

Through quantified gene analysis based on Graphical Gaussian Models, a Harvard group found that CXCL13 was one of two notable gene hubs (the other is MMP12) in breast cancer (BC).22 Many studies have reported that, compared with normal breast tissue, the expression level of CXCL13 is significantly higher in both tumor tissues and peripheral blood in BC patients.23–29 Panse et al. showed that peripheral serum CXCL13 level increased in patients with metastatic BC but decreased after removing the primary tumors by surgery.24 Those authors also reported that CXCR5 was positively related to the level of CXCL13.24 Several studies have suggested that the CXCL13-CXCR5 axis plays a critical role in lymph node metastasis as the tumor expression level of CXCL13 was significantly higher in lymph node (LN) positive BC patients.16,27,30 Furthermore, vascular invasion, as well as LN involvement, was found to be significantly related to expression of CCR5, CXCL13, and SDF-1.30 In addition, expression of CXCR5 was significantly higher in patients with stage 3 than those with stage 2 disease.30 Interestingly, one study reported that CXCL13 expression was higher in younger BC patients and closely associated with negative estrogen.16

![Figure 1](image-url)

Figure 1. Regulative role of CXCL13-CXCR5 axis in the tumor microenvironment. (1) CXCL13 can recruit CXCR5+ T cells and B cells into tumor tissues to enhance tumor immunity. (2) CXCL13-CXCR5 axis takes part in tumor growth, invasion, and migration. (3) CXCL13 expressed in lymphoid organs or other tissues may attract CXCR5+ tumor cells spreading to these sites and promote tumor metastasis.
It is difficult to determine the mechanism of action of this chemokine axis based on expression data from clinical specimens. Several studies turned to BC cell lines to investigate the functional activities of CXCL13 and CXC\(\text{R}\)5. Interestingly, recent studies have reported that CXCL13 gene expression is often lost in aggressive triple-negative breast cancers (TNBC).\(^{23-25}\) Anti-tumor immunity.\(^{23,24}\) Indeed, CXCL13 is a known critical factor for triggering development of secondary lymphoid organs.\(^{40}\) Interestingly, recent studies have proved that CXCL13 is also specifically related to induction of the formation of tertiary lymphoid structures (TLSs) in non-lymphoid tissues.\(^{41,42}\) The inhibition of CXCL13 can interfere with formation of TLSs,\(^{43}\) which are essential for shaping a favorable immune microenvironment to inhibit tumor growth.\(^{44-46}\) Another study detected CXCL13-producing CD4+ follicular helper T (TFHX13) cells in extensively infiltrated tumors, which contributed to organization of LN-like structures.\(^{14}\) Those TFHX13 may affect recruitment of immune cells to the tumor microenvironment, and also affect TLS formation, thus helping to create a niche in the tumor mass in which effective and durable antitumor immune responses can be generated.\(^{14}\) In addition, the major source of CXCL13 production was revealed to be CD4+PD-1\(^{+}\)CD200\(^{+}\) TFH cells infiltrating in BC.\(^{47}\) However, the initial attraction may be attributed to tumor-dependent secretion of CXCL13.\(^{23}\) A study by Gu-Trantien et al. found that, at the tumor site, TFHX13 cells can potentially initiate TLS formation and thereby generate germinal center B cell responses. In addition, in the BC microenvironment, TFHX13 cell differentiation may play a critical role in converting Treg-mediated immune suppression to de novo activation of adaptive antitumor humoral responses.\(^{19}\)

Pimenta et al. showed that IRF5 (interferon regulatory factor 5) can bind to the promoter of CXCL13 and directly regulate its expression in mammary epithelial tumor cells. In addition, their results revealed that IRF5-induced CXCL13 expression is responsible for recruiting CD19+CXCR5+ B-cell and CD4+CXC\(\text{R}\)5+ T-cell to the tumor.\(^{23}\) An in vivo study found that CCX-CKR (ChemoCentrinx chemokine receptor), also known as CCR11, a member of atypical chemokine binders, can decrease CCL19/21 and CXCL13 protein levels in CCX-CKR-transfected BC xenograft tumor mice models and can significantly inhibit tumor growth and lung metastasis.\(^{37}\)

