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Original Article

CXCR4 expression as a predictive biomarker for esophageal cancer

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Abstract: Background: The CXC chemokine receptor type 4 (CXCR4) has been linked to tumor growth, dissemination and local immune in many malignancies. However, the clinicopathological and prognostic significance of CXCR4 for survival of patients with esophageal cancer is still controversial. The aim of our study was to investigate the clinical significance of CXCR4 expression in esophageal cancer. Methods: Tumor samples were obtained from 105 patients who were diagnosed with esophageal carcinoma and had undergone routine esophageal resection. The streptavidin-peroxidase (SP) staining method was used to detect the protein level of CXCR4. The esophageal cancer specimens were classified into two groups according to the sum of the staining intensity score. The overall survival rate was evaluated by the Kaplan-Meier method and log-rank test. The univariate and multivariate Cox proportional hazards model were used to measure the survival prediction. Results: High level of CXCR4 expression was found in 52.4% of 105 esophageal tumor samples. High CXCR4 expression was statistically significantly associated with lymph node metastasis ($P = 0.037$), distant metastasis ($P = 0.027$), and pTNM stage ($P = 0.015$). For univariate and multivariate analyses, compared with the low expression, high levels of CXCR4 was identified as the independent prognostic factor associated with overall survival (HR = 1.75, 95% CI = 1.08 to 3.37, $P = 0.028$). Furthermore, compared with the low CXCR4 expression, the high expression was statistically significantly associated with a poor 5-year overall survival rate in our esophageal cancer cohort ($P = 0.007$ by log-rank test). Conclusions: High expression of CXCR4 in patients with esophageal cancer was associated with a worse 5-year overall survival rate as well as poor clinicopathological and prognostic features.

Keywords: CXCR4, lymph node metastasis, distant metastasis, pTNM stage, esophageal cancer

Introduction

Esophageal cancer (EC) is the sixth most common cause of death from cancer worldwide and one of the most difficult gastrointestinal tumors to treat [1]. Surgery is the most common treatment for localized and resectable esophageal cancer, yet even after curative operation, prognosis still remains poor and patients often suffer from distant metastasis or local recurrence [2]. Even at an early stage of the cancer, systematic metastasis and vascular invasion are present in many patients soon after surgery [3]. As a result, interest has centered on combination of preoperative chemotherapy and/or radiotherapy and surgery, but the overall picture emerging from the literature is still unfavorable and the reported 5-year survival after surgery is only 25% to 40% [4]. Thus, novel strategies against esophageal cancer contribute to improve patient prognosis need to be developed and established.

Chemokines are a family of chemoattractant proteins that are classified into four groups (CXC, CC, C, and CX3C) depending on the arrangement of their cysteine resides. CXCL12, also known as stromal cell-derived factor-1 (SDF-1), is a member of the CXC chemokine family that has chemotactic activity for hematopoietic progenitor [5]. The CXC chemokine receptor type 4 (CXCR4) is a seven-transmembrane G-protein-coupled receptor and the only known physiological receptor for SDF-1. Thus far, chemokine signaling regulates a range of immune responses to bacterial infections, inflammation, tissue repair, as well as the regulation of target genes that are associated with cell invasion, motility, interactions with the extracellular matrix (ECM) and survival [6]. Clinical

Table 1. Correlation between clinicopathological characteristics and CXCR4 levels in the esophageal cancer patients (n = 105)

