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The role of CXC chemokine ligand 4/CXC chemokine receptor 3-B in breast cancer progression

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ABSTRACT

Chemokines and their receptors participate in the development of cancers by enhancing tumor cell proliferation, angiogenesis, invasion, metastasis and penetration of tumor immune cells. It remains unclear whether CXC chemokine ligand 4 (CXCL4)/CXC chemokine receptor 3-B (CXCR3-B) can be used as an independent molecular marker for establishing prognosis for breast cancer patients. We evaluated CXCL4 and CXCR3-B expression in 114 breast cancer tissues and 30 matched noncancerous tissues using immunohistochemistry and western blot, and determined the correlation between their expression and clinicopathologic findings. We observed that breast cancer tissues express CXCL4 strongly and CXCR3-B weakly compared to noncancerous tissues. Strong CXCL4 expression was detected in 94.7% and weak CXCR3-B expression was detected in 78.9% of the tissues. Therefore, CXCL4/CXCR3-B might play a crucial role in breast cancer progression. We found no significant correlation between CXCL4 and age, tumor stage, tumor grade or TNM stage. CXCR3-B was associated significantly with tumor grade. Moreover, the Chi-square test of association showed that the expression of CXCL4/CXCR3-B might be an independent prognostic marker for breast cancer. Therefore, we suggest that CXCR3-B is an indicator of poor prognosis and may also be a chemotherapeutic target.

KEYWORDS
Breast; cancer; chemokines; chemokine receptors; CXCL4; CXCR3-B; tumor grade

Chemokine receptors are located on cells such as T cells and natural killer cells (Murphy et al. 2000; Murphy 2002). These receptors and their ligands function in chemotaxis by regulating the movement of leukocytes to secondary lymphoid organs and inflammation sites (Zlotnik and Yoshie 2000; Balkwill and Mantovani 2001). It has been suggested, however, that tumor cells express a variety of chemokines and that their receptors are associated with disease progression and poor prognosis (Suyama et al. 2005; Burns et al. 2006; Datta et al. 2006; Walser et al. 2006; Zipin-Roitman et al. 2007; Ma et al. 2009).

CXCR3 is a G protein-coupled receptor 9 (GPR9) that belongs to the CXC chemokine receptor family and exists in humans as CXCR3-A, CXCR3-B and CXCR3-alt (chemokine receptor 3-alternative) isoforms (Altara et al. 2016). CXCL4 ligand binds specifically to CXCR3-B, whereas CXCL9, CXCL10, CXCL11 ligands bind to both CXCR3-A and CXCR3-B (Clark-Lewis et al. 2003; Lasagni et al. 2003). CXCR3-A and CXCR3-B control opposite biological functions using distinct intracellular signals (Lasagni et al. 2003; Kelsen et al. 2004; Romagnani et al. 2004). Generally, activation of CXCR3-A enhances tumor cell growth, invasion and survival, whereas CXCR3-B causes suppression of proliferation, apoptosis and angiostasis. Although different tumor types express high ratios of CXCR3-A/CXCR3-B compared to normal cells, CXCR3-A predominates in tumors cells and tissues (Datta et al. 2008; Ma et al. 2015).

Renal cancer cells promote growth and migration through the CXCR3-A controlled signal in the absence of or under conditions of low amounts of CXCR3-B (Datta et al. 2010). Moreover, renal cancer cell proliferation is inhibited when CXCR3-B is overexpressed (Datta et al. 2008). Both mRNA and protein level heme oxygenase-1 (HO-1) are overexpressed in renal cancer tissues that express small amounts of CXCR3-B (Datta et al. 2010). The induction of CXCR3-B by CXCL4 promotes p38 MAPK activation and inactivates ERK1/2 (Datta et al. 2010). This promotes Nrf2 export from the nucleus and localizes Bach-1 to the nucleus to reduce breast cancer cell proliferation by increasing apoptosis. CXCR3-B proliferation-inhibitory events in breast cancer cells are controlled by decreasing HO-1 expression to promote increased apoptosis (Malhotra

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et al. 2010; Ma et al. 2015). Tumor necrosis appears to be correlated with CXCR3-B expression (Gacci et al. 2009).