**Role of CXCL13-CXCR5 axis in prostate cancer**

In recent decades, scientists discovered that CXC-chemokines play significant roles in cell adhesion to endothelium and extracellular matrix in prostate tumor cell lines.\(^{48}\) Recently, Singh et al. reported significantly higher serum CXCL13 levels in prostate cancer (PCa) patients than those in normal healthy donors and patients with other prostate diseases.\(^{49}\) Also, those authors found that CXCL13 was positively correlated with serum PSA in PCa patients.\(^{49}\) However, the result from another group showed that CXCL13 levels were not significantly different between PCa and non-PCa patients.\(^{50}\) Although they found that CXCL13 gene expression level was higher in PCa tissues compared with adjacent normal tissue, the difference was not
An analysis including 137 clinical PCa samples reported significantly higher gene expression and protein levels of CXCL13 in tumor tissues than those in adjacent normal tissues. Conversely, another study reported that CXCL13 was significantly reduced in prostate tumors compared with adjacent normal tissues. The structural and functional features of the prostate-associated lymphoid tissue (PALT) compartment can enable the gland to mount a local immune response against infections and tumors in the course of malignant lesions; its destruction, and qualitative or morphological changes can down-regulate CXCL13 expression. Thus, Wedel et al. deduced that CXCL13 and CCR5 gene expression were gradually decreased in the progression of PCa. In vitro, Fan et al. found that levels of CXCL13 were much higher in LNCaP and CWR22Rv1 than in DU145 and PC3.

In terms of the origin of CXCL13 in prostate tissue, some scientists concluded that IL-6, which is highly elevated in PCa patients, can induce CXCL13 production by human bone marrow endothelial cells and osteoblasts. However, in in vivo PCa models, evidence showed that CXCL13 was expressed by tumor-associated myofibroblasts. It was found that androgen deprivation could activate myofibroblasts and induce CXCL13 expression in both prostate tumor and normal prostate through inducing hypoxia, a condition which activates hypoxia-inducible factor 1 (HIF-1) and autocrine TGF-β signaling and CTGF. Moreover, after TGF-βR1 signaling was inhibited, myofibroblast activation, B cell infiltration, CXCL13-expressing myofibroblast induction, nuclear translocation of IKKα, and CRPC progression were all prevented.

In addition, a study found that androgen stimulation could enhance expression of CXCL13 in androgen receptor (AR)-expressing PCa cells. Knockdown of AR suppressed CXCL13 expression while AR over-expression enhanced CXCL13 expression in both LNCaP and CWR22Rv1 cell lines. AR ChIP-seq results from LNCaP cells revealed that AR regulated expression of CXCL13 by binding to its enhancer sequences. Also, CXCL13 is reported to be involved in AR-induced migration and invasion of PCa cells through its interaction with AR-responsive genes, such as EST-A, Snail, and Cyclin B.

However, for CXCR5, some studies argued that CXCR5 was either reduced significantly in the prostate tumor tissues or expressed identically in normal tissues. While other studies inferred that expression of CXCR5 was significantly higher in prostate tumor than in normal prostate tissues, and that the expression of CXCR5 was positively related to tumor stage and grade. Moreover, compared with normal prostate epithelial cells, PCa cell lines expressed a higher level of CXCR5.

In the case of chemokines, it is noted that mRNA expression patterns do not always mirror those of their encoded proteins. Generally, normal prostate tissues and BPH samples predominately express CXCR5 on the membrane and/or in the cytoplasm. In terms of PCa cases, those with Gleason scores ≤6 also showed predominantly membrane and cytoplasmic CXCR5 expression patterns, but interestingly, those with advanced disease had more nuclear CXCR5 expression patterns.