Characteristics	Number of patients	CXCR4 expression (%)		χ^2	*P* value
		Low	High		
Total	105	50 (47.6%)	55 (52.4%)		
Sex				0.125	0.724
Male	76	37 (74.0%)	39 (70.9%)		
Female	29	13 (26.0%)	16 (29.1%)		
Age (years)				0.920	0.338
< 60	45	19 (38.0%)	26 (47.3%)		
≥ 60	60	31 (62.0%)	29 (52.7%)		
Tumor type				1.091	0.296
Squamous cell carcinoma	56	24 (48.0%)	32 (58.2%)		
Adenocarcinoma	49	26 (52.0%)	23 (41.8%)		
Tumor location				2.008	0.367
Upper esophagus	31	14 (28.0%)	17 (30.9%)		
Middle esophagus	29	17 (34.0%)	12 (21.8%)		
Lower esophagus	45	19 (38.0%)	26 (47.3%)		
Tumor depth				0.033	0.984
sm1	26	12 (24.0%)	14 (25.5%)		
sm2	46	22 (44.0%)	24 (43.6%)		
sm3	33	16 (32.0%)	17 (30.9%)		
Histologic grade				0.936	0.626
Well	27	15 (30.0%)	12 (21.8%)		
Moderate	35	16 (32.0%)	19 (34.5%)		
Poor	43	19 (38.0%)	24 (43.6%)		
Lymph node metastasis				4.364	0.037
Negative	56	32 (64.0%)	24 (43.6%)		
Positive	49	18 (36.0%)	31 (56.4%)		
Distant metastasis				4.926	0.027
Negative	49	29 (58.0%)	20 (36.4%)		
Positive	56	21 (42.0%)	35 (63.6%)		
pTNM stage				5.944	0.015
I + II	52	31 (62.0%)	21 (38.2%)		
III	53	19 (38.0%)	34 (61.8%)		

studies have already revealed that expression of the chemokine receptor CXCR4 played key roles in migration and metastasis involved in tumor initiation, progression and poor prognosis in many malignancies [7-11].

To date, the clinicopathological and prognostic significance of CXCR4 for survival of patients with esophageal cancer is still controversial. Previous studies have demonstrated a role for CXCR4 in lymph node microinvolvement and bone marrow micrometastasis of esophageal cancer, and the further multivariable analysis showed that CXCR4 was identified as an independent variable associating with reduced disease-specific survival [12]. The similar evidence was presented by other studies, showing the association of persistent positive CXCR4 expression with tumor aggressiveness and poor prognosis in esophageal squamous carcinomas after chemoradiotherapy [13]. Gockel et al. demonstrated that, in 102 esophageal cancer tissues, the overall expression rate for CXCR4 in esophageal squamous cell carcinoma was 94.1% and CXCR4 overexpression was involved in a poorer long-term prognosis [14]. Goto et al. also reported high expression of CXCR4 in the cytoplasm and nuclei was associated with poor cause-specific survival of patients with esophageal squamous cell carcino-

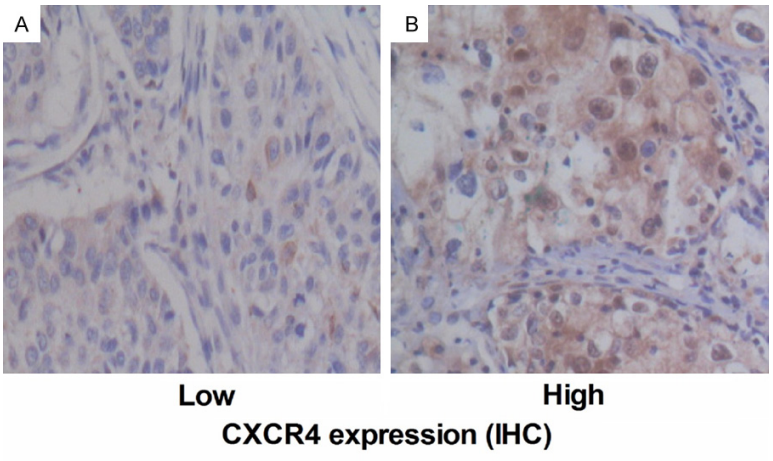

Figure 1. Immunohistochemical staining of esophageal tumor tissue for CXCR4 (200×). A. Low expression. B. High expression.

ma, and the expression level of CXCR4 mRNA was implicated in poor recurrence-free survival [15]. On the other hand, some studies revealed the opposite data. Results from the studies of Sasaki et al. demonstrated that CXCR4 expression has no correlation with lymph node metastasis in submucosal esophageal cancer [16]. A recent study investigated the serum concentrations of CXCL12 and its specific receptor CXCR4 and other classical tumor markers in 49 patients with EC and 30 healthy volunteers, which showed that compared to the healthy controls, the serum level of CXCL12 was significantly higher and CXCR4 was significantly lower in EC patients, indicating the diagnostic sensitivity, negative predictive value, and accuracy of CXCR4, which were the highest among all analyzed proteins and elevated in serum concentration with classical tumor markers [17].