Although the association between CXCR3-B expression and tumor migration has been investigated, the role of CXCL4 and CXCR3-B signals and how they are linked to clinical characteristics in breast cancer progression remains unclear. We investigated the role of CXCR3-B and its chemokine, CXCL4, in development of clinicopathologic characteristics in breast cancer progression.

Material and methods

Chemicals

Mouse anti-CXCR3-B, anti-CXCL4 monoclonal antibodies and streptavidin-biotin peroxidase immunohistochemical reagent kits were obtained from Santa Cruz Biotechnology (Santa Cruz, CA). Horseradish peroxidase labeled rabbit anti-goat IgG antibody and actin polyclonal antibody were purchased from Biosynthesis Bio (BIOSS, Beijing, China). All other chemicals were of analytical reagent grade.

Study subjects and tissue samples

The protocol for tissue sample collection was approved by the research and ethics committee of the First People's Hospital affiliated with Jiamusi University. Informed consent was obtained from all patients prior to surgery. Breast cancer and noncancerous tissue samples were collected from 114 patients from 2015 to 2017 who underwent surgery at the First People's Hospital affiliated with Jiamusi University. The selection criteria included no preoperative treatment, complete medical history, histopathologic analysis and regional lymph node metastasis, but absence of distant metastasis. The average age was 50 years with a range of 31 −80 years. The specimens consisted of 114 breast cancer tissues and 30 matched noncancerous (normal) tissues obtained from 30 of the 114 patients as paired specimens adjacent to the tumor. Clinicopathologic characteristics including age, tumor stage, node status, tumor grade and tumor node metastasis (TNM) stage were obtained from the patients' charts.

Histologic evaluations were confirmed by a pathologist using hematoxylin and eosin (H and E) stained formalin fixed, paraffin embedded (FFPE) tumor tissue (Yang et al. 2016). Breast cancer tissues fixed in 10% formalin for 1–2 days at room temperature were trimmed and embedded in tissue cassettes. They were dehydrated in 70, 80 and 95% ethanol for 1 h in each and three baths of 100% ethanol for 1.5 h each. Tissues were cleared in three changes of xylene for 1.5 h each and in two changes of paraffin for 2 h each and allowed to solidify. Blocks were sectioned at 4 μm, kept in a water bath at 40 °C, then mounted on slides and allowed to air dry for 30 min.

The tissue sections were deparaffinized in two changes of xylene for 15 min each and rehydrated for 5 min each through 100, 95, 90, 80% and 70% ethanols and rinsed for 1 min in distilled water. Sections were stained with hematoxylin for 15 min, rinsed in water and blotted dry. Sections were differentiated in 1% acid alcohol for 30 sec and rinsed with tap water. Sections then were stained with 0.5% eosin for 1 min and rinsed in water. Finally, the slides were dehydrated through 70, 80 and 90% ethanol for 30 sec each, twice in 95% ethanol for 1 min each, twice in 100% for 5 min each and cleared in three baths of xylene for 5 min each. Tumor stages were classified according to the American Joint Commission on Cancer TNM system (Edge and Compton 2010). The World Health Organization 2005 tumor grading standard was used to determine the tumor grade (Barnes et al. 2005).