As attested above, PCa cell lines express different levels of CXCR5. Of interest, the level of CXCR5 expression in a cell line positively correlates with its ability of migration and invasion of extracellular matrix components following interaction with CXCL13. In PCa cell lines (LNCaP and PC3), expression of collagenase-1 (MMP-1), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) were increased after CXCL13 treatment. These data suggest clinical and biological relevance of the CXCL13-CXCR5 pathway and its potential role in PCa cell invasion and migration. Evidence from studies using PC3 cells, an established hormone-refractory PCa cell line with ability of skeletal (osteolytic) metastases and tumor growth, proved that CXCL13 blockade can significantly delay growth of prostate tumor and its spread to bones, as well as osteolysis. This result indicates that the CXCL13-CXCR5 axis supports PCa bone metastasis and growth. Another study also concluded that CXCL13 was secreted by human bone marrow endothelial cells and osteoblasts cells after IL-6 stimulation. The CXCL13 secreted by these stromal cells could attract CXCR5+ PCa cells to bone site, which may partially explain why PCa cells tend to metastasize to bone. Additionally, this group found co-localization of α4β1 with CXCR5, and clustering of this integrin complex after CXCL13 treatment, which suggest that the CXCR5-CXCL13 axis was also involved in adhesion in PCa cells. Another study disclosed that tumor infiltrating B cells were critical inflammatory cells that promoted the progression to castration-resistant PCa after androgen-deprivation treatment. These B cells can produce LTαβ heterotrimermers that stimulate LTαR on PCa cells to induce IKKa nuclear translocation and STAT3 activation, thereby enhancing androgen-independent growth. CXCL13 could be a major signal to recruit these B cells, as a CXCL13 blocking antibody was used to successfully prevent castration-induced B-cell recruitment. In a mouse model, Garg et al. demonstrated that PKCα cooperates with loss of Pten to promote prostate cancer development by individually and synergistically up-regulating the CXCL13 via a non-canonical NF-κB pathway.

Chemokine receptors are coupled to heterotrimic G protein α, β, and γ subunits, thereby subsequently causing Class IA and IB PI3K activation. Geq/11/Gq/11/Gy/9 in LNCaP and Geq2/Gq/11/Gy/9 in C4-2B and PC3 cell lines were coupled to CXCR5 and dissociated the following CXCL13 stimulation. Both of these G-proteins can activate the phosphoinositide-3 kinase (PI3K)Akt pathway and the ERK1/2 pathway. Generally, in PC3 cells, CXCL13 mainly regulates the PI3K/Akt and stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase-1 (JNK) pathways. By means of binding to CXCR5, CXCL13 can activate PI3K/Akt, Raf/MEK/ERK, Integrin-ß3/Src/FAK (focal adhesion...
Role of CXCL13-CXCR5 axis in gastrointestinal cancers

Prominent overexpression of CXCL13 in liver cancer tissues and serum was observed in patients with hepatocellular carcinoma (HCC). Moreover, its level was positively associated with serum ALB, ALT, AST, and Child-Pugh scores. In patients with a heavy mass burden, advanced and metastatic HCC, serum CXCL13 expression was further increased. Duan et al. reported that the number of infiltrated CXCR5+CD45RA-CD4+ T cells was higher in tumor than in para-tumor tissues, and they found that serum CXCL13 was related to recurrence-free survival after surgery. Li et al. revealed that CXCL13 and Wnt/β-catenin signaling shared a positive feedback loop and that CXCL13 promoted liver cancer by activating Wnt/β-catenin pathway, inducing IL-12, IL-17, and IgG4.

Bai et al. showed that CD8+CXCR5+ T cells were abundant in pancreatic cancer patients, especially in the tumor microenvironment, responding to anti-FD-1/anti-TIM-3 blockade by functional upregulation. Moreover, Xing et al. reported that CD8+CXCR5+ T cells could also contribute to antitumor immunity in colorectal cancer. For gastric cancer, no studies have evaluated different expression levels of CXCL13-CXCR5 in tumor tissue and normal tissue. Only one study found that high intratumoral CXCL13 expression contributed to inferior prognosis in patients undergoing gastric cancer resection. Moreover, CXCL13 expression may act as an indicator of response to adjuvant chemotherapy after surgery in patients with T2-4 stage disease.

Compared with adjacent normal tissue, CXCL13 and CXCR5 expression were significantly higher in colorectal cancer (CRC) tissues. Furthermore, the expression levels of CXCR5 and CXCL13 were significantly higher in high stage CRC tissues (≥T3). Further evidence proved that high levels of CXCR5 and CXCL13 were also associated with poorer survival. The molecular mechanisms of the CXCL13-CXCR5 axis in gastrointestinal cancer remain elusive. A recent study revealed that CXCL13 promoted growth, invasion, and migration of colon cancer cells through the CXCL13-CXCR5-Pi3K/AKT pathway. Likewise, CXCL13 increased MMP-13 expression and secretion. Another study using an endoscopic orthotopic colon cancer model found that tumor growth in CXCR5-/- mice was severely increased, with a similar number of tumor-infiltrating CD4+ T cells to that in tumors of wild-type mice but significantly decreased number of B cells. Vice versa, mice bearing CXCL13-overexpressing MC38 cells had reduced tumor growth compared with wild-type mice, a conclusion that indicated the important role of CXCL13-CXCR5 signaling in recruitment of T and B cells into the tumor microenvironment and anti-tumor immune response in colorectal cancer.