The purpose of this study was to investigate the impact of CRCX4 expression on clinicopathological feature and survival outcome of esophageal cancer.

Material and methods

Tissue samples

A total of 105 patients (55 men and 50 women) who were diagnosed with esophageal carcinoma and had undergone routine esophageal resection in the First Affiliated Hospital of Zhengzhou Universityfrom 2009 to 2010, were included in this study. The age of the patients ranged from 41 to 82 years (mean 65.4 years). The histological diagnosis and differentiation were determined independently by two pathologists. The clinicopathological features of the patients are shown in **Table 1**. None of the patients had received preoperative radiotherapy or chemotherapy before the surgical resection. The project protocol has been approved by the local ethics committee. All patients provided written informed consent for the use of the tumor tissues for clinical research.

Immunohistochemical analysis

The streptavidin-peroxidase (SP) staining method was used to detect the CXCR4 expression. The tumor specimens were fixed with 10% formaldehyde in phosphate-buffered saline (PBS), embedded in paraffin, and cut into 4-5 m sections. They were dewaxed in xylene and dehydrated with descending ethanol. For antigen retrieval, sections were heated in a microwave oven for 10 min in 10 mmol/L sodium citrate (pH 6.0) and cooled to room temperature. After endogenous peroxide was blocked by 3% hydrogen peroxide (H_2O_2) for 15 min in methanol, the sections were rinsed with PBS, and further blocked by 1% bovine serum albumin for 30 min to block nonspecific reactions at room temperature. The blocked slides were incubated with primary antibody CXCR4 (R&D Systems, Minneapolis, MN, USA) at 4°C overnight, followed by the incubation with the secondary antibody conjugated with biotin at room temperature for 30 min, and then exposed to streptavidin-peroxidase for another 30 min. After the sections were rinsed with PBS, the reaction products of peroxidase were visualized by incubation with diaminobenzidine tetrahydrochloride. Finally, the samples were counterstained for nuclei with hematoxylin, and mounted. To examine the specificity of immunostaining, the primary antibodies were substituted with PBS for negative control.

Evaluation of immunostaining

The sections were assessed microscopically by two pathologists who were blinded to details regarding patient background. CXCR4 expression was classified into four grades based on the homogeneous staining intensity: absent =

Table 2. Univariate Cox regression analysis of parameters associated with prognosis of patients with esophageal cancer

Characteristics	Subset	Hazard ratio (HR)	95% confidence interval (CI)	*P* value
Sex	Male/Female	1.27	0.81-1.96	0.473
Age (years)	< 60/≥ 60	1.16	0.68-2.09	0.738
Tumor type	Squamous cell carcinoma/Adenocarcinoma	1.72	0.65-2.59	0.322
Tumor location	Upper + Middle/Lower	2.06	0.86-2.34	0.095
Tumor depth	sm1 + sm2/sm3	1.92	0.73-2.29	0.168
Histologic grade	Well + Moderate/Poor	1.47	0.62-2.86	0.408
Lymph node metastasis	Negative/Positive	2.57	1.58-3.24	0.009
Distant metastasis	Negative/Positive	3.29	1.56-4.61	0.006
pTNM stage	I + II/III	2.12	1.27-3.40	0.021
CXCR4 expression	High/Low	2.28	1.35-3.27	0.016

score 0, weak = score 1, moderate = score 2, and strong = score 3. The extent of staining was scored as 0 (0%), 1 (1%-25%), 2 (26%-50%), 3 (51%-75%), and 4 (76%-100%) based on the percentage of the positive staining areas in relation with the whole tumor area. The sum of the intensity score and the extent score was used as the final score (0-7) of CXCR4 expression. The samples that have a final score of 6 or higher were regarded as the high expression. If immunohistochemical evaluations of the observers differed, slides were reevaluated and reclassified according to the assessment given most frequently.