Expression of CXCL4 and CXCR3-B in breast cancer and noncancerous tissues

Sections were incubated at 60 °C for 40 min, deparaffinized, rehydrated through graded alcohols and rinsed three times in phosphate-buffered saline (PBS) for 5 min each. The sections were heated in citrate solution for 40 min, cooled and rinsed three times in PBS. Sections then were incubated with 5% bovine serum albumin (BSA) at 37 °C for 30 min and washed three times with PBS. Sections were incubated with primary antibody at 4 °C overnight: CXCL4 diluted 1:100 or CXCR3-B diluted 1:100. The next day, sections were incubated with biotinylated anti-rabbit immunoglobulin G (IgG) and streptavidin-biotin complex (SABC) at 37 °C for 20 and 30 min, respectively. The sections were rinsed thoroughly with PBS between incubations. The sections were developed for 10 min in 3,3′-diaminobenzene (DAB) and counterstained with Mayer's hematoxylin at room temperature. Sections then were washed in water, acid alcohol and PBS, then incubated in PBS at 37 °C for 40 min to 1 h. Finally, the sections were dehydrated, cleared, coverslipped and mounted. The brown and blue stained cells represented positive and negative cells, respectively.

The immunoreactivity of CXCL4/CXCR3-B was classified as: (-), negative; (1+), weak staining, ≤ 10% stained cells; (2+), moderate staining, 11–50% stained cells; (3+), strong staining, > 50% stained cells. Each

observer evaluated the stained cells and classified the intensity of immunostaining based on visual assessment of brown reaction product. The final immunostaining result was the average score for two observers.

Western blot expression of CXCL4 and CXCR3-B

Tumor tissues were minced and lysed for 30 min in 500 μl cell lysis buffer, then centrifuged at 12,000 x g for 15 min at 4 °C. The supernatant was collected and the Bradford method was used to determine the concentration of the protein. The protein and marker (26,617; Thermo Fisher Scientific, New York, NY) were loaded into the wells of the sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and run at 60 V for 15 min. Subsequently, the voltage was increased to 110 V to complete the run in about 2 h. The protein separated by SDS-PAGE was run at 100 V in an ice block tank and transferred to a PVDF membrane after approximately 2 h.

Milk-blocked PVDF membranes were incubated with the appropriate primary antibody (CXCL4, CXCR3-B, or β-actin) overnight, then washed three times for 5 min/wash with Tris-buffered saline with Tween 20 (TBST) the next day. The membranes were incubated further with horseradish peroxidase labeled rabbit anti-goat IgG at room temperature for 1 h, then washed three times with TBST. Proteins finally were visualized using an enhanced chemiluminescence kit and exposure to X-ray film. The protein band intensity was computed using LabWork 3.0 (UVP Inc., Upland CA).

Statistical analysis

We used SPSS 21.0 (SPSS Inc. Chicago, IL). Chi-square test was used to determine the relations between the expression of CXCL4 and CXCR3-B, and the clinicopathologic characteristics. Mantel-Haenszel-Cochran test was used to determine the relation between CXCL4/CXCR3-B expression and tumor grade. Values for $p \leq 0.05$ were considered statistically significant.

Results

We found that the expression of CXCL4/CXCR3-B was located in the cytoplasm (Figure 1). We found CXCL4 as follows: 0 cases of negative staining (-), six cases of weak staining (1+), five cases of moderate staining (2+) and 103 cases of strong staining (3+). We found 79 cases unstained for CXCR3-B (-), 11 cases with weak staining (1+), 24 cases with moderate staining (2+) and no case with strong staining (3+). We found that six (5.3%) patients expressed low CXCL4, 108 (94.7%) expressed high CXCL4, 90