Role of CXCL13-CXCR5 axis in other cancers

Head and neck squamous cell carcinomas have been found with high expression of CXCL13 as well as CCR7 and CXCR5 in tumor tissues compared with normal tissues. A high level of expression of CXCL13 was also identified in oral squamous cell carcinoma (OSCC), which was proven to be related to OSCC development and progression. An in vitro study identified that expression of both CXCR5 and MMP-9 was upregulated in the OSCC cell line, SCC14a, after treatment with exogenous CXCL13, a result that suggests CXCL13 could enhance CXCR5 receptor expression in an autocrine regulatory manner in OSCC cells. Fortunately, this corresponding response was also observed in a human bone marrow-derived stromal cell line (SAKA-T) and murine preosteoblast cell (MC3T3-E1). By establishing a subcutaneous OSCC model, Pandruvada et al. identified that CXCL13 was also attributed to bone invasion. In models bearing CXCL3 knock-down tumor, the tumor’s ability to invade into bone matrix was inhibited and the number of osteoclasts at the tumor-bone interface was also significantly decreased. Researchers uncovered that CXCL13 could significantly enhance the RANKL-RANK signaling pathway, which is an important pathway for promoting osteoclast growth and bone resorption. But a small difference of note is that CXCL13 stimulation increased the expression level of NFATc3 in OSCC cells and p-c-Myc in SAKA-T/MC3T3-E1 cells, respectively. And these two proteins both could further induce RANKL expression by targeting the RANKL promoter region and stimulating its activity.

Lu et al. found that IL-17A could contribute to migration and tumor killing capability of B cells in esophageal squamous cell carcinoma by inducing tumor cells to produce CXCL13, CCL2, and CCL20, which recruit B cells into the tumor microenvironment. Singh et al. reported increased expression levels of CXCR5 and CXCL13 in ovarian cancer cell lines and in
clinical samples compared with non-neoplastic ovarian tissues. Moreover, CXCR5 and CXCL13 expression levels were different among different types of cancerous ovarian tissues.78

Evidence of the role of the CXCL13-CXCR5 axis in terms of lung cancer is limited.79,80 In a study including a small sample of non-small cell lung cancer (NSCLC) patients, Singh et al. reported that CXCR5 expression was higher in tumor tissues compared with non-neoplastic tissues.79 Also, they found elevated serum CXCL13 in lung carcinoma patients compared with healthy volunteers.79 Furthermore, they uncovered that CXCR5 expression was only significantly increased in squamous cell carcinoma (SCC) sets with nodal metastases, not in other subtypes of lung cancer.79 Ma et al. reported that the frequency of CD4+CXCR5+ T cells was significantly lower in peripheral blood of NSCLC patients than that of healthy controls.81 They found that CD4+CXCR5+ T cells contributed to antitumor immunity and were related to better outcomes in NSCLC.81 Wang et al. proved that benzo(a)pyrene (BaP) could induce CXCL13 expression in lung epithelial cells and lung cancer formation in mice, while knockout CXCL13 or CXCR5 could significantly attenuate BaP-induced lung cancer in mice.82

Similar to breast cancer, intratumoral TLS in lung cancers is also associated with patients’ survival.83 The latest studies concluded that CXCL13 was strongly expressed in the germinal centers by CD21+ follicular dendritic cells in TLS and its higher expression was associated with CXCR5+ T cell recruitment to intratumoral TLS.84,85

Conclusion

The CXCL13-CXCR5 axis plays a critical role in tumor growth, invasion, and ultimately metastasis in a wide range of human malignancies. Understanding its potential mechanisms will likely lead to novel anti-tumor therapies.

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Conflict of interest

None declared.