Statistical analysis

All statistical analyses were performed using the SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). We used the χ^2 test to compare the categorical data. Survival was computed using the Kaplan-Meier method, and the log-rank test was used to assess statistical significance. Cox proportional hazards analysis was performed to measure the relative contribution of various factors to the risk of recurrence. $P < 0.05$ was considered to indicate statistical significance.

Results

CXCR4 expression in esophageal cancer

CXCR4 expression of 105 esophageal cancer specimens was measured by immunohistochemistry (IHC). **Figure 1** showed the representative staining patterns for CXCR4 in esophageal cancer specimens. Expression of CXCR4 was observed predominantly in cytoplasm of esophageal cancer, and in a few specimens with a weak membranous location. The specimens that have a final staining score of 6 or higher was regarded as the high expression, and the score of less than 6 was classified as the low expression.

Histopathologic characteristics and CXCR4 expression

To determine the relationship between CXCR4 and clinicopathologic characteristics, we further investigated the association between the levels of CXCR4 in esophageal tumor tissues and a battery of clinicopathologic factors (**Table 1**). In patients with esophageal cancer, significant differences between the two groups of CXCR4 expression were found in the lymph node metastasis ($P = 0.037$), distant metastasis ($P = 0.027$), and pTNM stage ($P = 0.015$), however, there was no significant correlation between the two groups of CXCR4 expression in other clinicopathological characteristics such as age, gender, tumor type, tumor location, tumor depth, and histological grade ($P > 0.05$ for all).

CXCR4 expression as an independent prognostic factor

The covariates that were statistically significantly associated with worse survival by univariate Cox proportional hazards analyses were included in the model as potential risk factors: lymph node metastasis (negative VS positive), distant metastasis (negative VS positive), pTNM stage (I-III), and CXCR4 expression (**Table 2**). In

Table 3. Multivariate Cox regression analysis of factors associated with prognosis of patients with esophageal cancer

Characteristics	Subset	Hazard ratio (HR)	95% confidence interval (CI)	*P* value
Lymph node metastasis	Positive/Negative	2.06	1.17-3.46	0.013
Distant metastasis	Positive/Negative	2.23	1.35-3.16	0.008
pTNM stage	I + II/III	1.84	1.06-3.21	0.025
CXCR4 expression	High/Low	1.75	1.08-3.37	0.028

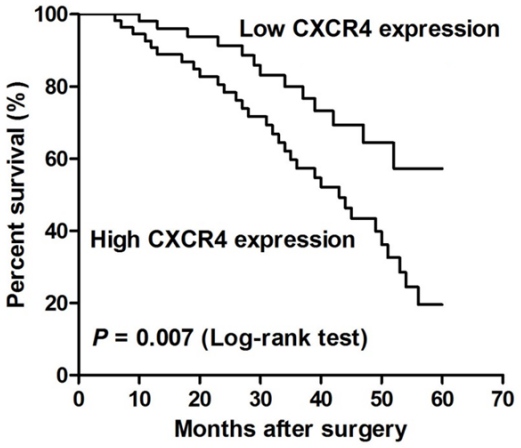

Figure 2. Kaplan-Meier survival analyses. The Kaplan-Meier survival and log-rank test were performed to determine whether CXCR4 expression level was associated with overall survival rate. Patients were grouped according to low (low CXCR4 expression) or high (high CXCR4 expression) immunostaining in esophageal cancer tissue.

addition, the multivariate Cox regression analyses were used to determine whether various factors were associated with overall survival (**Table 3**). We found that lymph node metastasis (HR = 2.06, 95% CI = 1.17 to 3.46, *P* = 0.013), distant metastasis (HR = 2.23, 95% CI = 1.35 to 3.16, *P* = 0.008), pTNM stage (HR = 1.84, 95% CI = 1.06 to 3.21, *P* = 0.025), and CXCR4 expression (HR = 1.75, 95% CI = 1.08 to 3.37, *P* = 0.028) were independently associated with the long-term prognosis in patients with esophageal cancer.