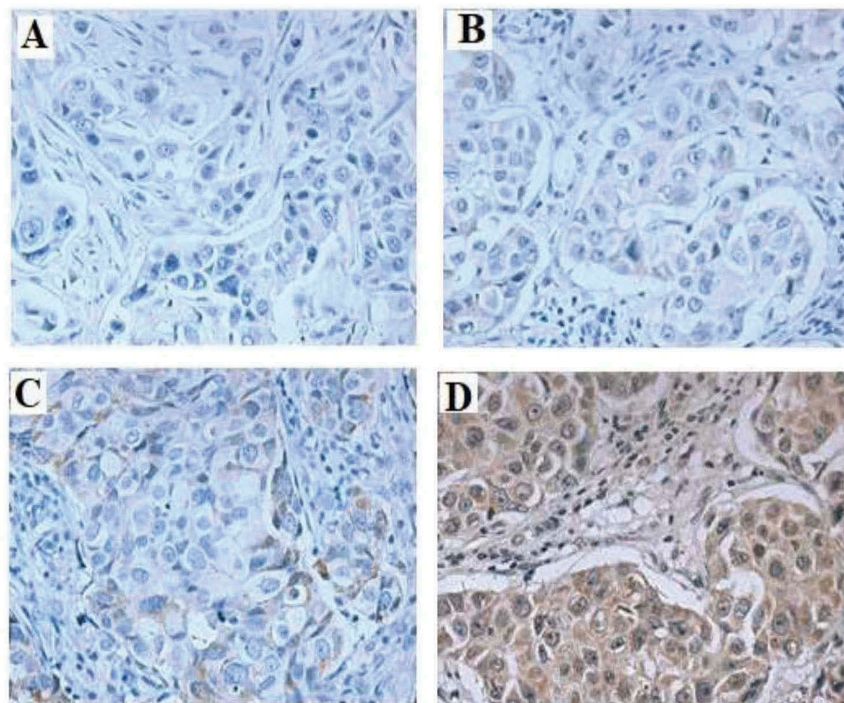

Figure 1. Immunohistochemical expressions of CXCL4/CXCR3-B in breast cancer tissue samples. A) Negative expression. B) Weak expression. C) Moderate expression. D) Strong expression. x 400.

(78.9%) expressed low CXCR3-B and 24 (21.1%) expressed high CXCR3-B in cancerous tissues.

Our findings concerning noncancerous (normal) and cancerous tissues (Figure 2) indicate that 24 (80%) of CXCL4 was up-regulated in the cancerous tissue compared to its corresponding noncancerous tissue (Figure 2a). CXCR3-B was down-regulated in 19 (63%) of the cancerous tissue compared to its corresponding noncancerous tissue (Figure 2b).

Correlation of CXCL4/CXCR3-B expression with clinicopathologic characteristics

Chi-square test p values were computed to determine the relation between CXCL4/CXCR3-B expression and clinicopathologic characteristics (Table 1). We found that CXCL4 expression was not correlated significantly with age, tumor stage, tumor grade or TNM. The expression of CXCR3-B was correlated significantly with tumor grade ($p < 0.05$), but not with age, tumor stage or TNM.