References

1. Balkwill F. Cancer and the chemokine network. Nat Rev Cancer 2004;4:540–50.
2. Latek D, Modzelewksa A, Trzaskowski B, et al. G protein-coupled receptors—recent advances. Acta Biochim Pol 2012;59:515–29.
3. Zlotnik A, Yoshie O. Chemokines: a new classification system and their role in immunity. Immunity 2000;12:121–7.
4. Palomino DC, Marti LC. Chemokines and immunity. Einstein (Sao Paulo, Brazil) 2015;13:469–73.
5. Wang J, Knaut H. Chemokine signaling in development and disease. Development 2014;141:4199–4205.
6. Gorbachev AV, Fairchild RL. Regulation of chemokine expression in the tumor microenvironment. Crit Rev Immunol 2014;34:103–20.
7. Roy I, Evans DB, Dwinell MB. Chemokines and chemokine receptors: update on utility and challenges for the clinician. Surgery 2014;155:961–73.
8. Zlotnik A. Chemokines in neoplastic progression. Semin Cancer Biol 2004;14:181–5.
9. Chow MT, Luster AD. Chemokines in cancer. Cancer Immunol Res 2014;2:1125–31.
10. Keeley EC, Mehrad B, Strieter RM. CXC chemokines in cancer angiogenesis and metastases. Adv Cancer Res 2010;106:91–111.
11. Amedei A, Prisco D, D’ Elias MM. The use of cytokines and chemokines in the cancer immunotherapy. Recent Patents Anticancer Drug Discov 2013;8:126–42.
12. Moser B. CXCR5, the Defining Marker for Follicular B Helper T (TFH) Cells. Front Immunol 2015;6:296.
13. Huber AK, Irani DN. Targeting CXCL13 During Neuroinflammation. Adv Neuroimmune Biol 2015;6:1–8.
14. Gu-Trantien C, Loi S, Garaud S, et al. CD4(+) follicular helper T cell infiltration predicts breast cancer survival. J Clin Invest 2013;123:2873–92.
15. Nagarsheth N, Wicha MS, Zou W. Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. Nat Rev Cancer 2017;17:559–72.
16. Chen L, Huang Z, Yao G, et al. The expression of CXCL13 and its relation to unfavorable clinical characteristics in young breast cancer. J Transl Med 2015;13:168.
17. Yang L, Gao L, Chen Y, et al. The Differential Expression and Function of the Inflammatory Chemokine Receptor CXCR5 in Benign Prostatic Hyperplasia and Prostate Cancer. Int J Med Sci 2015;12:855–61.
18. Fan L, Zhu Q, Liu L, et al. CXCL13 is androgen-responsive and involved in androgen induced prostate cancer cell migration and invasion. Oncotarget 2017;8:53244–61.
19. Gu-Trantien C, Migliori E, Buisseret L, et al. CXCL13-producing THF cells link immune suppression and adaptive memory in human breast cancer. JCI Insight 2017;2 pii:91487. doi: 10.1172/jci.insight.91487.
20. Lillard J, Singh R, Sharma P, et al. CXCL13 inhibition prevents bone metastasis in hormone-refractory prostate cancer (133.8). J Immunol 2010;184(1 Supplement):133.138–133.138.
21. Lazennec G, Richmond A. Chemokines and chemokine receptors: new insights into cancer-related inflammation. Trends Mol Med 2010;16:133–44.
22. Chu JH, Lazarus R, Carey VJ, et al. Quantifying differential gene connectivity between disease states for objective identification of disease-relevant genes. BMC Syst Biol 2011;5:89.
Regulative role of CXCL13-CXCR5 axis in the tumor microenvironment

23. Pimenta EM, De S, Weiss R, et al. IRF5 is a novel regulator of CXCL13 expression in breast cancer that regulates CXCR5 B- and T-cell trafficking to tumor-conditioned media. Immuno Cell Biol 2015;103:486–99.

24. Panse J, Friedrichs K, Marx A, et al. Chemokine CXCL13 is overexpressed in the tumour tissue and in the peripheral blood of breast cancer patients. Br J Cancer 2008;99:930–8.

25. Razis E, Kalogeras KT, Kotoula V, et al. Improved outcome of high-risk early HER2 positive breast cancer with high CXCL13-CXCR5 messenger RNA expression. Clin Breast Cancer 2012;12:183–93.

26. Schmidt M, van de Sandt L, Boehm D, et al. Prognostic significance of the chemokine CXCL13 in node-negative breast cancer. J Clin Oncol 2013;31(15 supplement):615.