5-year survival and CXCR4 expression

The relationship between CXCR4 expression and survival of patients with esophageal cancer was determined by the Kaplan-Meier method, and the statistical significance of each comparison was calculated with the log-rank test. The survival rates among patients with low CXCR4 expression compared with patients with high CXCR3 expression are shown in **Figure 2**. The high CXCR4 expression was statistically significantly associated with poorer survival rate than the low CXCR4 expression (*P* = 0.007 by log-rank test).

Discussion

Esophageal cancer is an aggressive solid tumor with the enormous malignant potential for local invasion and early dissemination, so it has a high rate of tumor recurrence after surgical resection [18]. Because clinical outcomes cannot be successfully predicted by most of the current clinical parameters, prognosis of patients with esophageal cancer remains unfavorable and identifying biologic predictors is warranted. Chemokines and their respective receptors were initially discovered to mediate multiple pro-and anti-inflammatory responses [19]. Certain chemokines have been implicated in the tumor growth, dissemination and local immune escape. Data from *in vitro* and *in vivo* studies indicated the crucial role of CXCR4 in tumor spread of prostate, breast, lung and esophageal cancer [20-23]. In the present study, to understand the prognostic significance of CXCR4 upregulation in esophageal cancer, we analyzed the impact of CXCR4 expression in esophageal tumor tissues on battery of clinicopathologic factors and patient survival. The results indicated that CXCR4 was an independent prognostic factor for survival in patients with esophageal cancer.

In diverse tumor entities, the CXCR4 expression has been associated with tumor dissemination and poor prognosis. Schimanski et al. showed that in patients with human hepatocellular carcinoma (HCC), CXCR4 expression significantly contributed to the progressed local tumors, lymphatic metastasis, distant dissemination and reduced 3-year overall survival rate [24]. In pancreatic cancer, strong CXCR4 expression was distinctly linked to advanced UICC stages, hematogenous metastasis and progressed local tumor stages [25]. The present study presented that CXCR4 is frequently observed in esophageal cancer and high CXCR4 expression is significantly associated with poor patient prognosis. The pathological vari-

ables significantly associated with CXCR4 expression were lymph node metastasis (P = 0.037), distant metastasis (P = 0.027), and pTNM stage (P = 0.015), consistent with previous studies in esophageal cancer showing that CXCR4 expression was statistically significantly associated with increased lymph node micrometastasis (P < 0.001) and bone marrow micrometastasis (P < 0.001) [12]. Other studies showed that although CXCR4 expression was not related to nodal metastasis, all patients with lymph node micrometastasis had positive CXCR4 expression in esophageal cancer tissue [16].

CXCR4 and its ligand have been proposed to distinctly contributed to the migration and trafficking of malignant B cells in several haematological cancers like chronic lymphocytic leukaemia, follicular lymphoma and diffuse large B cell lymphoma (DLBCL) [26-28]. A recent studies showed that CXCR4 expression was involved in cell migration *in vitro* and dissemination *in vivo* [28]. The CXCR4 expression was also contributed to increased engraftment and dissemination as well as the reduced survival time in mice model. For the clinical significance, CXCR4 expression was identified to be an independent prognostic marker for shorter overall survival in DLBCL patients [28]. Here, for univariate and multivariate Cox proportional hazards analyses, we found that CXCR4, as well as lymph node metastasis, distant metastasis and TNM stage, were identified to be independent prognostic factors for survival in patients with esophageal cancer.

In summary, we have demonstrated that high CXCR4 expression correlates with lymph node metastasis, distant metastasis and pTNM stage, and it provides an independent prognostic factor for esophageal cancer survival. Our studies strongly suggest that CXCR4 plays a crucial role in development of esophageal cancer and could provide a novel molecular target for the treatment of esophageal cancer.

Disclosure of conflict of interest

None.

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References

[1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-2917.