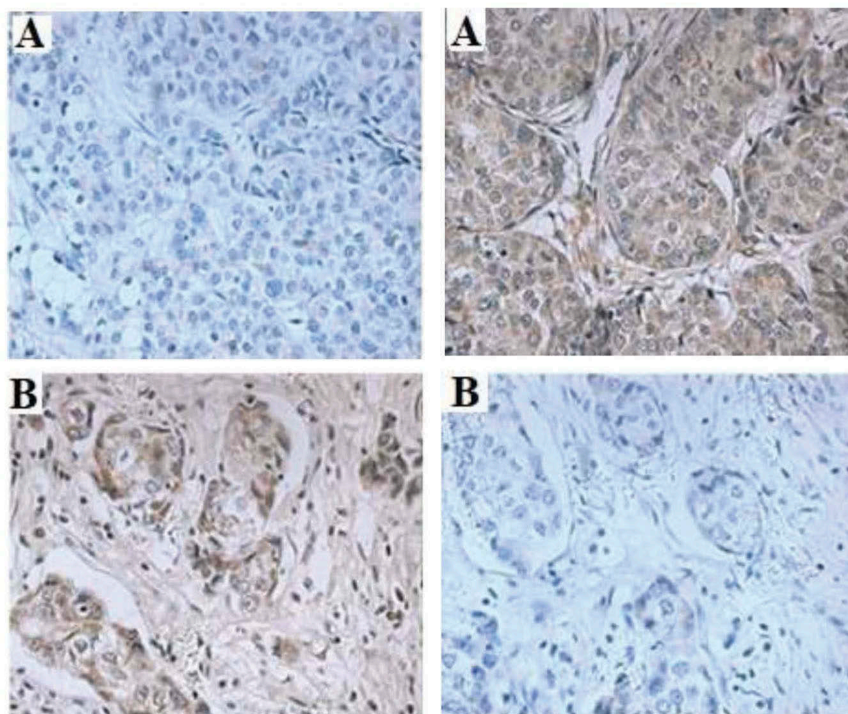

Figure 2. A) CXCL4 was down-regulated in noncancerous tissues (left) compared to cancerous tissue (right). B) CXCR3-B was higher in noncancerous tissue (left) than in cancerous tissue (right). x 400.

Table 1. Relation between CXCL4/CXCR3-B expression and clinicopathologic parameters.

		CXCL4 expression			CXCR3-B expression		
Parameters	Number of patients	Strong (%)	Weak (%)	p	Strong (%)	Weak (%)	p
All cases	114	n = 108	n = 6		n = 24	n = 90	
Age							
≥ 50	63	59 (54.6)	4 (66.67)	0.559	12 (50.0)	51 (56.7)	0.560
< 50	51	49 (45.37)	2 (33.33)		12 (50.0)	39 (43.3)	
Tumor stage							
T1–T2	75	71 (65.74)	4 (66.67)	0.963	17 (70.83)	58 (64.44)	0.554
T3–T4	39	37 (34.26)	2 (33.33)		7 (29.17)	32 (35.56)	
Node status							
N0 (negative)	0	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	
N+ (positive)	114	114 (100)	0 (0.00)		0 (.0.00)	114 (100)	
Tumor grade							
Well/moderate	89	83 (76.85)	6 (100)	0.080	24 (100)	65 (72.22)	0.000
Poor	25	25 (23.15)	0 (0.00)		0 (0.00)	25 (27.78)	
TNM							
I–II	47	45 (41.67)	2 (33.33)	0.683	10 (41.67)	37 (41.11)	0.961
III	67	63 (58.33)	4 (66.67)		14 (58.33)	53 (58.89)	

CXCL4, CXC chemokine ligand 4; CXCR3-B, CXC chemokine receptor 3-B; TNM, tumor-node-metastasis. Each p value compares the expression of CXCL4 or CXCR3-B to the clinical features

We calculated chi-square tests of association to determine whether CXCL4/CXCR3-B expression was associated independently with age, tumor stage, tumor grade or TNM (Table 2). We found that high or low expression of CXCL4 or CXCR3-B was not associated independently with age, tumor stage or TNM. The expression of CXCL4 or CXCR3-B, however, was associated independently with tumor grade, whether it was expressed strongly or weakly ($p < 0.05$).

MHC statistics were used to determine the correlation between CXCL4/CXCR3-B expression and tumor grade (Table 3). We found that the probability of strong expression of CXCL4 was 37.5 times that of strong expression of CXCR3-B in well/moderate differentiated cancers. The probability of strong expression of CXCL4 was far greater than for strong expression of CXCR3-B in poorly differentiated cancers ($p < 0.05$).

CXCL4 and CXCR3-B expression by western blot

Western blot analysis was used to investigate the expression of CXCL4/CXCR3-B in both noncancerous and cancerous tissues. CXCL4 expression was low in non-cancerous tissue compared to its corresponding cancerous tissue, while CXCR3-B expression was high in the noncancerous tissue and low in the cancerous tissue (Figure 3a); these findings were consistent with our immunohistochemistry findings (Figure 2). We also observed that compared to noncancerous tissues, CXCL4 was highly expressed in 24 (80%) and CXCR3-B expression was low in 19 (63%) of the cancerous tissues ($p < 0.05$) (Figure 3b,c).

Discussion

Chemokines and their receptors participate in tumor cell proliferation, angiogenesis, invasion and metastasis, and they affect the penetration of tumor immune cells

Table 3. Correlation between CXCL4/CXCR3-B expression and tumor grade.