27. Biswas S, Sengupta S, Chowdhury SR, et al. CXCL13–CXCR5 co-expression regulates epithelial to mesenchymal transition of breast cancer cells during lymph node metastasis. Breast Cancer Res Treat 2014;143:265–76.

28. Singh R, Gupta P, Grizzle W, et al. Expression of CXCR5 and its natural ligand CXCL13 in breast cancer (P6278). J Immunol 2013;190(Meeting Abstracts)1:46.10.

29. Narita D, Seclaman E, Anghel A, et al. Altered levels of plasma chemokines in breast cancer and their association with clinical and pathological characteristics. Neoplasia 2016;18:141–9.

30. Razmkhah M, Jaberipour M, Safaei A, et al. Chemokine and chemokine receptors: a comparative study between metastatic and nonmetastatic lymph nodes in breast cancer patients. Eur Cytokine Netw 2012;23:72–7.

31. Irshad S, Flores-Borja F, Lawler K, et al. RORgammat(-) Innate Lymphoid Cells Promote Lymph Node Metastasis of Breast Cancers. Cancer Res 2017;77:1083–96.

32. Teschendorff AE, Miremadi A, Pinder SE, et al. An immune response gene expression module identifies a good prognosis subtype in estrogen receptor negative breast cancer. Genome Biol 2007;8:R157.

33. Desmedt C, Haibe-Kains B, Wirapati P, et al. Biological processes associated with breast cancer clinical outcome depend on the molecular subtypes. Clin Cancer Res. 2008;14:5158–65.

34. Yau C, Esserman L, Moore DH, et al. A multigene predictor of metastatic outcome in early stage hormone receptor-negative and triple-negative breast cancer. Breast Cancer Res 2010;12:R85.

35. Yuan Y. Modelling the spatial heterogeneity and molecular correlates of lymphatic infiltration in triple-negative breast cancer. J R Soc Interface 2015;12:20141153.

36. Wirtz R, Leinonen M, Bone F, et al. Abstract PD10-06: CXCL13 mRNA predicts Docetaxel benefit in Triple Negative tumors. Cancer Res 2012;72(24 Supplement):PD10-06-PD10-06.

37. Schmidt M, Weyer-Eberich V, Hengstler JG, et al. Prognostic impact of CD4-positive T cell subsets in early breast cancer: a study based on the FinHer trial patient population. Breast Cancer Res 2018;20:15.

38. Song IH, Heo SH, Bang WS, et al. Predictive Value of Tertiary Lymphoid Structures Assessed by High Endothelial Venule Counts in the Neoadjuvant Setting of Triple-Negative Breast Cancer. Cancer Res Treat 2017;49:399–407.

39. Criscitiello C, Bayar MA, Curigliano G, et al. A gene signature to predict high tumor-infiltrating lymphocytes after neoadjuvant chemotherapy and outcome in patients with triple-negative breast cancer. Annal Oncol 2018;29:162–9.

40. van de Pavert SA, Olivier BJ, Govers E, et al. Chemokine CXCL13 is essential for lymph node initiation and is induced by retinoic acid and neuronal stimulation. Nat Immunol 2009;10:1193–9.

41. Weiss JM, Robinet M, Aich M, et al. Novel CXCL13 transgenic mouse: inflammation drives pathogenic effect of CXCL13 in experimental myasthenia gravis. Oncotarget 2016;7:7550–62.

42. Luther SA, Lopez T, Bai W, et al. BLC expression in pancreatic islets causes B cell recruitment and lymphoxygen-dependent lymphoid neogenesis. Immunity 2000;12:471–81.

43. Yamamoto K, Nishiumi S, Yang L, et al. Anti-CXCL13 antibody can inhibit the formation of gastric lymphoid follicles induced by Helicobacter infection. Mucosal Immunol 2014;7:1244–54.

44. Teillaud JL, Dieu-Nojesan MC. Tertiary Lymphoid Structures: An Anti-tumor School for Adaptive Immune Cells and an Antibody Factory to Fight Cancer? Front Immunol 2017;8:830.

45. Dieu-Nojesan MC, Giraldo NA, Kaplon H, et al. Tertiary lymphoid structures, drivers of the anti-tumor responses in human cancers. Immuno Rev 2016;271:260–75.

46. Di Caro G, Castino GF, Bergomas F, et al. Tertiary lymphoid tissue in the tumor microenvironment: from its occurrence to immunotherapeutic implications. Int Rev Immunol 2015;34:123–33.