[2] Omloo JM, Lagarde SM, Hulscher JB, Reitsma JB, Fockens P, van Dekken H, ten Kate FJ, Obertop H, Tilanus HW and van Lanschot JJ. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg 2007; 246: 992-1001.

[3] Hosch SB, Stoecklein NH, Pichlmeier U, Rehders A, Scheunemann P, Niendorf A, Knoefel WT and Izbicki JR. Esophageal cancer: the mode of lymphatic tumor cell spread and its prognostic significance. J Clin Oncol 2001; 19: 1970-1975.

[4] Ohigashi Y, Sho M, Yamada Y, Tsurui Y, Hamada K, Ikeda N, Mizuno T, Yoriki R, Kashizuka H and Yane K. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clin Cancer Res 2005; 11: 2947-2953.

[5] Jo DY, Rafii S, Hamada T and Moore MA. Chemotaxis of primitive hematopoietic cells in response to stromal cell-derived factor-1. J Clin Invest 2000; 105: 101-111.

[6] Locati M, Deuschle U, Massardi ML, Martinez FO, Sironi M, Sozzani S, Bartfai T and Mantovani A. Analysis of the gene expression profile activated by the CC chemokine ligand 5/RANTES and by lipopolysaccharide in human monocytes. J Immunol 2002; 168: 3557-3562.

[7] Mukherjee D and Zhao J. The role of chemokine receptor CXCR4 in breast cancer metastasis. Am J Cancer Res 2013; 3:46-57.

[8] Jung M, Rho J, Kim Y, Jung J, Jin Y, Ko YG, Lee J, Lee S, Lee J and Park M. Upregulation of CXCR4 is functionally crucial for maintenance of stemness in drug-resistant non-small cell lung cancer cells. Oncogene 2013; 32: 209-221.

[9] Yadav VR, Sung B, Prasad S, Kannappan R, Cho SG, Liu M, Chaturvedi MM and Aggarwal BB. Celastrol suppresses invasion of colon and pancreatic cancer cells through the downregulation of expression of CXCR4 chemokine receptor. J Mol Med 2010; 88: 1243-1253.

[10] Zhang SS, Han ZP, Jing YY, Tao SF, Li TJ, Wang H, Wang Y, Li R, Yang Y, Zhao X, Xu XD, Yu ED, Rui YC, Liu HJ, Zhang L and Wei LX. CD133+ CXCR4+ colon cancer cells exhibit metastatic