	CXCL4 vs. CXCR3-B	Probability	*p*
Well/moderate	Strong/weak	37.4653	0.0000
Poor	Strong/weak	infinity	0.0000

Well-differentiated, tumor cells look the most like normal tissue and are slow growing; moderately differentiated, tumor cells between well and poorly differentiated; poorly differentiated, tumor cells abnormal and fast growing.

(Moore et al. 1998; Dias et al. 2001). Information is limited concerning CXCL4/CXCR3-B expression in relation to clinicopathologic characteristics in breast cancer. CXCR3-B expression in breast cancer (Balan and Pal 2014) and prostate cancer (Wu et al. 2012) are associated with decreased invasion and proliferation. However, the role of CXCL4/CXCR3-B in breast cancer is still not well defined.

We found strong CXCL4 and weak CXCR3-B expression in cancerous tissue compared to noncancerous tissue. Therefore, CXCL4/CXCR3-B might play a role in breast cancer progression. The weak expression of CXCR3-B was strongly correlated with tumor grade, which means that it is a poor prognostic indicator.

We believe that there may be three reasons why CXCR3-B expression is linked to poor prognosis. Generally, activation of CXCR3-A enhances tumor cell growth, invasion and survival, whereas CXCR3-B appears to participate in suppression of proliferation, apoptosis and angiostasis. Cancer cells that exhibit small amounts of CXCR3-B imply a large number of proliferating cells that contribute to tumor proliferation. Calcineurin inhibitors may determine the development of human renal cancer by decreasing CXCR3-B and elevating proliferation via CXCR3-A (Datta et al. 2008). Weak expression of CXCR3-B resulted in increased HO-1 anti-apoptotic molecule and promoted cell proliferation in both breast and renal cancers (Balana and Pala 2014; Datta et al. 2010). Moreover, CXCR3-B expression is connected to tumor metastasis. It has been reported that alteration of the CXCR3-A/CXCR3-B ratio from low to high initiates

Table 2. Association between CXCL4/CXCR3-B expression and age, tumor stage, tumor grade or TNM.

		Age		Tumor stage		Tumor grade		TNM	
		≥ 50	< 50	T1–T2	T3–T4	Well/ moderate	Poor	I–II	III
CXCL4	Strong (%)	59 (54.63	49 (45.37)	71 (65.74)	37 (34.26)	83 (76.90)	25 (23.10	45 (41.67)	63 (58.33)
	Weak (%)	4 (66.67)	2 (33.33)	4 (66.67)	2 (33.33)	6 (100)	0 (0.00)	2 (33.33)	4 (66.67)
CXCR3-B	Strong (%)	12 (50.00)	12 (50.00)	17 (70.83)	7 (29.17	24 (100)	0 (0.00)	10 (41.67)	14 (58.33)
	Weak (%)	51 (56.67)	39 (43.33)	58 (64.44)	32 (35.56)	65 (72.20)	25 (27.80)	37 (41.11)	53 (58.89)
		p = 0.878		p = 0.950		p = 0.001		p = 0.982	

Each p value compares the expression of both CXCL4 and CXCR3-B to the clinical features