47. Feng LY, Ou ZL, Wu FY, et al. Involvement of a novel chemokine decoy receptor CXCR5 in breast cancer growth, metastasis and patient survival. Clin Cancer Res 2009;15:2962–70.

48. Engl T, Rieba B, Blumenberg C, et al. Prostate tumor CXCL13 chemokine profile correlates with cell adhesion to endothelium and extracellular matrix. J Immunol 2006;178:1784–93.

49. Singh S, Singh R, Sharma PK, et al. Serum CXCL13 expression correlates with prostate disease, prostate-specific antigen and mediates prostate cancer cell invasion, integrin clustering and cell adhesion. Cancer Lett 2009;283:29–35.

50. Tsaur I, Noack A, Makarevic J, et al. CCL2 chemokine as a potential biomarker for prostate cancer: a pilot study. Cancer Res Treat 2015;47:306–12.

51. Wedel SA, Raditchev IN, Jones J, et al. CXCl chemokine mRNA expression as a potential diagnostic tool in prostate cancer. Mol Med Rep 2008;1:257–62.

52. Di Carlo E, Magnasco S, D’Antuono T, et al. The prostate-associated lymphoid tissue (PALT) is linked to the expression of homing chemokines CXCL13 and CCL21. Prostate 2007;67:1070–80.

53. Ammirante M, Shalapour S, Kang Y, et al. Tissue injury and hypoxia promote malignant progression of prostate cancer by inducing CXCL13 expression in tumor myofibroblasts. Proc Natl Acad Sci USA 2014;111:14776–81.

54. Singh S, Singh R, Singh UP, et al. Clinical and biological significance of CXCR5 expression by prostate cancer specimens and cell lines. Int J Cancer 2009;125:2288–95.

55. El-Haibi CP, Sharma P, Singh R, et al. Differential G protein subunit expression by prostate cancer cells and their interaction with CXCR5. Mol Cancer 2013;12:64.

56. Lillard J, Singh R, Singh S, et al. Abstract 3377: CXCL13-directed therapy against bone metastasis in hormone-refractory prostate cancer. Cancer Res 2014;70(8 Supplement):3377.

57. Ammirante M, Luo JL, Grivennikov S, et al. B-cell-derived lymphoxygen promotes castration-resistant prostate cancer. Nature 2010;464:302–5.
58. Garg R, Blando JM, Perez CJ, et al. Protein Kinase C Epsilon Cooperates with PTEN Loss for Prostate Tumorigenesis through the CXCL13-CXCR5 Pathway. Cell Rep 2017;19:375–88.

59. El-Haibi CP, Singh R, Sharma PK, et al. CXCL13 mediates prostate cancer cell proliferation through JNK signalling and invasion through ERK activation. Cell Prolif 2011;44:311–9.

60. El-Haibi CP, Singh R, Gupta P, et al. Antibody Microarray Analysis of Signaling Networks Regulated by Cxcl13 and Cxcr5 in Prostate Cancer. J Proteomics Bioinform 2012;5:177–84.

61. El Haibi CP, Sharma PK, Singh R, et al. PI3Kp110-, Src-, FAK-dependent and DOCK2-independent migration and invasion of CXCL13-stimulated-stimulated prostate cancer cells. Mol Cancer 2010;9:85.

62. Li C, Kang D, Sun X, et al. The Effect of CXC Motif Chemokine 13 on Hepatocellular Carcinoma Associates with Wnt Signaling. BioMed Res Int 2015. 2015:345413.

63. Li B, Su H, Cao J, et al. CXCL13 rather than IL-31 is a potential indicator in patients with hepatocellular carcinoma. Cytokine 2017;89:91–7.

64. Duan Z, Gao J, Zhang L, et al. Phenotype and function of CXCR5+CD45RA-CD4+ T cells were altered in HBV-related hepatocellular carcinoma and elevated serum CXCL13 predicted better prognosis. Oncotarget 2015;6:44239–53.

65. Bai M, Zheng Y, Liu H, et al. CXCR5(+) CD8(+) T cells potently infiltrate pancreatic tumors and present high functionality. Exp Cell Res 2017;361:39–45.