potential and predict poor prognosis of patients. BMC Med 2012; 10: 85.
[11] Delongchamps NB, Beuvon F, Mathieu JR, Delmas S, Metzger I, Prats H and Cabon F. CXCR4 is highly expressed at the tumor front but not in the center of prostate cancers. World J Urol 2015; 33: 281-287.
[12] Kaifi JT, Yekebas EF, Schurr P, Obonyo D, Wachowiak R, Busch P, Heinecke A, Pantel K and Izbicki JR. Tumor-cell homing to lymph nodes and bone marrow and CXCR4 expression in esophageal cancer. J Natl Cancer Inst 2005; 97: 1840-1847.
[13] Koishi K, Yoshikawa R, Tsujimura T, Hashimoto-Tamaoki T, Kojima S, Yanagi H, Yamamura T and Fujiwara Y. Persistent CXCR4 expression after preoperative chemoradiotherapy predicts early recurrence and poor prognosis in esophageal cancer. World J Gastroenterol 2006; 12: 7585-7590.
[14] Gockel I, Schimanski CC, Heinrich C, Wehler T, Frerichs K, Drescher D, von Langsdorff C, Domeyer M, Biesterfeld S and Galle PR. Expression of chemokine receptor CXCR4 in esophageal squamous cell and adenocarcinoma. BMC Cancer 2006; 6: 290.
[15] Goto M, Yoshida T, Yamamoto Y, Furukita Y, Inoue S, Fujiwara S, Kawakita N, Nishino T, Minato T and Yuasa Y. CXCR4 Expression is Associated with Poor Prognosis in Patients with Esophageal Squamous Cell Carcinoma. Ann Surg Oncol 2015; [Epud ahead of print].
[16] Sasaki K, Natsugoe S, Ishigami S, Matsumoto M, Okumura H, Setoyama T, Uchikado Y, Kita Y, Tamotsu K and Sakurai T. Expression of CXCL12 and its receptor CXCR4 correlates with lymph node metastasis in submucosal esophageal cancer. J Surg Oncol 2008; 97: 433-438.
[17] Łukaszewicz-Zając M, Mroczko B, Kozłowski M and Szmitkowski M. The serum concentrations of chemokine CXCL12 and its specific receptor CXCR4 in patients with esophageal cancer. Dis Markers 2016; 2016: 7963895.
[18] Tachezy M, Zander H, Gebauer F, von Loga K, Pantel K, Izbicki JR and Bockhorn M. CXCR7 expression in esophageal cancer. J Transl Med 2013; 11: 238.
[19] Zlotnik A and Yoshie O. Chemokines: a new classification system and their role in immunity. Immunity 2000; 12: 121-127.
[20] Luker KE, Lewin SA, Mihalko LA, Schmidt BT, Winkler JS, Coggins NL, Thomas DG and Luker GD. Scavenging of CXCL12 by CXCR7 promotes tumor growth and metastasis of CXCR4-positive breast cancer cells. Oncogene 2012; 31: 4750-4758.
[21] Valkenburg KC and Pienta KJ. Mobilizing prostate cancer cells from the endosteal niche by targeting the SDF-1/CXCR4 axis. Cancer Research 2015; 75: 365.
[22] Liang JX, Gao W, Liang Y and Zhou XM. Chemokine receptor CXCR4 expression and lung cancer prognosis: a meta-analysis. Int J Clin Exp Med 2015; 8: 5163-5174.
[23] Wu J, Wu X, Liang W, Chen C, Zheng L and An H. Clinicopathological and prognostic significance of chemokine receptor CXCR4 overexpression in patients with esophageal cancer: a meta-analysis. Tumor Biol 2014; 35: 3709-3715.
[24] Schimanski CC, Bahre R, Gockel I, Müller A, Frerichs K, Hörner V, Teufel A, Simiantonaki N, Biesterfeld S, Wehler T, Schuler M, Achenbach T, Junginger T, Galle PR and Moehler M. Dissemination of hepatocellular carcinoma is mediated via chemokine receptor CXCR4. Br J Cancer 2006; 95: 210-217.
[25] Wehler T, Wolfert F, Schimanski CC, Gockel I, Herr W, Biesterfeld S, Seifert JK, Adwan H, Berger MR and Junginger T. Strong expression of chemokine receptor CXCR4 by pancreatic cancer correlates with advanced disease. Oncol Rep 2006; 16: 1159-1164.
[26] Bertolini F, Dell'Agnola C, Mancuso P, Rabascio C, Burlini A, Monestiroli S, Gobbi A, Pruneri G and Martinelli G. CXCR4 neutralization, a novel therapeutic approach for non-Hodgkin's lymphoma. Cancer Res 2002; 62: 3106-3112.
[27] López-Giral S, Quintana NE, Cabrerizo M, Alfonso-Pérez M, Sala-Valdés M, de Soria VGG, Fernández-Rañada JM, Fernández-Ruiz E and Muñoz C. Chemokine receptors that mediate B cell homing to secondary lymphoid tissues are highly expressed in B cell chronic lymphocytic leukemia and non-Hodgkin lymphomas with widespread nodular dissemination. J Leukoc Biol 2004; 76: 462-471.
[28] Moreno MJ, Bosch R, Dieguez-Gonzalez R, Novelli S, Mozos A, Gallardo A, Pavón MÁ, Céspedes MV, Grañena A, Alcoceba M, Blanco O, Gonzalez-Díaz M, Sierra J, Mangues R, Casanova I. CXCR4 expression enhances diffuse large B cell lymphoma dissemination and decreases patient survival. J Pathol 2015; 235: 445-455.