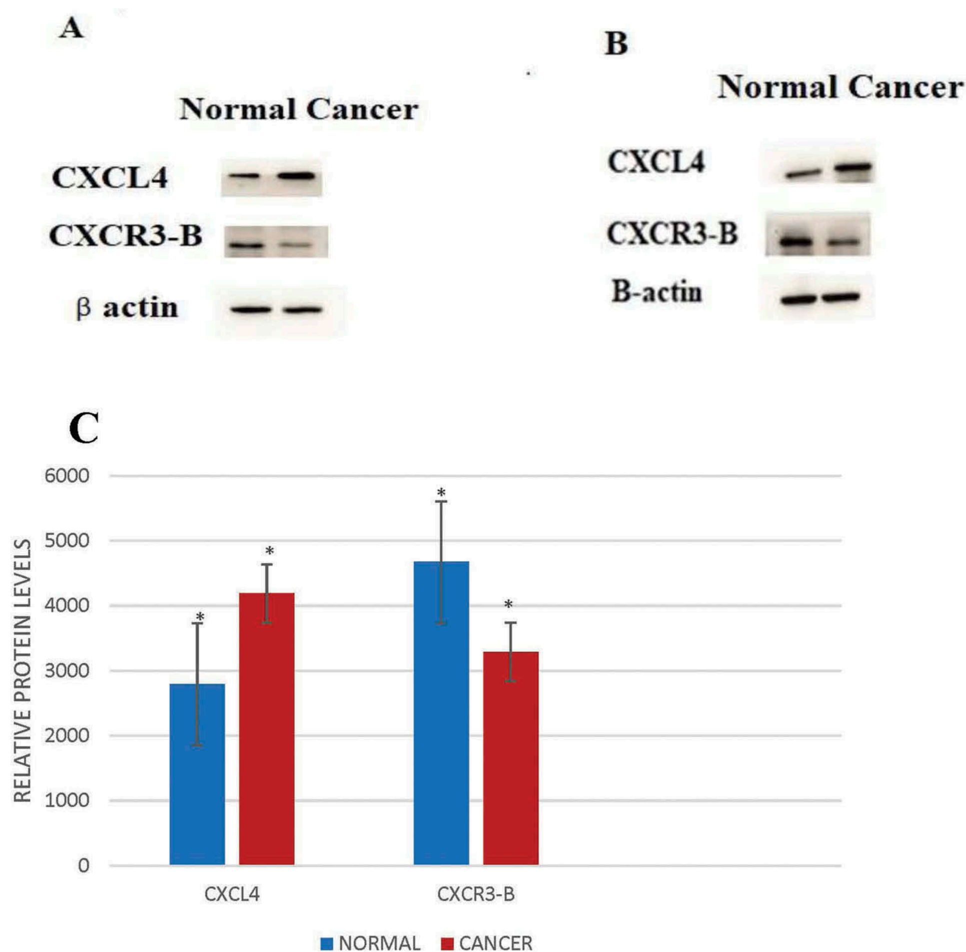

Figure 3. Western blot analysis for CXCL4 and CXCR3-B. A) Expression of CXCL4 and CXCR3-B for Figure 2. B) Western blot analysis for expression of CXCL4 and CXCR3-B with B-actin as a control. C) The intensity of bands of CXCL4 and CXCR3-B in B were quantified and are shown as relative expression levels after normalization by β-actin. *$p < 0.05$ vs. control.

cell migration and invasion, and promotes metastasis in prostate cancer (Wu et al. 2012). Tumors exhibit a high CXCR3-A/CXCR3-B ratio compared to normal tissue, which is increased further in metastatic tumor than in primary tumor as a result of up-regulated CXCR3-A or down-regulated CXCR3-B (Ma et al. 2015). Tumor angiogenesis, which is controlled by chemokines and chemokine receptors, also produces a poor prognosis (Moore et al. 1998; Dias et al. 2001). The angiostatic effect of CXCR3-B occurs by binding to CXCL4/CXCL10 (Petrai et al. 2008). Overexpressed CXCL10 in the absence or paucity of CXCR3-B can promote cell growth, invasion and tumor angiogenesis, possibly through CXCR3-A (Datta et al. 2006).

Regardless of breast cancer stage and tumor size, the poorer the tumor grade the poorer the prognosis. Our findings suggest that CXCR3-B may be a potential therapeutic target as well as a prognostic marker for breast cancer. We believe that ours is the first report concerning the role of CXCL4/CXCR3-B in breast cancer progression. We recommend further investigation, however, with a larger sample size and chemotherapeutic agents that target CXCR3-B.

Disclosure statement

No potential conflict of interest was reported by the authors.

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