66. Xing J, Zhang C, Yang X, et al. CXCR5(+)/CD48(+) T cells infiltrate the colorectal tumors and nearby lymph nodes, and are associated with enhanced IgG response in B cells. Exp Cell Res 2017;356:57–63.

67. Wei Y, Lin C, Li H, et al. CXCL13 expression is prognostic and predictive for postoperative adjuvant chemotherapy benefit in patients with gastric cancer. Cancer Immunol Immunother 2017;67:261–9.

68. Qi X, Xia S, Yin Y, et al. Expression features of CXCR5 and its ligand, CXCL13 associated with poor prognosis of advanced colorectal cancer. Eur Rev Med Pharmacol Sci 2014;18:1916–24.

69. Zhu Z, Zhang X, Guo H, et al. CXCL13-CXCR5 axis promotes the growth and invasion of colon cancer cells via PI3K/AKT pathway. Mol Cell Biochem 2015;400:287–95.

70. Waldner MJ, Bindea G, Mlecnik B, et al. 779 CXCL13-CXCR5 Signaling Is Required for the Anti-Tumor Immune Response in Colorectal Cancer. Gastroenterology 2014;146: S-131.

71. Müller A, Sonkoly E, Eulert C, et al. Chemokine receptors in head and neck cancer: association with metastatic spread and regulation during chemotherapy. Int J Cancer 2006;118:2147–57.

72. Zierb AF, Patel KR, Alawi F, et al. Identification of a gene signature for rapid screening of oral squamous cell carcinoma. Clin Cancer Res 2006;12:5960–71.

73. Vachani A, Nebozhyn M, Singhal S, et al. A 10-gene classifier for distinguishing head and neck squamous cell carcinoma and lung squamous cell carcinoma. Clin Cancer Res 2007;13:2905–15.

74. Pandravada SN, Yuvaraj S, Liu X, et al. Role of CXC chemokine ligand 13 in oral squamous cell carcinoma associated osteolysis in athymic mice. Int J Cancer 2010;126:2319–29.

75. Sambandam Y, Sundaram K, Liu A, et al. CXCL13 activation of c-Myc induces RANK ligand expression in stromal/precancerous cells in the oral squamous cell carcinoma tumor-bone microenvironment. Oncogene 2013;32:97–105.

76. Yuvaraj S, Griffin AC, Sundaram K, et al. A novel function of CXCL13 to stimulate RANK ligand expression in oral squamous cell carcinoma cells. Mol Cancer Res 2009;7:1399–1407.

77. Lu L, Weng C, Mao H, et al. IL-17A promotes migration and tumor killing capability of B cells in esophageal squamous cell carcinoma. Oncotarget 2016;7:21853–64.

78. Singh R, Grizzle WE, Singh S, et al. Expression of CXCR5 and its natural ligand CXCL13 in ovarian cancer. Cancer Res 2012;72(8 Supplement):3649–9.

79. Singh R, Gupta P, Kloecker GH, et al. Expression and clinical significance of CXCR5/CXCL13 in human non-small cell lung carcinoma. Int J Oncol 2014;45:2232–40.

80. Cheng ZH, Shi YX, Yuan M, et al. Chemokines and their receptors in lung cancer progression and metastasis. J Zhejiang Univ Sci B 2016;17:342–51.

81. Ma QY, Huang DY, Zhang HJ, et al. Function of follicular helper T cell is impaired and correlates with survival time in non-small cell lung cancer. Int Immunopharmacol 2016;41:1–7.

82. Wang GZ, Cheng X, Zhou B, et al. The chemokine CXCL13 in lung cancers associated with environmental polycyclic aromatic hydrocarbons pollution. eLife 2015;4 pii:e09419. doi: 10.7554/eLife.09419.

83. Dieu-Nojean MC, Antoine M, Danel C, et al. Long-term survival for patients with non-small-cell lung cancer with intratumoral lymphoid structures. J Clin Oncol 2008;26:4410–7.

84. de Chaisemartin L, Goc J, Damotte D, et al. Characterization of chemokines and adhesion molecules associated with T cell presence in tertiary lymphoid structures in human lung cancer. Cancer Res 2011;71:6391–9.

85. Silina K, Soltermann A, Attar FM, et al. Germinal Centers Determine the Prognostic Relevance of Tertiary Lymphoid Structures and Are Impaired by Corticosteroids in Lung Squamous Cell Carcinoma. Cancer Res 2018;78:1308–20.